

A Comparative Study of Radiotherapy Alone and Concurrent Chemoradiation using Cisplatin as Radiosensitizer in Stage 3 and Stage 4 Nasopharyngeal Carcinoma in an Institute

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Abstract: Introduction: Nasopharyngeal carcinoma is the most common nasopharyngeal malignancy. It is more common in males with the age-standardised male-female ratio between 2-3: 1. Radiotherapy (RT) has been the mainstay of treatment for NPC and leads to high 5 year overall and disease-free survival rates in early-stage disease. However, there are significant rates of local failure and distant metastasis subsequent to radiotherapy in the advanced stage of disease at which most NPC patient presents. Chemotherapy can achieve long-term survival rates of up to 15% to 20%, even in patients with recurrent or metastatic disease. Combining chemotherapy with radiotherapy improve local control, disease free and overall survival and decreases systemic metastasis in locally advanced stage III and IV nasopharyngeal carcinoma. Methods and material: A total of 68 patients diagnosed as stage III and IV nasopharyngeal carcinoma were studied. They were grouped into two arms – Arm A and Arm B. Arm A constituted 32 patients who were treated with radiation alone. And Arm B constituted 36 patients and they were treated with concurrent chemoradiation using Cisplatin as radiosensitizer. The treatment responses and the weekly assessment of toxicities were compared between the two arms. Results: Among the total of 68 cases, male : female ratio was 1.7 : 1, and the age range was 26-78 years with the mean age of 48.38±11.87 years. The toxicities of treatment i.e. mucositis, skin reactions, anaemia and nausea/vomiting developed earlier in Arm B compared to Arm A. The severity in terms of grade of toxicities was also more in Arm B. Arm B showed better overall treatment response. There was no case of progressive disease in any of the Arms. After 1 month follow-up, around 50% of those patients persisting with these symptoms at the end of treatment were recovered. Conclusion: Concurrent chemoradiation is opted a better treatment for stage III and IV nasopharyngeal carcinoma, as overall treatment response is better compared to radiation alone. Even though treatment-related toxicities are seen higher in concurrent chemoradiation, it is well tolerated and acceptable, and is never life-threatening.

Keywords: Nasopharyngeal carcinoma, radiosensitizer, concurrent chemoradiation, Cisplatin

1. Introduction

Neoplasms of the nasopharynx encompass all malignant tumours arising from the epithelial lining, lymphoid tissue and connective tissue, such as lymphomas and sarcomas. However, the most frequently encountered malignancies are those that arise from the epithelial lining and these are referred to as Nasopharyngeal Carcinoma (NPC). Though a rare cancer throughout the world but a leading form of cancer in Southeast Asia including the Southern China and Hong Kong, the Arctic, North Africa and the Middle East[1].

NPC is more common in males with the age-standardised male-female ratio between 2-3 : 1. The etiology of NPC is very likely multifactorial : genetic, environmental and viral. There are at least three major risk factors: (a) a genetically determined predisposition allowing an Epstein Barr Virus (EBV) infection of the type that permits (b) integration of the genome of the virus into the chromosomes of some nasopharyngeal epithelial cells, thereby priming them for (c) neoplastic transformation by some environmental cofactor. Alternatively, the environmental agents may trigger the viral genome in the cells to oncogenic activity[2].

Surgery plays a minor role in the treatment of NPC. Surgical access providing safe control of vessels and adequate exposure of the nasopharynx remains a challenge. Its anatomical position encased in the middle of the skull base flanked by vital structures superiorly and laterally restricts access. Dissection is very much intracavitary surgery and tumour margins are often difficult to define and excise to achieve complete removal. Surgery is limited to radical neck dissection in controlling radioresistant nodes and post-radiation cervical metastasis and in selected patients, salvage surgery for recurrence in the nasopharynx.

Radiotherapy (RT) has been the mainstay of treatment for NPC and leads to high 5 year overall and disease-free survival rates in early-stage disease. However, there are significant rates of local failure and distant metastasis subsequent to radiotherapy in the advanced stage of disease at which most NPC patient presents.

Chemotherapy (CT) is an integral part of treatment for patients with nasopharyngeal carcinoma. Chemotherapy can achieve long-term survival rates of up to 15% to 20%, even in patients with recurrent or metastatic disease. In the majority of studies reported, patients with previously untreated locally advanced stage III and IV nasopharyngeal carcinoma showed improved local control, decreased

systemic metastasis, and improved disease-free and overall survival when treated with Cisplatin (Platinol) – based combination chemotherapy in conjunction with radiotherapy.

2. Aims and Objects

The study is undertaken to compare two modalities of treatment i.e. Radiotherapy alone and concurrent chemoradiation using Cisplatin as radiosensitizer in stage 3 and 4 NPC with regards to their outcomes and complications.

3. Materials and Methods

The study was carried out in the Department of Otorhinolaryngology in collaboration with the Department of Radiotherapy in an institute during the period of September 2005 to August 2007. Both male and female patients of stage III and IV nasopharyngeal carcinoma irrespective of age, sex and socio economic status were studied.

Patients excluded from the study were as follows :-

- (1) Lost to follow-up.
- (2) Incomplete treatment due to financial problem or due to other associated illness.
- (3) <60% Karnofsky Performance status.
- (4) Expired due to other causes.

Total accrued patients were 68. The patients were then grouped into two Arms – Arm A and Arm B. 32 patients who received radiotherapy alone were in Arm A, and 36 patients receiving concurrent chemoradiation were in Arm B.

All the patients in Arm A were treated by radiation alone. Radiation was given by Telecobalt 60 upto a tumour dose of 7000 centigray(cGy)/35 exposures, 200 cGy/exposure for 5 days a week to face and neck by two/three radiation portals by shrinking field technique.

In Arm B, concurrent chemoradiation was given using Cisplatin as radiosensitizer. Radiation was given in the same manner as given to patients in Arm A. Chemotherapy was given weekly during the course of radiation before the exposures. Cisplatin 30 mg/m² along with premedication and adequate hydration were given. Complete hemogram and KFT were performed every week, a day before chemotherapy was given. Chemotherapy was given so long as the blood counts and KFT met the required parameters (i.e. Hb > 10 gm%, TLC > 4000 cells/mm³, Platelet count > 1 lac/mm³, Urea < 40 mg%, Creatinine < 1 mg%), otherwise it was deferred till the value became normal.

In patients of all the arms, the baseline Hb% level was assessed before treatment, and weekly during treatment. If patients were found anaemic, they were transfused with compatible blood to bring the level to normal before initiating or continuing the treatment.

Patients in all the arms were assessed every week during the course of treatment and 1 month after completion of treatment to note the response of treatment and to record any adverse or untoward side effects, noting down - oral mucositis, skin reactions, anaemia, gastro-intestinal irritation - nausea/vomiting, and diarrhoea, leucopenia and impaired creatinine level. These radiation reactions were graded as per ECOG criteria.

Response, along with radiation toxicities were measured just after completion of treatment and 1 month after completion of treatment. Response was graded as per Miller's WHO criteria as Complete Response (CR), Partial response (PR), No response (NR) and Progressive disease (PD).

4. Results and Observations

The study sample consisted of higher number of males (63.2%) than females (36.8%) in the ratio of 1.7 : 1 (p value – 0.044). Most common age range fell in 31 – 40 years and 51 – 60 years (27.9% each). The youngest in the series was 26 years, and the oldest 75 years. And the mean age was 48.38 ± 11.87 years.

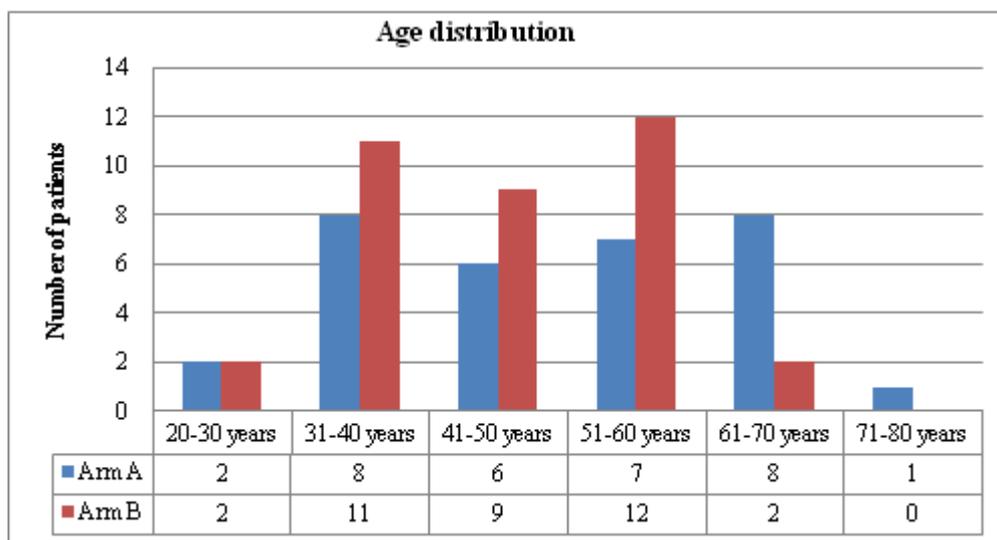


Figure 1: Age Distribution among The Study Samples

The onset of mucositis was seen in 2nd week (2000 cGy) for Arm A, but in Arm B, it was seen from 1st week itself (1000 cGy). During treatment, the grade of mucositis increased as the treatment progressed, and maximum grade was seen during 4th week i.e. at radiation dose of 4000 cGy, and slowly declined towards the end. At 4th week, 62.5% were affected in Arm A, and 83.3% were affected in Arm B (p value – 0.154). The severity too was seen more in Arm B, with few patients reaching grade 3 (5.6%), as depicted in Table 1.

Table 1: Weekly Assessment – Mucositis

Weeks	Arms	Grade 0	Grade 1	Grade 2	Grade 3	Total
1	A	32 (100.0)	-	-	-	0 (0.0)
	B	32 (88.9)	4 (11.1)	-	-	4 (11.1)
2	A	26 (81.3)	6 (18.8)	-	-	6 (18.8)
	B	17 (47.2)	14 (38.9)	5 (13.9)	-	19 (52.8)
3	A	13 (40.6)	15 (46.9)	4 (12.5)	-	19 (59.4)
	B	9 (25.0)	14 (38.9)	12 (33.3)	1 (2.8)	27 (75.0)
4	A	12 (37.5)	13 (40.6)	7 (21.9)	-	20 (62.5)
	B	6 (16.7)	17 (47.2)	11 (30.6)	2 (5.6)	30 (83.3)
5	A	18 (56.3)	12 (37.5)	2 (6.3)	-	14 (43.8)
	B	10 (27.8)	15 (41.7)	10 (27.8)	1 (2.8)	26 (72.2)
6	A	22 (68.8)	10 (31.3)	-	-	10 (31.3)
	B	12 (33.3)	15 (41.7)	9 (25.0)	-	24 (66.7)
7	A	17 (53.1)	15 (46.9)	-	-	15 (46.9)
	B	12 (33.3)	18 (50.0)	6 (16.7)	-	24 (66.7)

A (N=32), B (N=36)

Total = Total patients affected (i.e. Grade 1 + Grade 2 + Grade 3)

Table 2: Weekly Assessment – Skin Reactions

Weeks	Arms	Grade 0	Grade 1	Grade 2	Grade 3	Total
1	A	31 (96.9)	1 (3.1)	-	-	1 (3.1)
	B	32 (88.9)	4 (11.1)	-	-	4 (11.1)
2	A	23 (71.9)	9 (28.1)	-	-	9 (28.1)
	B	17 (47.2)	13 (36.1)	6 (16.7)	-	19 (52.8)
3	A	14 (43.8)	14 (43.8)	4 (12.5)	-	18 (56.3)
	B	10 (27.8)	12 (33.3)	12 (33.3)	2 (5.6)	26 (72.2)
4	A	12 (37.5)	14 (43.8)	4 (12.5)	2 (6.3)	20 (62.5)
	B	6 (16.7)	12 (33.3)	14 (38.9)	4 (11.1)	30 (83.3)
5	A	12 (37.5)	14 (43.8)	5 (15.6)	1 (3.1)	20 (62.5)
	B	9 (25.0)	15 (41.7)	10 (27.8)	2 (5.6)	27 (75.0)
6	A	14 (43.8)	14 (43.8)	4 (12.5)	-	18 (56.3)
	B	9 (25.0)	17 (47.2)	9 (25.0)	1 (2.8)	27 (75.0)
7	A	8 (25.0)	18 (56.3)	6 (18.8)	-	24 (75.0)
	B	9 (25.0)	20 (55.6)	7 (19.4)	-	27 (75.0)

The onset of skin reactions was seen during 1st week of treatment in few patients in both the Arms i.e. radiation dose of 1000 cGy. The severity increased again as the treatment progressed. In this case too, patients in Arm B were affected more, with 11.1% having grade 3 reactions in the 4th week (4000 cGy). Here again, as shown in Table 2, maximum cases of skin reactions were seen in 4th week, 62.5% in Arm A and 83.3% in Arm B (p value – 0.154). The severe grade (grade 3) seen in few patients in Arm A was due to use of Orfit Head and Neck Mould (thermoplastic material) for immobilisation of patient during radiation.

Table 3: Weekly Assessment – Anaemia

Weeks	Arms	Grade 0	Grade 1	Grade 2	Total
1	A	31 (96.9)	1 (3.1)	-	1 (3.1)
	B	33 (91.7)	3 (8.3)	-	3 (8.3)
2	A	26 (81.3)	5 (15.6)	1 (3.1)	6 (18.8)
	B	16 (44.4)	18 (50.0)	2 (5.6)	20 (55.6)
3	A	20 (62.5)	10 (31.3)	2 (6.3)	12 (37.5)
	B	15 (41.7)	17 (47.2)	4 (11.1)	21 (58.3)
4	A	21 (65.6)	8 (25.0)	3 (9.4)	11 (34.4)
	B	16 (44.4)	14 (38.9)	6 (16.7)	20 (55.6)
5	A	26 (81.3)	5 (15.6)	1 (3.1)	6 (18.8)
	B	25 (69.4)	10 (27.8)	1 (2.8)	11 (30.6)
6	A	28 (87.5)	4 (12.5)	-	4 (12.5)
	B	30 (83.3)	6 (16.7)	-	6 (16.7)
7	A	30 (93.8)	2 (6.3)	-	2 (6.3)
	B	32 (88.9)	4 (11.1)	-	4 (11.1)

Anaemia was seen more in Arm B. Patients in both the Arms were affected most during 3rd week, 37.5% in Arm A and 58.3% in Arm B (p value – 0.128). Grade 1 and grade 2 cases were observed in both Arms, but frequency was more in Arm B.

Gastro-intestinal toxicities, nausea and vomiting were seen more again in Arm B patients. The severity reached as much as grade 3 in few patients in Arm B in the middle of treatment (2.8% in 3rd week and 5.6% in 4th week) as seen in Table 4. Maximum case was seen during 4th week in both Arm A and Arm B, 40.6% and 61.1% respectively (p value – 0.232).

Mild grade i.e. grade 1 diarrhoea was seen in 3 cases (8.3%) of Arm B, 2 cases (5.6%) in 3rd week and 1 case (2.8%) in 4th week. It was not seen in any case of Arm A (not shown in table).

Table 4: Weekly Assessment – Nausea / Vomiting

Weeks	Arms	Grade 0	Grade 1	Grade 2	Grade 3	Total
1	A	32 (100.0)	-	-	-	0 (0.0)
	B	32 (88.9)	4 (11.1)	-	-	4 (11.1)
2	A	30 (93.8)	2 (6.3)	-	-	2 (6.3)
	B	28 (77.8)	6 (16.7)	2 (5.6)	-	8 (22.2)
3	A	24 (75.0)	6 (18.8)	2 (6.3)	-	8 (25.0)
	B	17 (47.2)	12 (33.3)	6 (16.7)	1 (2.8)	19 (52.8)
4	A	19 (59.4)	7 (21.9)	6 (18.8)	-	13 (40.6)
	B	14 (38.9)	8 (22.2)	12 (33.3)	2 (5.6)	22 (61.1)
5	A	20 (62.5)	6 (18.8)	6 (18.8)	-	12 (37.5)
	B	16 (44.4)	12 (33.3)	8 (22.2)	-	20 (55.6)
6	A	22 (68.8)	6 (18.8)	4 (12.5)	-	10 (31.3)
	B	20 (55.6)	12 (33.3)	4 (11.1)	-	16 (44.4)
7	A	28 (87.5)	4 (12.5)	-	-	4 (12.5)
	B	26 (72.2)	10 (27.8)	-	-	10 (27.8)

Other rare toxicities seen in very few patients of the study sample during treatment were leucopenia and impaired creatinine level (not shown in table). Leucopenia was observed in 4 patients (11.1%) in Arm B, 2 patients each (5.6%) in 2nd and 3rd week, and they all fell in grade 1. In Arm A too, 3 patients (9.4%) had grade 1 leucopenia during 3rd week. Grade 1 impaired creatinine level was seen in 6 patients (16.7%) of Arm B, 4 cases (11.1%) in 3rd week and 1 case (2.8%) each in 2nd and 4th week, while no patient had such problem in Arm A. None of the patients developed thrombocytopenia during treatment in either Arm A or Arm B.

Table 5: Early Treatment Response – At Completion of Treatment

Response	Arm A [N=32]	Arm B [N=36]	Total [N=68]	p-value
CR	11 (34.4)	19 (52.8)	30 (44.1)	0.147
PR	16 (50.0)	15 (41.7)	31 (45.6)	0.393
NR	5 (15.6)	2 (5.6)	7 (10.3)	0.232
CR + PR	27 (84.4)	34 (94.4)	61 (89.7)	0.268

34.4% of patients had Complete Response (CR) in Arm A, followed by 50.0% Partial Response (PR) and 15.6% No Response (NR). Whereas in Arm B, 52.8% had CR, 41.7% had PR and 5.6% had NR. There were no cases of Progressive Disease in both the Arms. Thus, the Overall Treatment Response i.e. CR + PR is 84.4% in Arm A, and 94.4% in Arm B (p value – 0.268) as shown in Table 5.

Table 6: Toxicities – 1 Month After Completion of Treatment

Toxicities	Arms	Grade 0	Grade 1	Grade 2	Total
Mucositis	A	24 (75.0)	8 (25.0)	-	8 (25.0)
	B	26 (72.2)	9 (19.4)	3 (8.3)	12 (33.3)
Skin Reactions	A	12 (37.5)	17 (53.1)	3 (9.4)	20 (62.5)
	B	14 (38.9)	17 (47.2)	5 (13.9)	22 (61.1)
Anaemia	A	32 (100.0)	-	-	0
	B	35 (97.2)	1 (2.8)	-	1 (2.8)
Nausea/ Vomiting	A	32 (100.0)	-	-	0
	B	36 (100.0)	-	-	0

46.9% of patients in Arm A had grade 1 mucositis at completion of treatment i.e. at 7th week, which was reduced to 25% after 1 month follow-up. Whereas in Arm B, 50% had grade 1 and 16.7% had grade 2 mucositis at completion of treatment, which was reduced to 19.4% and 8.3% respectively after 1 month of follow-up. Thus, in Arm B, 66.7% of total affected cases at completion of treatment were reduced to 33.3% after 1 month follow-up. Therefore, almost 50% of symptoms was recovered at follow-up.

75% of patients, affected with skin reactions in Arm A at completion of treatment were reduced to 62.5% after 1 month follow-up. While in Arm B, 75% at treatment completion was reduced to 61.1% after 1 month. 56.3% and 18.8% had grade 1 and grade 2 skin reactions respectively in Arm A, which was reduced to 53.1% and 9.4% respectively after 1 month. In Arm B, 55.6% grade 1 and 19.4% grade 2 were seen at completion of treatment, which was reduced to 47.2% and 13.9% respectively after 1 month.

2 patients (6.3%) of grade 1 anaemia were seen in Arm A at discharge, but after 1 month, no anaemic patients were seen. But in Arm B, 11.1% grade 1 anaemia was seen at completion of treatment, which was reduced to 2.8% after 1 month.

12.5% of Arm A and 27.8% of Arm B patients had nausea and vomiting at time of completion of treatment, but none was seen after 1 month of follow-up.

5. Discussion

Treatment outcome for RT alone for patients with American Joint Committee on cancer (AJCC) 1997 stage I-II NPC was

studied in 141 patients in Queen Mary Hospital, Hong Kong with median follow-up of 82 months. It was found that patients with stage I disease had an excellent outcome after they were treated with RT alone. Patients with stage II disease, especially those with T1-T2N1 disease, had a relatively worse outcome, and more aggressive therapy such as combined modality treatment, may be indicated for those patients[3].

As a means of oncological treatment, chemotherapy has a radiosensitising role in reducing the rate of distant metastasis, but it can also be used in the case of recidivism or metastasis, in order to prolong the patients' lifespan and improve the quality of their lives. Irradiation is the basic treatment to be chosen to fight the tumour. The side effects are disagreeable and sometimes almost unbearable [4]. The most effective cytostatic drugs seem to be Adriamycin, Cisplatin and Bleomycin[5].

Lee AW et al in 2006 compared the benefit achieved by concurrent chemoradiotherapy (CRT) and/or accelerated fractionation (AF) vs. radiotherapy (RT) alone with conventional fractionation (CF) for patients with T3-4N0-1M0 nasopharyngeal carcinoma (NPC) and concluded that concurrent chemoradiotherapy with accelerated fractionation could significantly improve tumour control when compared with conventional RT alone[6].

Cisplatin and its analogue Carboplatin have comparable radiosensitising effects. They are preferable to 5-Fluorouracil (5-FU) as radiosensitising agents, as they are more potent. Moreover, with 5-FU, there is added mucosal toxicity from chemotherapy and radiotherapy. 5-FU also has a very short biological half-life and synchrony of this brief timing with radiation effect is critical.

Cisplatin has clear advantages as an agent for concurrent therapy because its toxicities do not overlap with those of radiation. Myelosuppression is uncommon, and therefore optimal doses can be delivered. Because cisplatin is also one of the most active agent against NPC, it is logical to use this agent for concurrent chemoradiation.

Overall, the study sample consisted of 63.2% males and 36.8% females, making a ratio of 1.7:1. Similarly, male : female ratio of 2 : 1 was found in a study conducted by Fatusi O et al (2006) in Nigeria[7].

The most frequent age group presenting with nasopharyngeal carcinoma in the study was found to be 31-40 years and 51-60 years with 27.9% each. The mean age was found to be 48.38 ± 11.87. This almost tallies with views of Chan AT et al (1998), where median age was found to be 40-50 years[8].

Radiation-induced mucositis was seen earlier in patients receiving chemoradiation (1st week) compared to that of patients receiving radiotherapy alone (2nd week). Throughout the week, the patients receiving chemoradiation were affected more in terms of frequency and grade. Maximum patients were affected during 4th week, 62.5% in those receiving radiation alone and 83.3% in those receiving chemoradiation. This was similar with the findings of

Wolden SL et al in 2001, where 84% acute mucositis was seen in chemoradiation patients and 43% was seen in patients with radiation alone[9].

Skin reactions occurred most during 4th and 5th week in patients receiving radiotherapy (RT) alone with 62.5%, while it occurred most in 4th week in patients receiving chemoradiation (CTR) with 83.3%. 6.3% of patients with RT alone had grade 3 reactions during 4th week, while it is 11.1% with CTR. This result is comparable with the findings of Chua DT et al (2004), who studied on concurrent chemoradiation with Cisplatin followed by adjuvant ifosfamide, 5-fluorouracil and leucovorin in NPC patients and found that 11.5% developed grade 3 dermatitis during concurrent chemoradiation [10].

37.5% of patients receiving RT alone developed anaemia during treatment, with 9.4% reaching grade 2. While in patients receiving CTR, 58.3% developed anaemia with 16.7% reaching grade 2.

Nausea and vomiting was seen more in patients receiving CTR. 40.6% were affected in patients receiving RT alone, while 61.1% were affected in patients with chemoradiation. A similar observation was made in a study by Demizu Y et al (2006), where 63% of nausea and vomiting was seen in patients receiving chemoradiation [11].

Grade 1 leucopenia was observed in 11.1% of patients receiving CTR, while 9.4% grade 1 leucopenia was seen in patients receiving RT alone. Similar finding was observed in the study of Chan et al (2002), who found that 13% of patients of NPC receiving concurrent chemoradiation with Cisplatin developed leucopenia [12].

None of the patients developed thrombocytopenia during treatment. Very few cases of thrombocytopenia (2%) were observed in the study by Chan et al (2002) who conducted a similar study [12].

Grade 1 impaired creatinine level was seen in 16.7% of patients receiving CTR, while no patients had such problem in patients receiving RT alone. This finding was similar to that of Demizu Y et al (2006), where 18.8% (3/16) patients receiving cisplatin-based concurrent chemotherapy developed grade 1 impaired creatinine level [11].

All these complications i.e. mucositis, skin reactions, anaemia, nausea and vomiting, leucopenia and impaired creatinine level, may be the effects of cumulative toxicities of cisplatin as Chang JT et al (2004) had pointed out [13].

In the study, 52.8% had Complete Response (CR), 41.7% Partial Response (PR) and 5.6% had No Response (NR) in patients receiving chemoradiation (Arm B), while for Arm A, 34.4%, 50% and 15.6% had CR, PR and NR respectively. Sapna M et al in 2006 observed that patients receiving alternate chemoradiation with Cisplatin had 72% CR and 28% PR, while patients receiving radiation alone had 44% CR, 36% PR and 20% NR [14]. Another study by Chan et al (1998) with cisplatin-based chemotherapy found encouraging response rates of 50-91%. Yet in another study conducted by Al-Kourainy K et al (1998) in Wayne State

University / Harper-Grace Hospital, Detroit, 100% (4/4) CR was achieved in locally advanced nasopharyngeal carcinoma patients receiving concurrent chemoradiation with Cisplatin [15].

Thus, it is observed that, patients receiving concurrent chemoradiation had better overall treatment response i.e. CR+PR (94.4%) compared to that of RT alone (84.4%).

6. Conclusion

The study comprises of 68 patients that were diagnosed as nasopharyngeal carcinoma (NPC). Male : female ratio in the study is 1.7:1, and majority of patients fall in the age group of 31-40 and 51-60 years, with mean age of 48.38 ± 11.87. Overall treatment response (complete response + partial response) was better in patients receiving concurrent chemoradiation compared to patients receiving radiation alone. But the treatment related toxicities were seen in higher percentage in terms of frequency and grade in patients receiving concurrent chemoradiation. But the toxicities were acceptable, and in none of the patients, the toxicities were life-threatening. And also, around 50% of those patients persisting with these symptoms at the end of treatment were recovered 1 month later at follow-up.

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