Addition of Daily Synchronous 3-Dimensional Conformal Boost to Gross Tumor Volume in Concurrent Chemoradiation plus Adjuvant Chemotherapy in Locally Advanced Nasopharyngeal Carcinoma

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Abstract: Purpose: We evaluated the efficacy, survival, and toxicity of synchronous three- dimensional (3-D) conformal boost to the gross tumor volume (GTV) versus conventional fractionation in concurrent chemoradiation (CCRT) plus adjuvant chemotherapy (AC) for patients with locally advanced nasopharyngeal carcinoma (LANPC). **Patients and methods:** We enrolled 45 patients (31males and 14 females, median age 43 years) with stage III-IV nasopharyngeal carcinoma, all were randomized into 2 treatment arms; **group A;** Included 23 patients, who have received a dose of 1.8 Gy to the planning target volume (PTV) with concomitant boost of 0.6 Gy to the GTV, with a total dose of 72 Gy to the GTV and 54 Gy to PTV in 30 fractions during 6 weeks by using 3-D conformal radiotherapy, and **group B;** Included 22 patients, who have received, a dose of 1.8 Gy for 25 fractions to PTV then another 10 fractions to GTV with a total dose of 63 Gy during 7 weeks. Both arms received concurrent chemotherapy consisted of weekly cisplatin in dose of 35 mg/ m^2 given during irradiation then two cycles of cisplatin 80 mg/ m^2 plus docetaxel 75 mg/ m^2 every three weeks. All patients were monitored for mucositis, vomiting, weight loss and hematological toxicities. **Results:** The tumor response was evaluated 4 weeks after the end of the adjuvant chemotherapy, where the overall response (OR) was 91% in group A versus 77% in group B (P-value >0.05). The 2-year overall survival (OS) was 74% in group A vs. 64% in group B, the 2-year progression free survival (PFS) was 61% in group A vs. 54% in group B, the 2-year distant metastases free survival (DMFS) was 57% in group A vs. 50% in group B (P- value >0.05). Mucositis and vomiting were the most common acute toxicities as 64%, 48% respectively for mucositis and 55%, 41% respectively for vomiting. Both groups experienced grade 3-4 toxicities, grade 3-4 anemia and leucopenia were seen in 35% in group A and 32% in group B (*P*- value >0.05), but all toxicities were tolerable. **Conclusion**: The addition of daily 3- D conformal concomitant boost in concurrent chemoradiation is feasible and well tolerated achieving higher local control and improved tumor response rate, in patients with LANPC as compared to concurrent conventional chemoradiation especially with adjuvant chemotherapy to eradicate the distant micrometastases decreasing the incidence of distant failure.
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Key words: Locally advanced nasopharyngeal carcinoma, Chemoradiation, Three- dimensional conformal radiotherapy, concomitant boost.

1.Introduction

Nasopharyngeal carcinoma (NPC) is a unique neoplasm of head and neck that commonly seen in Southern China and Southeast Asia [1]. The incidence is high in the third to fifth decade of life with a male predominance; Majority of patients (≥70%) had locally advanced NPC at time of presentation [2]. The world health organization (WHO) classified the NPC into 3 types: Type I is keratinized squamous cell carcinoma (SCC), type II is non- keratinized SCC, and type III is undifferentiated carcinoma. WHO types II & III were associated with elevated Epstien Barr virus titer and considered more radiosensitive and chemosensitive [3]. The common presentation was cervical lymphadenopathy (82%), aural fullness (62%), nasal obstruction (42%), epistaxis (16%) and bloody sputum (14%) [4]. The surgical option was very difficult because of inaccessible anatomical location, so the use of radiation therapy in addition of chemotherapy was the optimal solution, for achieving locoregional control and eradication of distant micro-metastases [1]. The concurrent chemoradiation (CCRT) now is considered the standard of care, the progression free survival (PFS) was significantly improved with chemoradiation in nasopharyngeal carcinoma especially in advanced stages [5]. Many randomized trials searched for optimal dose of radiotherapy and benefits from modification of dose fractionation like hyperfractionation or accelerated fractionation versus standard fractionation aiming for better locoregional control. [6] The situation of chemotherapy as induction, plus concurrent chemoradiation is still disapointed, as several trials failed to prove that induction chemotherapy is more effective and tolerable when added to (CCRT) [7]. While many studies reported that adjuvant

chemotherapy (AC) with (CCRT) was significantly minimizing the locoregional relapse incidence, so the progression free survival rate increased, the relative risk ratio for locoregional recurrence of CCRT plus AC was 0.65 (95% CI, 0.45 to 0.95) when compared with CCRT without AC; 0.74 (955 CI, 0.47 to 1.17), both versus radiotherapy alone. [8-10]. Weekly cisplatin in low dose was reported as less toxicity and better outcome [11].

Many trials reported that radiotherapy dose less than 60 Gy was sub-therapeutic, so we are evaluating the use the addition of daily synchronous concomitant boost to increase the total dose to 72 Gy in 6 weeks with concurrent cisplatin to increase radiosensitizing effect, and use of adjuvant chemotherapy aiming for decreasing the distant failure rate that influence the overall survival as the distant metastases was still the most common cause of treatment failure and situation of chemotherapy as an adjuvant was still need further evaluation.

2.Patients and Methods

Eligibility:

Forty- Five patients with stage III-IV NPC according to American Joint Committee on Cancer (AJCC) staging system [12], who met the following eligible criteria were enrolled into the study: informed consent, histopathologically and immunohistochemically (positive cytokeratin) proven squamous cell carcinoma. Eastern Cooperative Oncology Group (ECOG) performance score of 0-2. No previous chemotherapy or radiotherapy. No cranial nerves affection or distant metastases. Adequate bone marrow function (absolute neutrophil count 1,500/μL, platelets 100,000/μL, and hemoglobin 10 g/dL at least), renal function (serum creatinine ≤ 2 mg/dL), and hepatic function (bilirubin less than 1.5 mg/dL and AST/ALT less than twice the upper limit of normal value).

Patient assessment:

All patients had pretreatment evaluation, including complete medical history and detailed clinical and cranial nerves examination; full ENT examination including direct and indirect endoscopy and biopsy, assessment of performance status using ECOG performance score, complete blood count (CBC), liver functions test (LFT) and kidney function test (KFT). Radiological studies were routinely done including chest roentgenography, head and neck CT or MRI, pelvi-abdominal ultrasonography, isotopic bone scan when indicated.

Treatment Schedule:

Radiotherapy:

All patients were allocated into two groups; the concomitant boost arm (Group A): Included 23 patients who have received a dose of 1.8 Gy to the PTV with concomitant boost of 0.6 Gy to the GTV, with a total dose of 72 Gy to the GTV and 54 Gy to PTV in 30 fractions during 6 weeks by using 3-D conformal radiotherapy, the conventional arm (group B): included 22 patients, who have received a dose of 1.8 Gy in 25 fractions to PTV then another 10 Fractions to GTV with a total dose of 63 Gy to the GTV during 7 weeks.

Chemotherapy:

Both arms received concurrent chemotherapy consisted of weekly cisplatin in dose of 35 mg/ m^2 given during irradiation followed by two cycles of cisplatin 80 mg/ m^2 plus docetaxel 75 mg/ m^2 on day one every three weeks, in the presence of adequate hydration and anti-emetic drugs.

Radiotherapy plan:

Patient was simulated, lying supine; fixation was done using a thermoplastic mask. CT based planning was performed and the patient was CT scanned at 3 mm sections in the treatment position, the GTV encompassed the primary tumor bed and neck lymph nodes, the clinical target volume (CTV) included GTV plus 5-10 mm to cover the subclinical regions at risk including the posterior part of nasal cavity, maxillary sinus, pterygopalatine fossa, posterior ethmoidal sinus, parapharyngeal space, skull base, anterior third of clivus, inferior sphenoidal sinus, cavernous sinus and neck nodes from level II to level V, the PTV was created with an additional 3-mm allowing for setup variability. Critical normal structures including the brain stem, spinal cord, parotid gland, optic nerve, chiasm, larynx, tempromandibular joints and cochlea were contoured and set as organs at risk.

The 3D conformal radiotherapy was used for all patients; treatments were delivered by using linear accelerators with a 6MeV.

Dose modification for chemotherapy:

Chemotherapy was withheld if the absolute neutrophil count was<2500 cells/μL, the platelet count was <100,000 cells/μL, Hgb was less than 9 g/dl or the serum creatinine was >2 mg/dL, but if neutrophil count was 2500-3000 cells/μL, the platelet count was 75000-100,000 cells/μL Hgb was 9-9.5 g/dl or the creatinine level was 1.5-2 mg/dL, chemotherapy was given at 70% of the initial dose. Radiotherapy was withheld only if neutrophil count was<2000 cells/μL, Hgb was less than 8.5 g/dl or if the platelet count was <75,000 cells/μ.

Response and toxicity criteria:

Patients were evaluated weekly during treatment for toxicities and one month after treatment for tumor response, and treatment toxicities. All patients underwent full clinical assessment, ENT examination including endoscopy and biopsy, all laboratory studies, CT or MRI nasopharynx, chest X-ray, pelvi-abdomen ultrasound and bone scan when indicated

every 3 months and evaluated for response, toxicities and survival.

Response criteria as defined by *WHO 1979* [13] were used; complete response (CR) was defined as the disappearance of all known disease as determined by two observations not less than 4 weeks apart, partial response (PR) was defined as more than 50% decrease in total tumor size of the lesions that have been measured, stable disease (SD) was defined as 50% decrease in total tumor size cannot be established, progressive disease (PD) was defined as at least 25% increase in the size of measurable lesions or the appearance of new lesions. Treatment toxicities were evaluated using the common toxicity criteria of the national Cancer Institute [14], mucositis, weight loss and hematological toxicities were evaluated weekly during treatment and monthly thereafter.

Statistical methods:

Data were collected and analyzed using SPSS (Statistical Package for the Social Sciences) version 19. Data were presented as mean ± standard deviation (SD), median, range for quantitative variables & number and percentage for qualitative variables. Comparison of variables between the two groups was performed by the Chi-square test, Fisher exact test and student's t test. [15]. The Kaplan-Meier method was used for survival analysis and the log rank test was used to compare between survival curves [16]. Survival times were calculated from the date of registration to the date of death and patients last known to be alive were censored at date of last contact, progression free survival times were calculated from the date of registration to date of first documentation of progression. Statistical significance was accepted as a *p*- value of less than 0.05.

3. Results

Patient characteristics:

This study included 45 patients with LA-NPC stage III&IV presented to clinical oncology department, Zagazig University Hospitals, during period from January 2010 to December 2012. About 74% of all patients were in the 4th and 5th decades of life with range (24-61 years), 31 patients were males representing 69% of all patients, with male to female ratio of 2.3:1, 74% of all patients had ECOG performance score of 0-1, 78% of all patients presented with stage III , where T3 was staged in 61% & 55% and N2 in 52% & 55% of patients in group A & B respectively, also, T3N1/ T3N2 were representing 60% of all patients with stage III. 74% of patients in group A and 68% in group B diagnosed with WHO type one. The most common presenting symptoms and signs were neck mass in about 83% in all patients, aural fullness in about 65% and nasal obstruction in about 44% in both groups .Table (1).

Treatment response:

As regard overall response; 91% of patients in group A and 77% of patients in group B achieved OR as seven patients had CR (33%) versus five (22%) in groups A& B respectively, only one patient in group A had stable disease versus three patients in group B, progressive disease was seen in one patient in group A and another two in group B. The difference between both groups was statistically insignificant (P > 0.05%). Table (2), Fig. (1).

Treatment related toxicity:

Mucositis, vomiting and weight loss were the common treatment related toxicity, but all were tolerated and accepted; Ten patients in group A and seven in group B needed more than one injection of antiemetic medication like ondansetron (8mg) to control severe vomiting, five patients in group A and other four in group B needed more than two GM-CSF injection to control severe neutropenia, three patients needed whole blood transfusion in both groups. Iron preparation was needed in most of patients to guard against anemia; use of antifungal oral preparation was mostly used. Grade 3-4 mucositis was experienced in 15 patients (64%) in group A versus 12 (55%) in group B, vomiting and weight loss was recorded in 12 patients (48%) in group A versus 9 (41%) in group B, with statistically insignificant difference (P > 0.05). Myelosuppression occurred subsequently, including leucopenia in 35% vs. 32%, anemia 34% vs. 32%, neutropenia 21% vs. 18%, and thrombocytopenia 13% vs. 9% in groups A&B respectively, without significant difference. The renal impairment was recorded in only one patient (4%) in each group. Table (3).

Survival:

The median follow up time was 26.4 months with range (7-31months). The 2-year overall survival rate (OSR) was 74% (17/23) for patients in group A and 64% (14/22) in group B, and the 2- year progression free survival rate (PFSR) was 61% (14/23) vs. 54% (12/22) in groups A & B respectively. The 2-year distant metastases free survival rate (DMFSR) was 57% (13/23) vs. 50% (11/22) in groups A&B respectively. But without statistically significant difference (P > 0.05). Table (4), Fig. (2).

Table (1): Patient characteristics

Characteristics	Group A cCRT (23 patients) with concomitant boost NO. (%)	Group B cCRT (22 patients) without concomitant boost NO. (%)	*P*- value
Age in years Mean±SD Median Range	 45.3±9.1 42 26 -60	 45.7±9.5 44 24-61	0.892
Sex Male Female	 16 (70%) 7 (30%)	 15 (68%) 7 (32%)	0.92
Stage III IV	 18 (78%) 5 (22%)	 17 (78%) 5 (22%)	0.936
PS 0-1 2	 17 (74%) 6 (26%)	 16 (73%) 6 (27%)	0.928
Histopathology WHO type I WHO type II WHO type III	 17 (74%) 3 (13%) 3 (13%)	 15 (68%) 4 (18%) 3 (14%)	0.884
Symptoms Neck mass Aural fullness Nasal obstruction Epistaxis	 19 (83%) 15 (65%) 10 (43%) 4 (17%)	 18 (82%) 14 (64%) 10 (45%) 5 (23%)	0.983
Tumor stage T1 T2 T3	 3 (13%) 6 (26%) 14 (61%)	 3 (14%) 7 (31%) 12 (55%)	0.901
Nodal stage N1 N2 N3	 6 (26%) 12 (52%) 5 (22%)	 5 (23%) 12 (55%) 5 (23%)	0.966
Abbreviation: cCRT; concurrent conformal chemoradiotherapy, PS; performance score, WHO; World Health Organization			

Table (2): Response Rate

	Group A with concomitant boost		**Group B Without concomitant boost**		***P*-value**
	No	**%**	**No**	**%**	
OR	**21**	**91**	**17**	**77**	**0.332**
CR	**7**	**33**	**5**	**22**	**0.436**
PR	**14**	**58**	**12**	**55**	**0.803**
SD	**1**	**4**	**3**	**14**	**0.414**
PD	**1**	**4**	**2**	**9**	**0.607**

Abbreviation: OR; overall response**, CR;** complete response**, PR;** partial response**, SD;** stable disease**, PD;** progressive disease

Table (3): Treatment toxicity

	Group A with concomitant boost				**Group B without concomitant boost**				
Toxicity	**G3**		**G4**		**G3**		**G4**		***P*-value**
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	
Mucositis	**9**	**39**	**6**	**25**	**7**	**32**	**5**	**23**	**0.523**
Vomiting	**8**	**35**	**4**	**13**	**6**	**27**	**3**	**14**	**0.323**
Leucopenia	**8**	**35**	**0**	**0**	**7**	**32**	**0**	**0**	**0.438**
Anemia	**7**	**30**	**1**	**4**	**5**	**23**	**2**	**9**	**0.467**
Neutropenia	**4**	**17**	**1**	**4**	**2**	**9**	**2**	**9**	**0.522**
Thrombocytopenia	**3**	**13**	**0**	**0**	**2**	**9**	**0**	**0**	**0.131**
Weight loss	**8**	**35**	**4**	**13**	**6**	**27**	**3**	**4**	**0.323**
Renal impairment	**1**	**4**	**0**	**0**	**1**	**4**	**0**	**0**	**0.241**

Table (4): Survival Rate

	Group A with concomitant boost		Group B Without concomitant boost		*P*-value
	No	%	No	%	
2-year OSR	**17/23**	**74**	**14/22**	**64**	**0.457**
2-year PFSR	**14/23**	**61**	**12/22**	**54**	**0.534**
2-year DMFSR	**13/23**	**57**	**11/22**	**50**	**0.558**

Abbreviation: OSR; overall survival rate**, PFSR;** progression free survival rate**, DMFSR;** distant metastases free survival rate

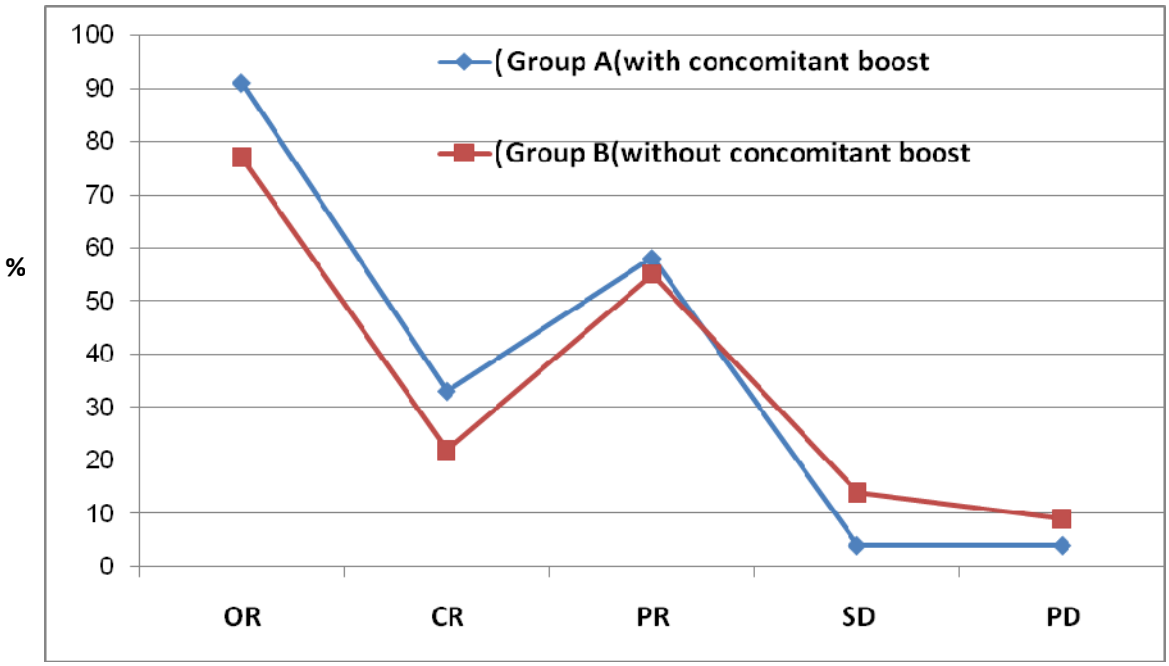

Figure (1): Response rate of group A with concomitant boost versus group B without concomitant boost

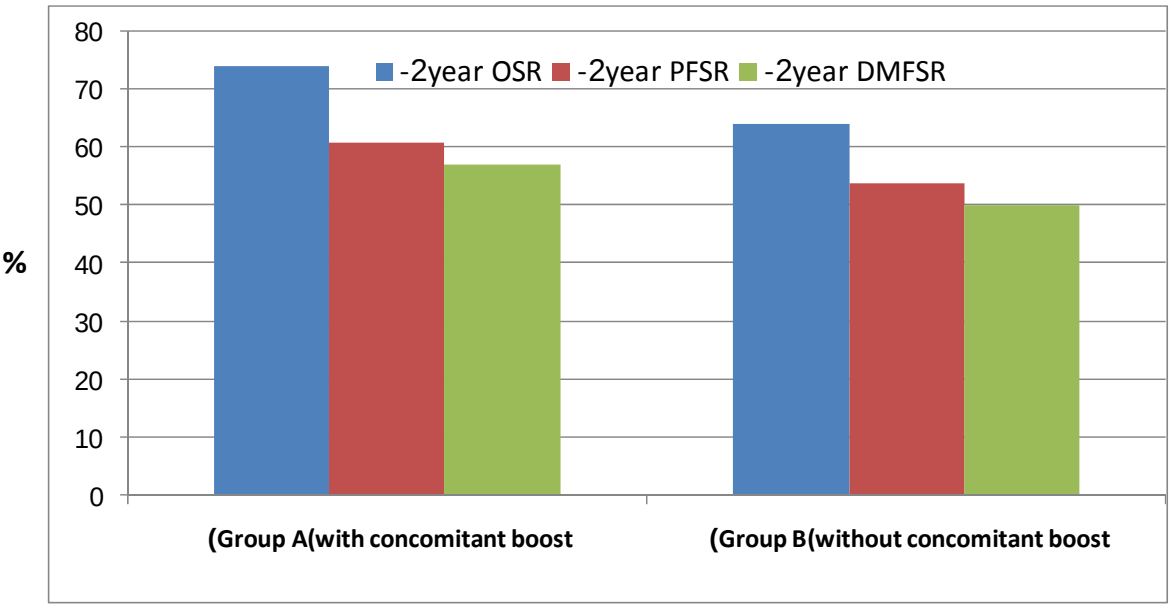

Figure 2:- Survival Rate of group A with concomitant boost versus group B without concomitant boost

4.Discussion

Nasopharyngeal carcinoma is a common head and neck cancer, more than 70% of patients presented with locally advanced stage, The incidence is high in the third to fifth decade of life with a male predominance; concurrent chemoradiation considered now the standard line of treatment, when we use concomitant boost that considered form of altered fractionation that increase the dose of radiation to GTV aiming to improve local control. Meanwhile the distant metastases is still the main cause of treatment failure, so addition of 2 cycles of adjuvant chemotherapy could improve the overall treatment success by lowering the incidence of distant failure that influence positively on survival. We carried out this study which included 45 patients with LANPC presented to clinical oncology department between January 2010 to December 2012.

In our study, all patients had median age of 43 years with age range of 24-61 years which was similar to that reported in the study by Tanadetch *et al.* [4], and very close to that reported by Fareed *et al.* [17]; (46 years) with age range of 15-78 years, and Wee *et al.* [9]; (47 years) with age range of 14-76 years. Also, about 74% of all our patients in the 4th and 5th decades of life with male predominance accounting for 69% with male to female ratio of 2.3:1, which was close to that stated by Fareed *et al.* [17]; (66%), and Chan *et al.* [2], but Perri *et al.* [18] , reported that males were representing 82.5% in his study.

According to ECOG performance status, 74% of all patients had P.S of 0-1 that was comparable with that reported by Tanadetch *et al.* [4]

As regard histopathology; 71% of all cases had WHO type I and this type is more radio-resistant and benefit more from concurrent chemoradiotherapy [19] , and this was higher than reported by Tanadetch *et al.* as in his study WHO type I represented 52%.[4]

According to AJCC; 78% of all patients had been staged as stage III, and majority of them was T3N1/ T3N2; (21/35) and this was comparable with the study of Mackie *et al.* [20]

As regard clinical presentation, 83% of all our patients presented with neck mass, aural fullness 65%, nasal obstruction 44%, and epistaxis in 20%, these data were quietly similar to that reported by Tanadetch *et al.* [4]; 82%, 62%, 42% and 16% respectively.

As regard the efficacy of treatment; The overall response (OR) was 91% in group A versus 77% in group B, meanwhile the complete response was recorded in 7 patients (33%) in group A who received concomitant boost versus 5 (22%) in the other arm, stable disease was observed in 1 case (4%) versus 3 (14%), and progression of the disease was occurred in one patient (4%) versus two (9%) in groups A&B respectively. These differences were statistically insignificant, and were similar to that reported by Wee *et al.* [9]; (91%), and that recorded by Tatsuya *et al.* [21]**;** (89%) as OR was recorded in 91% for N2 patients and 86% for N3 patients when he used CRT with weekly cisplatin followed by adjuvant chemotherapy. Also, Fu *et al.*[6]; reported that use of accelerated fractionation with concomitant boost had significantly better local control (P=0.05) and there was a trend toward improved PFSR (P=0.054).

The toxicities related to our treatment was tolerable and controlled even in patients who received concomitant boost and all patients were completed the whole course of treatment, stage 3-4 toxicities needed some medical interference like; ondansetron (8mg) to control severe vomiting, GM-CSF injection once or twice in severe neutropenia, iron preparation for anemia and lastly use of oral gel preparation for mucositis, which considered the most common acute toxicity that observed in 64% in group A versus 55% in group B, that was very close to that mentioned by Lee *et al.* [1]; (61%)**,** but higher than results of tanadetch et al [4]; (42%), and Chua et al [21]; (37%) when he used concurrent chemoradiation in form of cisplatin 100 mg/m^2 on days 1, 22, and 43 followed by adjuvant chemotherapy with ifosfamid 1.4 g/m^2, fluorouracil 450 mg/m^2 , leucovorin 20 mg/m^2 daily for 5 days every 3 weeks for three cycles. The second common acute toxicities were vomiting and weight loss was 48% and 41% in all cases experienced grade 3-4 that was close to results of Tanadetch *et al.* [4]; 42% for weight loss, but incidence of vomiting recorded in his study was only 8% and this difference was attributed to his use of carboplatin instead of cisplatin that was used in our study. Myelosuppression was occurred subsequently including; leucopenia (35%), anemia (34%), neutropenia (21%) and thrombocytopenia (13%) in group A, while these incidences were as follow for group B; 32%, 32%, 18% and 9%. All the incidence of hematological toxicity was comparable with that recorded by Tanadetch *et al.* [4] , except for anemia (12%) and this may be due to use of docetaxel in our study instead of fluorouracil used in his trial, but the incidence of neutropenia in our study was much lower than that recorded by Chua *et al.*; (48%)[22]. Renal impairment was recorded in only one patient in each group (4%) that was comparable with that reported by Lee and his coworkers in their study that used cisplatin in concurrent and adjuvant setting [23], but slightly differs than reported by Tanadech *et al.* as his study recorded no renal impairment that was attributed to his use of carboplatin instead of cisplatin. [4]

As regard overall survival, the median follow up time was 26.4 months with range (7-31 months). The 2-year overall survival rate (OSR) was 74% (17/23) for patients in group A and 64% (14/22) in group B,

and the 2- year progression free survival rate (PFSR) was 61% (14/23) vs. 54% (12/22) in groups A & B respectively. Our results were also comparable to the results of Ang *et al.* as the 2-year OSR in his study was 71.6%, but our (PFSR) was slightly higher than his result;(53.5%), when he used concomitant boost radiation plus concurrent cisplatin.[24] The progression free survival rate of our study was higher due to that Ang *et al.* did not use adjuvant chemotherapy which had modest effect on locoregional failure rate and also distant failure rate. But our (OSR) and (PFSR) were slightly lower than those reported by Wee *et al.* [9]; (85%),and (75%) respectively when he and his coworkers used concurrent chemoradiotherapy as 70 Gy in 7 weeks with concurrent cisplatin (25mg/m^2 on days 1 to 4) every 3 weeks during radiotherapy course and adjuvant cisplatin plus fluorouracil for 3 cycles, and the distant metastasis rate was 16%, while, our 2-year distant metastases free survival rate (DMFSR) was 57% (13/23) vs. 50% (11/22) in groups A & B respectively. The difference between results reported by Wee *et al.* [9], and our results was attributed to that 90% of patients in his work was WHO type III that was more responsive to chemoradiation than the type I which constitute 71% of patients in our study. Finally our result was comparable with that reported by Tasuya and his colleagues [21] as the 3-year OSR was 66%.

Ng WT *et al.* [25] Reported 2-year progression free survival, distant metastasis free survival and overall survival rates as 95%, 90%, and 92% respectively when use intensity modulated radiotherapy (IMRT) instead of 3-D conformal RT, thus confirming what reported by Fareed *et al.* [17] , when also used IMRT with simultaneous modulated accelerated boost concurrently with weekly cisplatin plus 2-3 cycles of neoadjuvant chemotherapy achieving 3- year DFS 60%, these previous results were confirming that use of IMRT provides more local control as it can deliver multiple small radiation beams of varying intensities to radiate a tumor in a precise way more accurately than 3-D conformal RT, which had positive effect on survival.

Conclusion

In conclusion, our study showed that the addition of concomitant boost in form of synchronous three dimensional conformal radiotherapy aiming to increase the total dose of radiation to 72 Gy concurrent with chemotherapy; weekly cisplatin plus adjuvant chemotherapy; two cycles of docetaxel and cisplatin showed modest improvement of overall survival, progression free survival, and distant metastases free survival, with accepted and tolerable toxicity in locally advanced nasopharyngeal carcinoma, and this benefit may be of greater value in high risk patients and in endemic area whereas type II and III were more common than type I that considered more resistant to radiotherapy and chemotherapy.

Finally, the new advanced type of radiation therapy technique; IMRT when used in the setting of concurrent chemoradiation in management of LANPC was achieving more local control than 3-D conformal RT and better protection to organs at risk that yielded better overall and progression free survival rates.

Conflict of interest (none)

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