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Research Article

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Nasopharyngeal Carcınoma in Chıldren and Adolescents; Experıence of EGE Unıversıty from Turkey

Nazan Çetingül[1], Akkız Şahin[1], Haldun Öniz[2], Bengü Demirağ[3], Serra Kamer[4], Mehmet Kantar[1], Serap Aksoylar[1], Savaş Kansoy[1], Salih Gözmen[1], Ali Veral[5], Hüdaver Alper[6] and Yavuz Anacak[4]

[1]*Ege University, Faculty of Medicine, Department of Pediatric Oncology*

[2]*İzmir Tepecik Training and Research Hospital, Department of Pediatric Oncology*

[3]*İzmir Dr. Behcet Uz Pediatric Hospital, Department of Pediatric Hematology-Oncology,*

[4]*Ege University, Faculty of Medicine, Department of Radiation Oncology*

[5]*Ege University, Faculty of Medicine, Department of Pathology*

[6]*Ege University, Faculty of Medicine, Department of Radiology*

***Corresponding author**

Akkız Şahin Yaşar, Ege University Faculty of Medicine, Erzene Mahallesi, Gençlik Caddesi Ege Üniversitesi Kampüsü, 35040 Bornova/ İzmir, Turkey, E-mail: akkz_shn83@gmail.com

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Abstract

Nasopharynx cancer is a rare (3%) epithelial cancer which is seen in childhood and adolescence. It accounts for 30-50% of the nasopharynx malignities at this age group. Incidence is high in China, South East Asia and Mediterranean countries. Genetic and geographic components play a major role in this high incidence. In these endemic regions, non-keratinized and undifferentiated carcinoma (type 2 and type 3) are histopathologically frequent and it is found that Ebstein – Barr virus (EBV) genes are related to the tumor. In our country, especially undifferentiated nasopharynx cancer is closely related to EBV infection. In childhood and adolescence, it is seen in localized advanced disease, also systemic disease characteristics are high. In recent years, primarily with cisplatine based chemotherapy protocol and appropriate doses of radiotherapy (RT), survival rates have reached 80-90%.

In this retrospective study, our aim was to evaluate the clinical features, histophathology, treatment results and survival rates along with late toxicities of patients with NPC.

Introduction

Nasopharynx cancer (NPC) is a rare (1- 3%) epithelial cancer which is seen in childhood and adolescence. It accounts for 30-50% of the nasopharingeal malignities at this age group. Incidence is high in China, South East Asia and Mediterranean countries. Genetic and geographic components play a major role in this high incidence [1,2]. In these endemic regions, non-keratinized and undifferentiated carcinoma (type 2 and type 3) are histopathologically frequent and it is found that Ebstein-Barr virus (EBV) genes are related to the tumor [2,3]. In childhood and adolescence, it is seen in locoregional advanced disease and also systemic disease characteristics are high. The optimal treatment modality in children has not been established yet, and the treatment strategy has been adopted from the protocol for adults. For non-metastatic patients with NPC radiotherapy (RT) is the mainstay treatment. As the results for RT alone for locoregional advanced disease are suboptimal, these patients are generally treated with combined chemoradiotherapy (CT-RT). In recent years primarily with cisplatine based neoadjuvant chemotherapy protocol and appropriate doses of radiotherapy (RT), survival rates have reached 80-90% .The overall survival (OS) and relapse-free survival (RFS) rate of patients treated by 2D-RT with or without CT-RT was reported to be 49% to 80% and 47% to 69% respectively; in the locoregional disease RFS rate was estimated to be 80%, with an incidence of late sequelae of 65% to 85% [1-5].

In this retrospective study, our aim was to evaluate the clinical features, histophathology, treatment results and survival rates along with late toxicities of patients with NPC.

Patients and Method

Between January 1988 and July 2014, thirty-one cases were diagnosed with NPC in three different pediatric oncology centers (Ege University Faculty of Medicine, Dept. of Pediatric Oncology; Dr. Behcet Uz State Pediatric Hospital, Dept. of Pediatric Hematology-

Oncology, and Tepecik State Pediatric Hospital, Dept. of Pediatric Oncology), and chemotherapy was applied to the patients in these departments. All patients received radiotherapy in Ege University, Department of radiation oncology after induction chemotherapy.

Chemotherapy

Sixteen patients were given 5 fluoro-urasil , cisplatin, methotrexate (3 cures) and then RT, followed by interferon β for six months, and 15 patients received 5 fluoro-urasil, cisplatin (3 cures) without MTX but with RT and interferon β [5].

Radiotherapy

Radiotherapy was applied following CT to all patients, who also underwent radical IMRT with simultaneous integrated boost technique using 6 MV photons. The prescribed radiation dose was 61 Gy to PGTVnx, 59 Gy to PGTVnd, 54 to 66 Gy to PTVnx, 30 or 33 fractions. Radiation was delivered once daily, five fractions per week, over 6 to 6.5 weeks for IMRT planning. The dose to OAR was limited on the basis of the RTOG 0225 protocol [6].

Results

Mean age of the 31 patients was 13 years (range: 8 - 17.5). Male/female ratio was 1.5/1. Findings of patients at diagnosis can be seen in Table 1. Histopathologically, 25 cases (80.6%) had undifferentiated carcinoma and 6 cases (13.4%) had non-keratinized carcinoma. Patients were staged using "TNM staging system" that includes AJCC's evaluation of tumor localization and extension, lymph node involvement and distant metastasis. All of the cases were identified as high risk advanced stage (Stage III-IV) (Tables 2 and 3).

Tablel : Symptoms at diagnosis of patients

Findings	N %
Cervical LAP	21 (67,7)
Epistaxis	5 (16,1)
Headache	7 (22,5)
Loss of hearing	4 (12,9)
Stuffy nose (blocked up nose)	4 (12,9)
Hoarseness	4 (12,9)
Otitis 111edia	3 (9,6)
EB serology	
Monospot (+)	16 cases
EBV VCAIEBNA (+)	2 cases
EBV-DNA (+)	I case
Not evaluated	12

Table 2: Nasophariugeal cancer staging according to AJCC

Stage I	Tl,	NO,	MO	→	Risk Low Risk
Stage I I	T2,	NO,	MO		
Stage I I I	T3,	NO,	MO	→	High Risk
	Tl,	N I,	MO		
Stage I V	T4,	Nx,	MO		
	Tx,	N2or N3,	MO		
	Tx.	Nx.	MO		

Table 3: TNM classification and staging of cases according to AJCC

Findings	N (%)
Tumor extension	
T1-2a	6 (19.4)
T 2b-T3-T4	25 (80,6)
Node involvement	29 (93,5)
Distant Metastasis	2 (6,5)
Staging	
Stage I	None.
Stage II	None.
Stage III(A,B)	29 (93,5)
Stage IV	2 (6,5)

Complete response to neoadjuvant chemotherapy was obtained in all cases. Three cases (9.6%) experienced relapse. Median relapse time was 6 months (with a mean of 7.8 months) and the relapse localizations were: lungs (1), bones (1) and soft tissue (1). Two of the relapses were Stage 4 and one was Stage 3. Of the relapsed patients, 1 had RT + simultaneous CPDD; 1 had RT+ simultaneous CPDD and then paclitaxel; and the other received CPDD, 5-FU, MTX and RT. However, the patients couldn't be saved. The mean follow-up time was 6.5 years (min. 1.11, max. 14.9 years) and 2 of the cases were out of the follow-up. In all of the cases, a 7-year RFS was 87.1%, and OS was 92.9% (Tables 5,6).

Table 4: NPC-91 chemotherapy diagram (5)

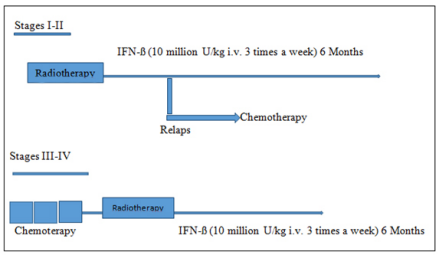


Table 5: 7-year OS in the patients

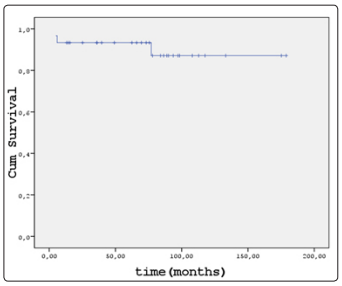
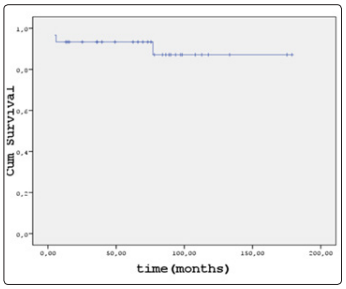


Table 6: 7-year RFS in the patients



When the group that received MTX regimen was compared to the one that did not receive it; there was no significant difference in 5-year RFS (93% and 84%, respectively) (p: 0.68) and 5-year OS was 93% for both groups (p: 0.91).

The most common acute complications after chemotherapy were: grade 2-3 nausea and vomiting (70.9%), weakness (70.9%), grade 2-3 mucositis (23%) and myelosuppresion (37.6%). Mucositis was generally found in MTX receiving chemotherapy patients (86.3%). However, in this group due to the use of amifostine, which is a multi-protective agent especially for CPDD, we observed milder side effects. On the other hand, xerostomia developed in 70.9% of the patients while receiving RT.

Xerostomia was detected in 70.9% of the patients during and after RT, and fibrosis in the neck (16 cases; 51.6%), hypothyroidism (11 cases; 35.4%) and loss of hearing (4 cases; 12.9%) as the late side effects which developed after a long follow- up.

Discussion

Nasopharyngeal carcinoma is one of the few malignant tumors in children and young adults, with an incidence rate of approximately 0.1% to 2.3% in China [1,2]. NPC in children differs from that of their adult counterparts in its rarity, its closer association with the Epstein– Barr virüs (EBV) infection, the high incidence of advanced disease at diagnosis, and a superior outcome than in adults. In our country, especially undifferentiated nasopharynx cancer is closely related to EBV infection [3,4]. Nasopharynx cancer is frequently seen during the ages of 13-14 in children and adolescents; and histopathologically undifferentiated carcinoma is the most common type [1-4]. In our series the mean age was 13 years, and histopathologically, undifferentiated carcinoma was the most common type (80.6%). Also, association with EBV was determined in 61% (in 19 patients) of the patients (Table 1).

In childhood and adolescence, NPC is seen in locoregional advanced disease and also systemic disease characteristics are high. All of our cases were in the high risk group (locoregional advanced stage disease was 93.5% and systemic disease was 6.5%).

Children and adolescents with NPC generally have a good chance of survival. As the results for RT alone for locoregional advanced disease are suboptimal, these patients are generally treated with combined chemoradiotherapy (CT-RT). In the POG study 9486, 4 cycles of neoadjuvant chemotherapy comprising methotrexate (MTX), cisplatin (CDDP), 5-fluorouracil (5-FU), and leucovorin were given before RT, with the total RT dose of both the primary tumor and positive lymph nodes being 61.2 Gy. In this study, 4-year EFS and OS were found as 77% and 75% respectively. They suggested that RT doses <60 Gy were feasible [1]. In the NPC-91-German Society of Pediatric Oncology and Hematology, and NPC-2003-German Society of Pediatric Oncology and Hematology /Dutch Childhood Oncology Group which were similar prospective studies, MTX, CDDP, 5-FU were used as neoadjuvant chemotherapy before RT, followed by β -interferon. Here the radiation dose given was 59,4 Gy [2]. In another study of the second group (NPC-2003), complete response with RT reduced to 50 Gy was shown. The OS and EFS rates were 95% to 97% and 91% to 92.4% after a median follow-up of 48 months and 30 months respectively, which were superior to all other reported results [2,3,7-11].

Our treatment protocol included "5-FU, CDDP and MTX /3 cures + RT/IMRT + IFN-β" (Tables 4,5). (Mertens R, Cancer 1997, GPOH-NPC-91 study). But 16 patients received MTX while 15 did not. There was a complete response to neoadjuvant chemotherapy in our cases. The mean follow-up time was 6.5 years. Three cases (9.6%) on median 6th month showed relapse. In all of the cases, a 7-year RFS was 87.1%, and OS was 92.9% (Tables 5-6). When the group that received MTX regimen was compared to the group that did not receive it; we did not find a significant difference in 5-year RFS (93% and 84% respectively) (p: 0.68) and 5-year OS was 93% for both groups (p: 0.91).

There is generally a good chance of survival in children and adolescents, but longterm complications occur due to 2D-RT. So, intensity-modulated radiotherapy (IMRT) could offer the best target volume coverage while protecting the normal tissues adjacent to the target with the aim of reduced toxicity. However, studies that examined the use of IMRT in pediatric and adolescent NPC patients are limited [12,13]. In a recent study of locoregionally advanced NPC, 95 childhood and adolescence patients received combined CT (CDDP, Paclitaxel, Gemcitabine) and IMRT [14]. All the patients had been treated with neoadjuvant chemotherapy before IMRT with or without concurrent chemotherapy/adjuvant chemotherapy. At the end of the study it was reported that IMRT combined with platinum-based chemotherapy produced a superb treatment outcome and was well-tolerated in children and adolescents with stage III to IVB NPC. Concurrent chemotherapy with IMRT has not been an additional benefit. Also, distant metastasis was the main failure condition and the 4-year OS, PFS, locoregional RFS, and distant metastasis FS were 90.8%, 79.1%, 94.9%, and 84.0% respectively [14].

The most common acute complications during CT are nausea, vomiting, mucositis, and myelosuppression; and also xerostomia is the most frequently encountered complication during and after RT. In one study, the most common acute toxicities were reported as mucositis, skin toxicity, and bone marrow suppression, most of them developed within grade 1 to 2, and the incidence of grades 3 to 4 acute toxicities were 20%, 4,2%, and 14.7% respectively [14]. During CT our cases showed grade 2-3 nausea and vomiting (70.9%), weakness (70.9%), grade 2-3 mucositis (23%) and myelosuppresion (37.6%). Mucositis was generally found in MTX receiving chemotherapy patients (86.3%). However, in this group due to the use of amifostine, which is a multi-protective agent especially for CPDD, side effects were observed to be milder, which led us to think that this was due to the use of this drug [15].

Guo et al reported that the most common late complications were xerostomia (48.42%), hearing impairment (28.42%), and neck fibrosis (41.05%), and all were detected within grade 2 and no endocrine disorders, growth retardation, and second malignancy were documented during routine follow-up [14]. Also they emphasized that these complications have been associated with RT modality. With the total doses > 60Gy in the 2D-RT they have been found significantly higher than IMRT. However, in small cohort of pediatric cases with NPC, Louis et al did not observe a significant decrease in long-term toxicities with IMRT plus chemotherapy [16]. In addition, brachytherapy may be a good option to increase radiation to the nasopharynx, and protect the normal tissues due to minimized RT doses [17]. New modern techniques such as proton-beam therapy also will lead to a substantial reduction in the long-term sequelae in the pediatric population [18].

We detected xerostomia in 70.9% of patients during and after RT, and fibrosis in the neck (51.6%), hypothyroidism (35.4%) and loss of hearing (12.9%) as the late side effects which developed after a long-term follow-up. In our cases the other endocrine disorders, growth retardation, or second malignancy were not detected. In one case a mild lung fibrosis occured 4 years after the end of treatment.

Distant metastasis remains a major obstacle in the cure of NPC in children and adolescents [13]. In some studies with locoregional advanced disease T and N classifications have been shown as a significant prognostic factor. But this issue is disputable, because in childhood and adolescence generally there is a good chance of survival. In other studies N classification is generally consistent and is the only independent unfavorable prognostic factor affecting treatment outcome [19]. In three of our cases, who were 2 distant disease and 1 nodal involvement positive, relapse occured and the patients couldn't be saved.

In summary, RT/IMRT combined with platinum-based chemotherapy produced a superb treatment outcome and was well-tolerated in children and adolescents with locoregional advanced disease NPC; distant metastasis was the main failure pattern. As in our patients RFS and OS results were similar to those found in the literature, so we concluded that this treatment protocol is successful. Since RFS and OS were similar in patients treated with MTX and without MTX-CT, due to the mucositis effect of MTX, removing it from the treatment protocol may be an option. Recently very few studies have focused on new therapeutic options aimed to improve the results of treatment. In the future, every effort should be made to reduce late complications and the distant failure rate. These include response-based total RT dose reduction, use of brachytherapy, use of new chemotherapeutic modality.

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