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Research Article

Prognostic Impact of Neoadjuvant Chemotherapy on Juvenile Nasopharyngeal Carcinoma

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Abstract: **Objective:** To study the efficiency of neoadjuvant chemotherapy (NACT) and the impact of chemotherapy (CT) response on prognosis of juvenile nasopharyngeal carcinoma (NPC). **Methods:** From 1995 to 2005, 108 non-metastatic undifferentiated carcinoma NPC patients younger than 25 years old were treated with NACT at Salah Azaiz Institute and received three cycles of doxorubicin and cisplatin followed by conventional radiation therapy (RT). Tumor response to NACT was assessed on the basis of clinical examination (100%) and CT-scan (66%). Response was evaluated according to WHO criteria. **Results:** The overall CT response rate was 88% at cervical lymph node with while overall response was83% at primary tumor. A no response (NR) or progressive disease (PD) after NACT at both cervical nodes and primary tumor had a statistically significant pejorative impact on disease free survival (DFS) (P<0.001 and P=0.04, respectively) and overall survival (OS) (P <0.001 and P =0.037). Five-year DFS and OS rates in patients reached complete response (CR) after initial CT at cervical nodes was significantly better than the other patients (partial response (PR), NR, or PD) (94% *vs*. 66% and 94% *vs*. 73%, respectively). **Conclusion:** A regimen of induction CT followed by RT is feasible and could provide excellent antitumor effect in juvenile NPC. A CR response to chemotherapy might indicate better survival.

Keywords: NPC; Chemotherapy; Radiation therapy; Response; Survival

Introduction

The incidence of nasopharyngeal carcinoma (NPC) in the pediatric age group varies widely with ethnic and geographical origin. In endemic areas, NPC is rare in children accounting for less than 1% of all childhood malignant diseases; whereas a bimodal age repartition with an early peak at 10 to 20 years of age has been observed in southern Mediterranean region countries[1-4]. In North Africa, NPC comprises 5%–10% of all childhood tumors[5]. The most common histologic type seen in children is undifferentiated carcinoma, which is strongly associated with Epstein-Barr virus infection. In addition

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young patients are more likely to have locoregionally advanced disease at onset, but they generally have a significantly better chance of survival[6–7]. Many previously reported studies on pediatric NPC have documented the benefit of combined radiotherapy (RT) and chemotherapy (CT) compared with RT alone to achieve locoregional control, sterilize micrometastases, and improve survival[8–12]. Optimal treatment modality for pediatric NPC has not yet been established. Concurrent chemo-radiotherapy became the standard of care following guidelines of adults[13–15]. Interestingly several reports seem to support preradiation CT in parallel with other pediatric protocols [16–18]. Therefore, it is important to evaluate the efficiency of neoadjuvant CT (NACT) and the impact of CT response on prognosis of juvenile NPC.

Patients and Methods

Patient Characteristics: One hundred and eight patients who were younger than 25 years old with a histologically confirmed diagnosis of non-metastatic NPC were treated with preradiation CT at Salah Azaiz Institute between March 1995 and December 2005. The patient age at presentation ranged from 9 to 25 years (median, 17). The gender ratio (male/female) was 1.6. Pretreatment evaluation included a clinical history and physical examination, endoscopic examination of the nasopharynx, blood tests with serum titers of EBV infection, CT-scan of the head and neck, X-ray studies of the chest, abdominal ultrasonography, and a bone scintigraphy. Histological diagnosis was made according to the World Health Organization (WHO) classification on biopsies of the primary tumor; all patients had undifferentiated carcinoma (WHO Type III). Patients underwent clinically staging according to the 2002 TNM staging system; T3–T4 locally advanced tumors and N3 nodal status rates were 64% and 52%, respectively. Table 1 lists the features of the patient population.

Table 1. Patient characteristics

Characteristics	No. of patients	Percentage (%)
Age		
Median	17 years	Range (9-25 years)
Gender		
Male	66	61
Female	42	39
Pathology		
WHO type III	108	100
T stage (TNM 2002)		
T0	2	2
T1	2	2
T2	35	32
T3	42	39
T4	27	25
N stage (TNM 2002)		
N0	2	2
N1	15	14
N2	35	32
N3	56	52

Treatment: All patients were treated with three cycles of NACT every 21 days combining doxorubicin (90 mg/m^2, day 1) and cisplatin (100 mg/m^2, day 1), followed by locoregional RT. They received conventional 2D RT with a total dose of 70 Gy to the primary tumor and the cervical areas initially involved. Later 54 Gy was given to the remaining cervical areas bilaterally. A photon beam of cobalt-60 gamma rays was used. RT was delivered using a two-phase technique to the target volumes: 2 bilateral parallel opposing fields to the primary tumor and upper neck, and a single anterior field to the lower neck with a central shield were used up to 42 Gy. After completion of 42 Gy, the primary tumor was boosted using bilaterally opposed reduced portals and the posterior cervical lymphatic chains were treated with appropriate electrons (6–9 MeV).

Response Evaluation and Follow-Up: Tumor response to NACT was assessed after the third cycle on the basis of clinical examination in

100% of cases and CT-scan of the nasopharynx in 66% of cases. A CT scan or MRI of head and neck was performed for all patients at 3 months after treatment completion. Follow-up was every 3 months for the first 2 years, every 6 months the next 2 years, and then yearly. Response was evaluated according to WHO criteria[19]. A Complete response (CR) was defined as the disappearance of all evident disease, a decrease of >50% was defined as a partial response (PR), a decrease of <50% was considered no response (NR)/stable disease (SD), and progressive increase in the size of the tumor or the appearance of new lesions was defined as progressive disease (PD). Acute and late toxicities were evaluated and scored according to the Radiation Therapy Oncology Group guidelines [20].

Statistics: Overall and disease-free survival rates were estimated using Kaplan-Meier analysis, and survival differences for prognostic factors were compared with the log-rank test.

Results

Response to Treatment: All patients completed three cycles of CT and could be evaluated further. After a head-and-neck examination, a CR at cervical nodes was found in 35% of cases, a PR was found in 53% of cases, and a SD was found in 12% of cases. Among the 71 patients (66%) who had a CT-scan after the third cycle, 20% achieved CR at primary site, while achieved 63% PR. Finally, 17% had no response or progressive disease. The overall response rate to NACT was 88% at cervical lymph node and 83% at primary tumor. RT was initiated with a median delay of 48 days after CT completion. Of the 108 patients of our study, 7 (6.5%) stopped the irradiation of their own during the second phase and consulted again after a median delay of 17 months with locoregional progressive disease in which 3 cases presented distant metastasis. At the first evaluation at the end of the treatment program, 98 patients (91%) were in complete remission, and 3 patients (2.7%) had locoregional progressive disease including bone metastasis in 2 cases.

Survival: Patients who stopped RT of their own (6.5%) and those with progressive disease 3 months after termination of treatment protocol (2.7%) died during follow-up. After a median follow-up of 83 months (3–94 months), 16 patients (14.8%) who had achieved tumor remission, developed disease recurrence. Eight patients (7.4%) developed a locoregional relapse after a median time of 44 months (21–89 months) from the end of treatment. Overall, 14 distant metastasis (13%) were registered and 90% of metastases occurred during the first two years. Five-year DFS and OS rates were 75% and 81%, respectively.

Prognostic Factors: Univariate analysis of prognostic factors is shown in Table 2. Statistically significant unfavorable factors were T4 disease for DFS(P=0.005) and OS (P=0.01), N3 disease for DFS (P=0.003) and OS (P=0.004), and no response or progressive disease after initial CT at both cervical nodes and primary tumor for DSF (P<0.001 and P=0.04, respectively) and OS (P<0.001 and P=0.037, respectively) (Fig. 1). On the other hand, patients who achieved CR after NACT at cervical nodes had a significantly better outcome compared with those who did not (PR, SD or PD); five-year DFS and OS rates for these two groups were 94% *vs*. 66% and 94% *vs*. 73%, respectively. Five-year DFS and OS rates of patients in CR after initial CT at primary tumor was better than the other patients (PR, NR, or PD), but this difference was not significant (P=0.11 and P=0.12, respectively) (Fig. 2).

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Table 2. Prognostic factors

Prognostic factors	DFS		OS	
	5-y (%)	*P*	5-y (%)	*P*
Age				
< 16 years	80	0.36	84	0.41
≥ 16 years	73		78	
Gender				
Male	75	0.72	79	0.74
Female	79		84	
T stage				
T0T1T2	89	0.05	89	0.01
T3	79		87	
T4	55		63	
N stage				
N0N1	93	0.003	93	0.004
N2	87		90	
N3	65		72	
Clinical response to NACT at cervical nodes				
CR	94	<0.001	94	<0.001
PR	75		80	
NR-PD	30		46	
Radiological response to NACT at primary tumor				
CR	92	0.04	92	0.037
PR	79		84	
NR-PD	52		71	
Clinical response to NACT at cervical nodes				
CR	94	<0.001	94	<0.001
PR-NR-PD	66		73	
Radiological response to NACT at primary tumor				
CR	92	0.11	92	0.12
PR-NR-PD	75		82	

Treatment Toxicity: No severe acute toxicity was reported. The major toxicities from CT were Grade 1–2 nausea and vomiting (40%), neutropenia (19%), and alopecia (18%). No patient had major infectious complications, although twelve patients (11%) had Grade 3–4 neutropenia. Acute side-effects during RT were tolerated well. They were marked by mucositis (83%), skin reaction (76%), and dysphagia (55%), with Grade 1–2 rates in 86%, 89% and 96%, respectively. The incidence of sequelae was evaluated in surviving patients with a follow-up of at least 6 months after RT completion, 99 patients were evaluated. Late side effect information and grade were not thorough for all the patients reported and should be considered limited for interpretation. They were dominated by xerostomia (94%), neck fibrosis (70%), and trismus (55%). Dental caries, hearing loss and facial bone hypoplasia were reported in 23%, 17% and 5% of cases, respectively. Fourteen patients (14%) developed endocrine abnormalities: hypothyroidism (12%), amenorrhoea (4%) and growth retardation (1%).

Discussion

NPC is a relatively rare childhood malignancy. Although the treatment guidelines for juvenile NPC has generally followed those established for adults, it must be emphasized that is a distinct entity. The close association with undifferentiated histology subtype, which is highly responsive to CT and RT, the high incidence of locoregionally advanced disease, and the important rate of metastatic failure have dictated the need for special considerations in the treatment of these young people [6–8]. Moreover, the risks of long-term treatment-related toxicity may be more severe in younger individuals[2, 21].

Nowadays, concurrent CT during the course of RT is accepted as the standard of care for adults with locally advanced NPC; several retrospective studies have confirmed the efficacy of combined chemoradiotherapy[8,22–24]. The role of NACT still remains controversial [13–15]. However, several reports seem to support initial CT strategy for young patients with 5-year overall survival ranges between 73% and 91%[16–18, 25–27]. In our study we applied RT after three cycles of CT combining doxorubicin and cisplatin. The 5-year OS rate of 81% and DFS of 75% in our group matches well with series in youths, although some of them have prescribed a lower RT doses [16–18, 25–27] (Table 3).

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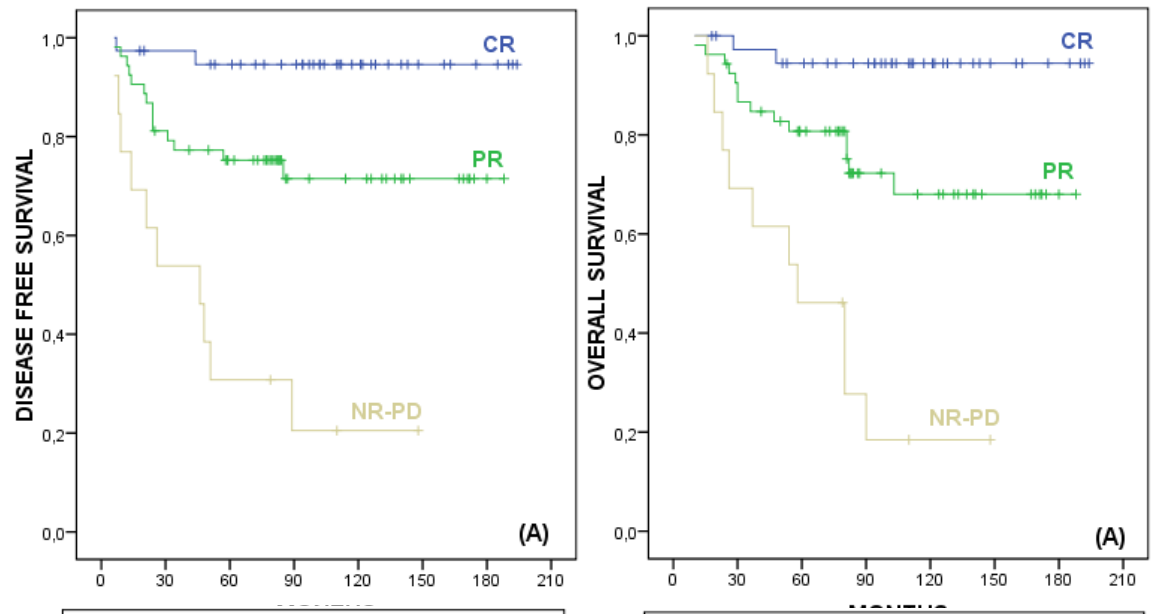

Figure 1. Comparison of DFS and OS in groups achieving CR, PR, or NR-PD after CT at cervical nodes (A) and primary tumor (B).

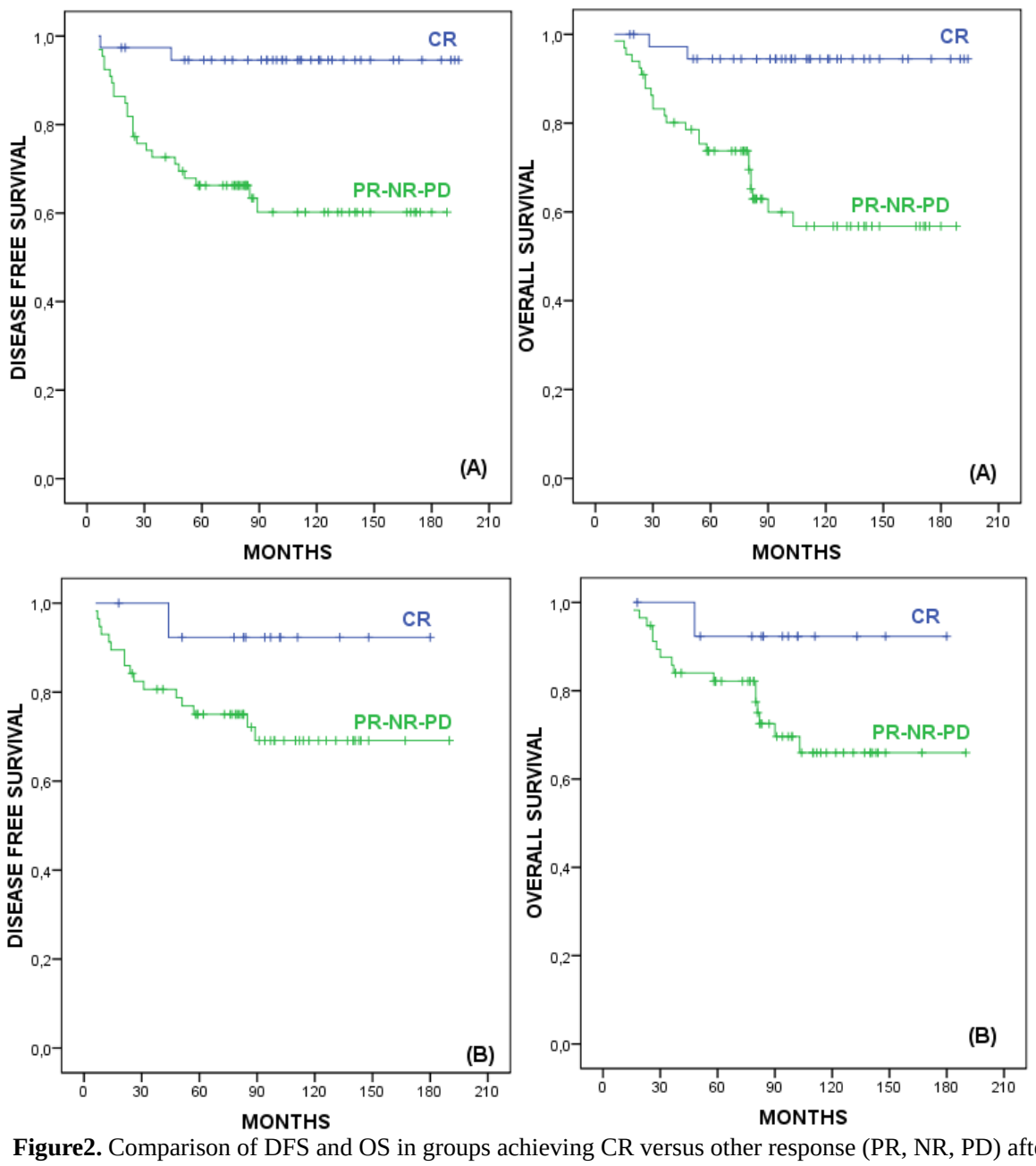

Figure2. Comparison of DFS and OS in groups achieving CR versus other response (PR, NR, PD) after CT at cervical nodes (A) and primary tumor (B).

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Table 3. Comparative results of selected series

Authors	N	Age (median, yrs)	NACT	T-Np/N0 RT dose (median/Gy)	5-year OS (%)	5-year DFS (%)
Casanova *et al*. [16]	46	13	CF	60/45 (stage I-IIA) 65/45 (stage IIB-III-IV) (+ concomitant C)	80.9	79.3
Rodriguez *et al*.[17]	16	13	CFML	61.2/50.4	75 (4-year)	77 (4-year)
Zubizaretta *et al*. [18]	11	12	CFB	55/45	91	61
Varan *et al*. [25]	10	14	CT	59.4/50.4	90 (2-year)	70 (2-year)
Jmal *et al*. [26]	48	13.7	CD	70/54	79.1	68.9
Mertens *et al*. [27]	58	13	CFM	59.4/45 (+ adjuvant IFN-β)	95 (4-year)	91 (4-year)
Present study	108	17	CD	70/54	81	75

C: Cisplatin, F: 5-Fluorouracil, B: Bleomycin, M: Methotrexate, L: Leucovorin, T: Docetaxel, D: Doxorubicin, T-Np: Primary tumor and involved lymph nodes, N0: uninvolved lymph nodes.

As illustrated in this series, NPC is highly chemosensitive with a response rate at cervical lymph node and primary tumor of 88% and 83%, respectively. The CR for NACT on the primary tumor and cervical nodes before receiving the RT were 35% and 20%, respectively. The RT augmented this response, and a complete remission at the end of the treatment program was observed in 91% of cases. Thus RT is still an important part of the treatment. Daoud and his colleagues[5] found a CR of 13.6% at the primary site and 31.8% at the cervical nodes in a series of 22 patients younger than 20 years old treated with three cycles of primary CT comprising epirubicin and cisplatin. Another study [18] described a CR of 45% in a series of 11 evaluable children with stage IV NPC after three cycles of CT combining 5-fluorouracil, bleomycin and cisplatin. A CR of 42% was reported in a study of 57 patients younger than 18 years old treated with two cycles of CT based on cisplatin, bleomycin and methotrexate [9]. The differences in CR among these studies could be due to differences in the treatment regimen and the assessment criteria.

Clinical and radiological response after NACT was the most important prognostic factor studied in our series; a NR or PD after NACT at both cervical nodes and primary tumor had a statistically significant pejorative impact on DFS and OS. Lascar and his colleagues[9] also reported similar results in their reports of 57 patients; NR to initial CT had a significant impact on DFS and OS with 5-year DFS and OS rates of 25% and 16%, respectively. In our series, a CR after NACT at cervical nodes was associated with a significantly better prognostic on DFS and OS. However, a CR after NACT at primary site tended to be a good prognostic factor without significant difference; this could probably be attributed to the lack of radiological evaluation in 37 patients who had not undergone CT-scan for CT response. Orbach and his colleagues [28] also reported that children who achieved a response ≥90% after initial CT had better outcome compared with those who did not; 5-year DFS and OS rates in these two groups were 100% *vs*. 64% (*P*=0.04) and 100% *vs*. 66% (*P*=0.06), respectively.

The optimal RT dose is still controversial, particularly when combined with CT. Several investigators have examined the correlation between radiation dose and treatment outcomes. In fact, a few reports have demonstrated a significant survival advantage for patients receiving doses greater than 60–66 Gy [8, 9, 12]. In a published series [9], 5-year DFS and OS rates of children who had been irradiated with more than 60 Gy was better than those irradiated with lower doses (DFS rate:

68% *vs*. 40%, *P* = 0.020; OS rate: 73% *vs*. 46%, *P* = 0.012).

However, administration of high dose RT in children and adolescents will always be a matter of concern for oncologists. Of particular concern are the long-term effects. The reported toxicities specific to this age group include xerostomia, neck fibrosis, hearing loss, dental problems, stunted growth, endocrine disorders, and secondary cancer [2, 5, 8, 9, 18]. In our series, although all patients developed some degree of xerostomia, neck fibrosis, dental problems, and endocrine disorders, no development of second malignancy was reported. Therefore, every effort should be made to prevent severe late sequelae and maintain good disease control. NACT appears to be beneficial, so lower RT doses may be possible. Three prospective studies showed that dose reduction to 60 Gy to primary sites and 45–50 Gy to the neck was possible in chemoresponsive patients without compromising the outcome [16, 17, 27]. Five-year OS in children receiving reduced cervical radiation dose after a good response to induction CT was 78%, not different from the OS of children treated with more than 50 Gy: 72% (*P*=0.89)[28]. Similary, a retrospective analysis of 74 paediatric patients treated with cisplatin-based CT multiregimens at the Gustave Roussy Institute revealed that low dose RT (50 Gy) to good responders achieved better event-free and overall survival rates compared with the high dose group (65–70 Gy) (*P*=0.003 and *P*=0.02, respectively). Late toxicity was improved in the low dose group as well. The investigators concluded that response adapted dose reduction seemed to be plausible in selected patients[30]. Another alternative to reduce late effects of treatment could be to use new techniques of irradiation, which might preserve good local control while decreasing the unwanted side-effects such as implementation of IMRT[31].

Conclusion

NPC is a very chemosensitive neoplasm and suggest that a regimen of induction CT followed by high-dose RT can provide excellent antitumor effect. Moreover, the prognosis was better in patients with a good response to CT. The impact of this modality on long-term therapeutic results remains to be answered by well-conducted randomized trials.

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