

Radiotherapy alone versus concomitant chemoradiation in Early Stage Nasopharyngeal Carcinoma

Ahmad Z. Alattar¹, Abdel Raouf saied² Khaled M. El-Gerby³

¹ Clinical Oncology & Nuclear Medicine, ² ENT, and, ³ Radiology departments¹. Faculty of Medicine, Zagazig University, Egypt.

ahmedenbedo@hotmail.com

Abstract: Purpose: Early stage nasopharyngeal carcinoma (NPC) is usually treated with radiotherapy (RT) alone and carries a treatment failure rate of 15% to 30%. The benefit of concurrent chemoradiotherapy (CCRT) in early stage NPC is a new challenge. The purpose of this work is to evaluate the outcome in early stage NPC after CCRT. This randomized trial compared CCRT versus radiotherapy alone in patients with early stage NPC. **Patients and methods:** Forty four patients presented with stage I-II NPC disease according to the American Joint Committee on Cancer staging system. Patients were treated between 2008 and 2012. Twenty-two of these patients were treated with radiotherapy alone and 22 with CCRT. Radiotherapy was administered at 1.8 Gy per fraction per day for 5 days per week for a total dose of 70.2 Gy. Chemotherapy consisting of: cisplatin weekly with radiotherapy. **Results:** forty four patients were registered and eligible for primary analysis for locoregional control, toxicities and survival after radiotherapy alone or CCRT. The 3 year locoregional control rate in the radiotherapy group was 90.9 % (median follow-up period 32 months) and was 100 % in the CCRT group (median follow-up period 28 months) ($P > 0.05$) The disease free survival rate (DFS) at 3 years for the radiotherapy group was 90.9 % and 95.5 % for the CCRT group ($P > 0.05$). **Conclusion:** In the present study, it was concluded that chemoradiotherapy was superior to radiotherapy alone for patients with stage II NPC with respect to locoregional control and survival.

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Key words: Nasopharyngeal carcinoma, radiotherapy, chmoradiation

1. Introduction

Nasopharyngeal carcinoma is a common neoplasm among northern African populations¹. Early stages NPC usually is treated traditionally by radiotherapy as it is a radiosensitive tumor², It has been thought that RT alone is sufficient treatment for stage I to II NPC³. Radiotherapy alone is Comparable With Neoadjuvant Chemotherapy Followed by Radiotherapy in Early- Stage Nasopharyngeal Carcinoma⁴ and radiotherapy (RT) remains the cornerstone of treatment for all stages of non metastatic diseases. RT alone for earlystage disease results in good results. Patients with stages I and II disease have overall survival (OS) rates of 84% - 90%⁵. Stage IIB NPC is defined as T1T2a N1 M0 or T2b N0 N1M0. T2b and N1 are two key factors of stage IIB NPC. Survival analysis has indicated that categories T2 and N1 are highrisk factors of distant metastasis in patients with earlystage NPC, especially stage IIB NPC⁶.

Leung et al. , reviewed the results of treatment of 1070 NPC patients treated by using RT, distant failure occurred in 5.7% and 14.9% in stage IIA and stage IIB disease respectively⁷.

The 5 year survival rate of patients with parapharyngeal extension was 12.6% lower than that of patients without parapharyngeal extension (73.6% vs. 86.2%)⁸. NPC is chemo responsive to^{9, 10, 11}. Many previous randomized trials for NPC have used

different staging systems including the 1992 American Joint Committee on Cancer (AJCC) system and Ho's stage, a standard treatment for 1997 AJCC stage II is not well defined¹². patients with Early stage I-II NPC have a favorable prognosis, although excluded from the majority clinical trials of the chemoradiation. The National Comprehensive Cancer Network has recommended CCRT for stage II NPC, however with weak evidence for its value¹³. studies on concurrent chemoradiotherapy (CRT) in NPC for the optimal schedule in combining both modalities for this disease are limited¹⁴.

2. Patients and Methods

Forty-four patients with biopsy proven NPC and without evidence of systemic metastasis (M0) were eligible for this trial with no prior history of radiotherapy or chemotherapy. Patients were randomized into two groups (A and B). Twenty-two of these patients were a control group (group A) and treated with radiotherapy alone and twenty two patients (group B) were treated with CCRT during the period between 2008 and 2012 in clinical oncology department Faculty of medicine Zagazig university. Pretreatment evaluation included a complete history, physical examination with assessment of patient's performance status, fiberoptic endoscopic examination of the nasopharynx,

oropharynx and larynx, magnetic resonance imaging (MRI) of the nasopharynx and computed tomography (C. T.) of the neck, chest x-ray, radionuclide bone scan, abdominal ultrasonography, CBC, serum chemistry measurements. All patients examined by Multislice computed tomography to acquire a rapid, high spatial resolution volume and data. It provides particular benefits in the early stage, minimizing artifact due to swallowing and movement. MDCT slice thickness is scanner-dependent; however, 1-1.5 mm collimation is generally used with images reformatted at a 2-3 mm thickness. The volume is acquired to cover the superior extent of the primary tumor to the thoracic inlet and the neck should be imaged with arms by the side. The patient should be instructed not to swallow and to breathe gently. Intravenous contrast medium should be always administered (unless allergy or renal function prohibit this) A 4-6 hours fasting before examination .One technique is to use a long bolus (for example ,100 ml at 1 ml/s with imaging commenced at 90-100 sec).

Patients who were eligible for CCRT had to have the following laboratory values: WBCs ≥ 4000 / μ l, platelet count ≥ 100000 / μ l, creatinine concentration ≤ 1.4 mg/dl and /or creatinine clearance ≥ 60 ml/min .All patients were required to have a dental examination and appropriate care . All patients treated with CCRT were required to provide written informed consent before registration. Patients were also required to have Eastern Cooperative Oncology Group performance score ²²of 0 to 2. All patients were identified as having stage I and II NPC.

Radiotherapy

All patients were treated with 3D radiotherapy using cobalt 60 machine. For tumor localization all patients were simulated and the simulator films were submitted for rapid review. C.T. scans for the head and neck region were used to assess the extent of the primary tumor as well as the neck nodes. All isodose plans were submitted for review. Port films taken in the treatment machine were submitted for rapid review. Variations within the target volume was not exceed $\pm 10\%$ of the target dose ICRU 50/62. The dose to the nasopharynx was specified. The dose to the neck nodes was separately specified and the dose prescribed to at least 3cm below the skin surface at the appropriate level of anatomic spread. The spinal cord dose was not to exceed 45Gy at the midline. The dose to the supraclavicular nodes was calculated to 3cm depth. Fractionation was 180 cGy per fraction per day for 5 days per week for a total dose 7020 cGy to the lry tumor. The minimum total dose to the neck nodes was 5040 cGy for N0 disease, 6660 cGy for nodes ≤ 2 cm and 70 Gy for nodes > 2 cm in size.

Chemotherapy

Patients on the investigational arm were scheduled to receive 40 mg/m² cisplatin in 2 L of normal saline over 2 hours on a weekly basis during external beam RT, starting on the first day of RT and day 1 weekly during radiotherapy. All patients received an antiemetic prophylaxis consisting of 5-hydroxytryptamine-3 receptor antagonist plus 8 mg of dexamethasone, zantac. Complete blood counts and blood chemistry were checked before each chemotherapy cycle. Dose modification for cisplatin during CCRT was not allowed, and cisplatin was delayed until the absolute neutrophil count was at least 1500/ μ L and the platelet count was at least 100000 / μ L. Cisplatin was stopped if creatinine clearance fell to less than 50 mL/min.

An antiemetic such as ondansetron 4 mg i.v. was given 30 minutes before cisplatin then every 8 hours as needed. Six courses of chemotherapy were simultaneously with radiotherapy on weekly basis Serum creatinine was measured two days before each course cisplatin administration and as needed. CBC was obtained weekly, before each course of chemotherapy and as needed. Performance status, weight, symptoms and tumor measurements were recorded.

Statistical consideration

The locoregional control, disease free survival and overall survival rates were calculated from date of start of treatment until the day that tumor recurrence or patient death was observed. Survival and recurrence estimates were calculated according to the methods of Kaplan and Meier ⁴³. Response to treatment evaluation done during or after treatment was reviewed and documented as per WHO criteria; (CR), (PR), (NR) or (SD). Progressive disease (PD) Recurrence/ relapse were defined as reappearance of disease after achieving CR or PR at the end of planned therapy.

3. Results

Forty four patients were registered into the study and considered for 3 years local control, complications and survival analysis. There was good balance in the prognostic factors including performance status, tumor stage, histology, male to female ratio and age distribution between the two groups (Table 1). By the end of December 2012 with a minimum follow-up period of 24 months and a median follow-up interval of 36 months (radiotherapy group median 27 months, range 13 to 40 months), (CCRT group median 35 months, range 12 to 38 months), two of the 22 patients in the radiotherapy group who had T1N0 disease and no patients in the CCRT group experienced local recurrence. In the CCRT group two of the 22 patients developed distant

metastases, these patients were classified as having T2bN1M0 disease. There were no distant metastases in the radiotherapy group. The two patients who developed local recurrence in the radiotherapy group underwent salvage surgery and remained disease free for 24 months after surgery. Six patients had persistent disease after receiving 70 Gy of radiation; four in the radiotherapy group and two in the CCRT group. The 3-year disease free survival rate was 90.9 % in the radiotherapy group and 95.5 % in the CCRT group (fig 1). The locoregional control rate calculated by Log-rank test was better in the CCRT group than in the radiotherapy group although there is no statistically significant difference (100% versus 90.9% respectively, $P > 0.5$). The overall survival rates at 3 years in both groups were 100 %. Patients' compliance in the CCRT group was excellent. The overall treatment time ranged from 49 to 63 days. Sixteen (72.7 %) patients in group (A) completed radiotherapy within 7 weeks, while in group (B) 20 (91%) patients completed radiotherapy within 7 weeks.

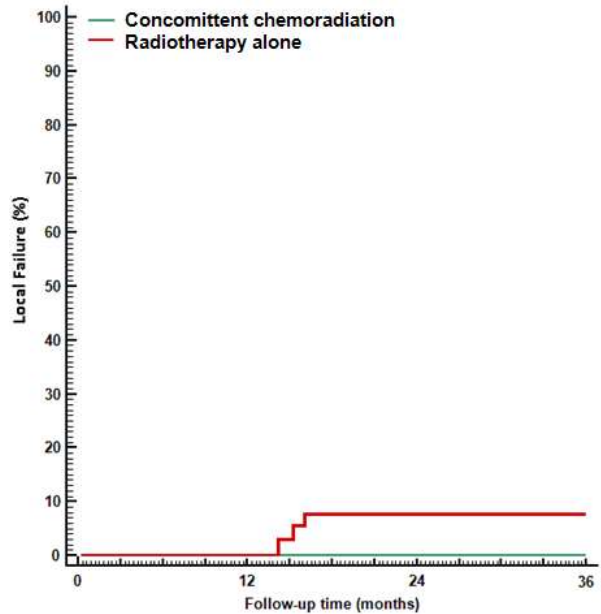
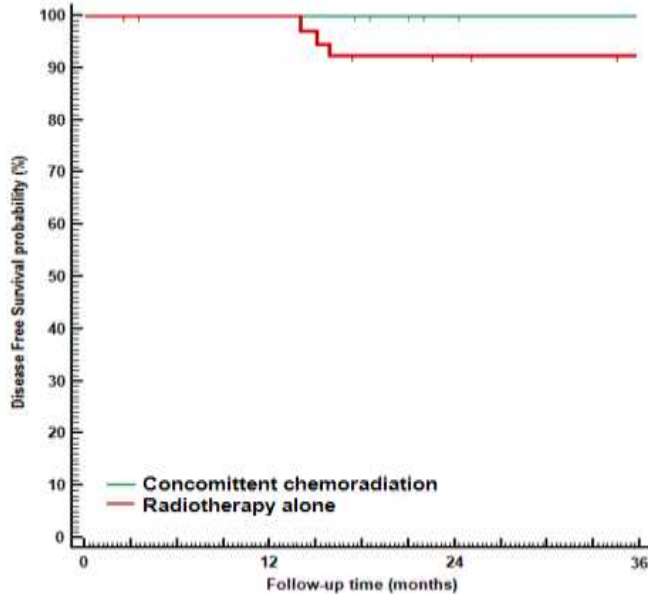
Toxicities

All patients were evaluated for acute toxicities according to WHO toxicity criteria¹⁵. The incidence of

grade 1 or 2 leukopenia, nausea and vomiting for patients in group B (CCRT) was higher than that for patients in group A (RT) ($P > 0.5$). A higher incidence of grades 2 and 3 stomatitis was observed in group (B) than that in group (A) but not reach statistically significant difference. The incidence of grade 3 weight loss was higher in group B than in group A (54.5% Vs 45.5% respectively). There were no treatment-related deaths in both groups.

Table 1: patients' characteristics

Characteristic	Group A		Group B	
	No.	%	No.	%
Age in years				
Median	52		50	
Range	14-81		16-79	
Sex				
Male	17	77.3	16	72.7
Female	5	22.7	6	27.3
Performance status				
0-1	20	90.9	20	90.9
2	2	9.1	2	9.1
Stage				
I	20	100	0	0
II A (T2aN0)	0	0	4	18.2
II B	0	0	18	81.8
Histology				
KSCC	6	27.2	5	22.6
NKSCC	7	31.8	8	36.4
UDC	9	41	9	41



Disease – free survival rates in early stage NPC treated with (RT) alone or (CCRT). The 3-year DFS rate for the RT group is 90.9 % and 95.5 % for the CCRT group ($P > 0.5$).

The 3-year locoregional control rate for the RT group is 90.9 % and 100 % for the CCRT group ($P = > 0.5$)

Fig.1: DFS , locoregional control rate for the two groups ($P = > 0.5$).

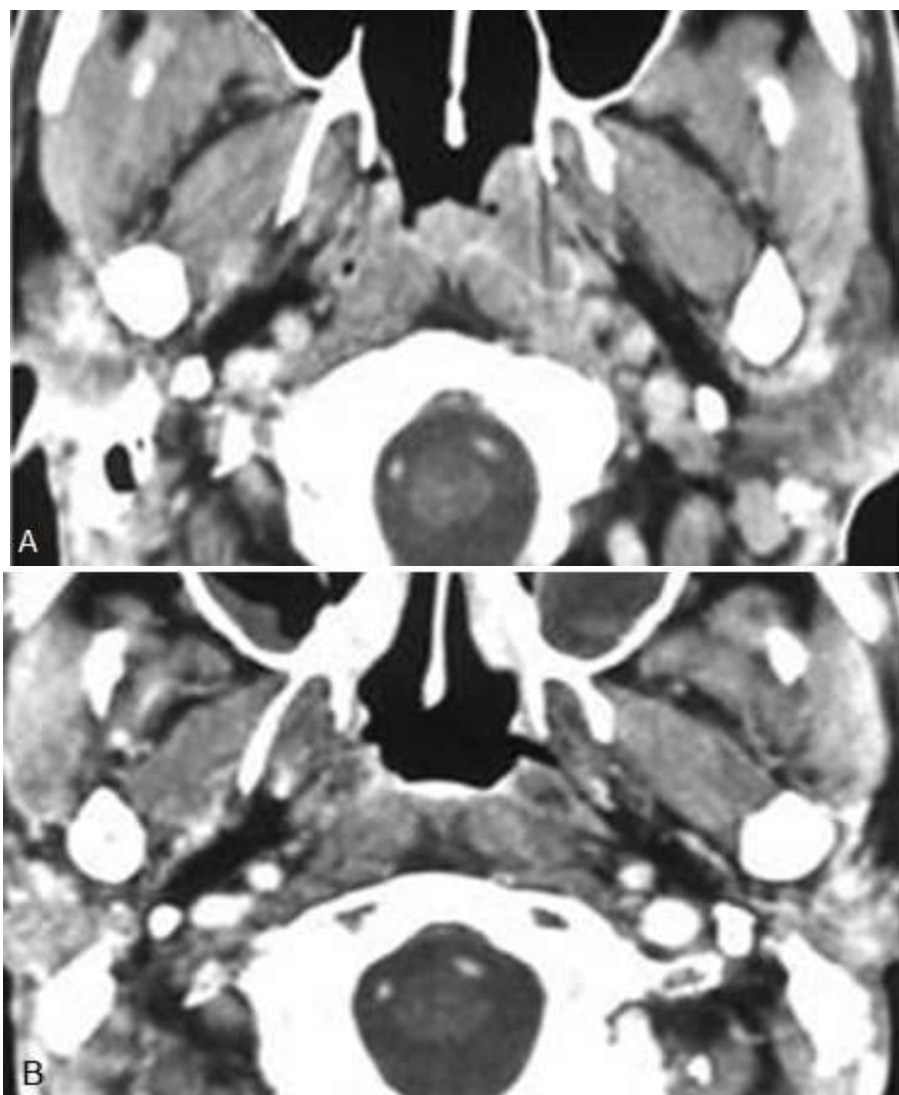


Fig. 2: Axial postcontrast CT scan obtained through the nasopharynx. (A) CT scan before radiation shows asymmetry of the fossa of Rosenmüller with nasopharyngeal mass obliterates the left lateral wall with irregular margins. (B) CT scan performed 20 months after radiation, shows the mass markedly decreased in size.

Table 2: Acute toxicities.

Toxicity		G 0		G 1		G 2		G 3		G 4	
		No.	%	No.	%	No.	%	No.	%	No.	%
Hematological											
Leukopenia	Group A	20	90.9	2	9.1	-	-	-	-	-	-
	Group B	14	63.5	6	27.3	2	9.1	-	-	-	-
Anemia	Group A	21	95.5	1	4.5	-	-	-	-	-	-
	Group B	22	100	-	-	-	-	-	-	-	-
Thrombocytopenia	Group A	19	86.4	2	9.1	1	4.5	-	-	-	-
	Group B	21	95.5	1	4.5	-	-	-	-	-	-
Gastrointestinal											
Nausea/ Vomiting	Group A	19	86.4	2	9.1	1	4.5	-	-	-	-
	Group B	4	18.2	10	45.5	8	36.4	-	-	-	-
Stomatitis	Group A	-	-	4	18.2	17	77.3	1	4.5	-	-
	Group B	-	-	2	9.1	8	37	2	9.1	-	-
Weight loss	Group A	8	36.4	2	9.1	1	4.5	10	45.5	1	4.5
	Group B	6	27.3	1	4.5	1	4.5	12	54.5	2	9.1

4. Discussion

weekly chemotherapy may have more therapeutic gains than conventional every 3 week chemotherapy may have, though this hypothesis requires more testing¹⁶. concomitant chemoradiotherapy has two major advantages: First, chemotherapy and radiotherapy exert a synergistic effect. Chemotherapeutic agents directly kill cancer cells, or cause G2/M arrest in cancer cell cycle to enhance tumor cell sensitivity to radiotherapy, or inhibit the repair of sublethal injuries in cancer cells to enhance the effect of radiotherapy on tumors. Second, chemotherapy could eliminate potential subclinical metastatic lesions and circulating metastatic cells. Thus, in theory, concurrent chemotherapy could not only increase the local control rate but also reduce distant metastasis¹⁶. some authors recommended CCRT for stage II patients^{17,18}. Cheng et al. reported that stage II patients treated with concurrent chemo-irradiation have comparable disease-free survival of patients with stage I disease treated with RT alone¹⁷.

Xiao et al, reported that patients with early stage (T2N1) disease (Chinese 1992 staging system) have 5-year OS rate of 73.1%, which with statistically significant difference from those of the other groups of early-stage and the distant metastasis rate was 21.2% for that group, which differed from those of the other groups. They reported that distant metastasis was the main cause of treatment failure in the early stage (T2N1) group after curative RT¹⁹.

Stage II NPC had a small distant tumor burden, and chemotherapy was more effective in eliminating distant metastases. There were the 5 year DFS improvement by 10.9% addition of cisplatin-based chemotherapy to, suggesting that concurrent cisplatin chemotherapy is not only radiosensitizer but also has systemic cytotoxic effect. Cisplatin based chemotherapy has been shown to improve response rates in chemo-naïve, recurrent, or metastatic NPC versus non-cisplatin regimens^{20,21}.

A randomized trial conducted by Chen²² found that the 5 years OS rate (94.5% vs. 85.8%, $p = 0.007$), PFS rate (87.9% vs. 77.8%, $p = 0.017$), and DMFS rate (94.8% vs. 83.9%, $p = 0.007$) in the concurrent chemoradiotherapy group ($n = 116$) were significantly higher than those in the radiotherapy alone group ($n = 114$), respectively. However, the concurrent chemoradiotherapy group had a significantly higher incidence of acute toxic reactions, than did the radiotherapy alone group. Although acute toxic reactions may decrease compliance, the patients presented with good tolerance and successfully completed the whole treatment.

There are many schedules for combination of cisplatin and RT; daily low dose, weekly intermediate-dose, and 3 week high dose regimens have been used. High toxicity is considerable with the regimen of cisplatin at 100 mg/m² every 3 weeks during RT. In the intergroup study by Al-Sarraf et al.²³ only 63% of patients completed 3 courses of concurrent 100 mg/m² cisplatin. Chan et al.²⁴ reported that CCRT using a weekly intermediate dose of cisplatin (40 mg/m²) improved the survival rate vs. RT alone in locoregionally advanced NPC; although only 44% of patients actually completed 6 weekly cycles of chemotherapy during RT. Weekly cisplatin at a dose of 30 mg/m² has less toxic effects without decrease in tumor control rates in patients who receive CCRT for locally advanced squamous cell carcinoma of the head and neck²⁵. weekly cisplatin 40 mg/m² for up to 8 weeks concurrently with RT was used NPC²⁶⁻²⁹. Chen et al¹³ reported that the proper distant control in his trials is related to the better compliance with the CCRT. Good compliance with CCRT in his trials as they use intravenous nutrition when the patients had weight loss by 5%. CCRT regimen was tolerated by most patients although they suffered from more severe acute toxicity.

Nasopharyngeal carcinoma is highly responsive to radiotherapy²² and chemotherapy³⁰⁻³³. Chemotherapy has been given concurrently with radiotherapy. There appeared to be improved local control and survival rates for chemotherapy and radiotherapy when compared to radiotherapy alone especially as compared with the use of concurrent chemoradiotherapy.³⁴⁻³⁷ The 44 stage I and II patients in this trial had good locoregional control, disease free survival, and overall survival rates after CCRT or radiotherapy alone. For stage II patients the 3-year locoregional control rate was 100% while the disease free survival rate was 95.5% after CCRT and adjuvant chemotherapy (fig 1). The 5-year survival rates for stage I patients who are usually treated with radiotherapy alone are 85% to 100%^{34,38}. Patients with stage II disease who are treated with radiotherapy alone have 5-year survival rates of about 55% to 65%.^{35,38} Similar survival results were observed on the basis of Ho's classification. Sham and Choy reported that the 5-year survival rates for patients with stage I and II disease (similar to AJCC 1997 stage I and II disease) were 80.8% and 71.5% respectively³⁷. In the present study it was observed that stage II patients who were treated with CCRT had an equal or better survival when compared with the results of stage I patients who were treated with radiotherapy alone as reported in the literature. The

treatment result was much better than that for stage II patients who were treated with radiotherapy alone as previously mentioned.³⁸⁻⁴⁰ The better survival rate of the CCRT group in our series is attributed to the high locoregional control rate and the lower incidence of distant metastases. The study presented here demonstrated that the locoregional control rate for stage II patients who were treated with CCRT is equal or better than those who were treated with radiotherapy alone. The excellent locoregional control in our series is attributed to a more precise delineation of the tumor volume⁴¹⁻⁴³. There was previously reported an excellent 3-year primary tumor control rate of 92 % for AJCC T4 patients⁴⁴. More favorable histology types such as non-keratinizing carcinoma and poorly differentiated carcinoma are probably another reason for the improvement of locoregional control. These histologic types are known to have greater radio-sensitivity and hence better local control when compared with well-differentiated squamous histology⁴⁵. The main differences between our study and the other series cited previously are that the radiological evaluation before treatment (C.T, versus MRI) and the treatment modality (radiotherapy alone versus CCRT) are different. The radiological evaluation by MRI before treatment may shift the patients from an early stage disease to a more advanced stage.

Distant metastases in early stage NPC are not common. Geara et al⁴⁴ reported that the risk of distant metastases for patients with N0-N1 or N2 (similar as AJCC 1997 N1) classification was 11 % - 13 % and 37 % respectively in a long term follow-up. With T1-T2 and N0 patients the risk of distant metastases will probably less than 10 %. Therefore post-radiation adjuvant chemotherapy in this subset of patients may not be necessary. However for patients with AJCC 1997 T1-T2 and N1 disease, whether adjuvant chemotherapy after radiotherapy is beneficial warrants further evaluation. The study of CCRT group presented here primary included T2N1 patients and included more patients with WHO type III histologies, the distant metastases rate at 3-years was only 3.2 %. In a different series, by Teo et al⁴⁵ in which patients were evaluated by C.T. and treated with radiotherapy alone, the 3-year distant metastases rate in T2aN0 patients was 4 %, was 22 % in T2bN0 patients. This series involved cases with more advanced disease (more than T2aN1 and T2bN1 patients.) but a far lower incidence of distant metastases. The primary differences between the Teo et. al study and our study are that we used MRI evaluations before treatment and a combination of radiotherapy and concomitant chemotherapy³⁹. The patients in this study had a good compliance to

CCRT. This good compliance to CCRT was attributed to the immediate intervention of nasogastric tube feeding when patients developed 5 % weight loss or grade III mucositis. The intergroup study by AL-Sarraf et al²³ revealed that only 55 % of patients completed the combined modality treatment as planned. Our concomitant treatment is better tolerated by patients because we administered two cycles of chemotherapy with cisplatin and 5-fluorouracil at a 60 % dose reduction during radiotherapy and another two cycles of the same regimen in full doses after the end of radiotherapy. Moreover, we allowed patients to have 1-week break during radiotherapy treatment. Patients in CCRT group have more severe mucositis and vomiting than patients who were treated by radiotherapy alone. The intergroup study concluded that CCRT is superior to radiotherapy alone in patients with AJCC 1992 stage III and IV disease. However the present series supported this conclusion that patients with stage II (similar as AJCC 1992 stage III) can achieve a more favorable outcome with CCRT.

5. Conclusions:

For patients with early disease (stage I), RT alone rather than a combined modality approach is recommended (Grade 1B). For patients with intermediate (stage II) disease, concurrent chemoradiation rather than RT alone is suggested (Grade 2B).

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