Nasopharyngeal Carcinoma Treatment in Children and Adolescents: Analysis of Outcomes in a Single Institution Cohort Treated with Risk-adapted Radiotherapy Dose

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OBJECTIVE

Nasopharyngeal cancer (NPC) in childhood is rare. In this study, we retrospectively report the results of adolescent and childhood NPC patients treated with different doses of intensity-modulated radiation therapy (IMRT) and 3D-conformal radiotherapy (RT) (3D-RT).

METHODS

Between 2007 and 2020, 20 patients were included in our study, 18 of whom received induction chemotherapy before chemoradiotherapy (CRT) (n=16) or RT (n=2). High-risk planning target volumes of 61.2 Gy (complete or good partial response) and 63–70 Gy (partial response) included the primary tumor and metastatic lymph nodes. Survival analyses were made using the Kaplan–Meier method.

RESULTS

The median follow-up time was 107 months (range: 6–168). The median age was 16 years (range 11–22). All patients had a complete response after CRT. The 5-year local control, disease-free survival, and overall survival were 100%. One patient developed distant metastasis (bone) at 62 months of treatment. There were no grade 4 acute side effects. Acute and late toxicity were observed lower in patients treated by dose reduction with IMRT.

CONCLUSION

In our study, over 60% of patients were treated with IMRT and dose reduction. Although lower-dose RT was administered, local-regional control was excellent, and the incidence rate of side effects was low.

Keywords: Chemotherapy; children and adolescents; nasopharyngeal carcinoma; radiotherapy.

INTRODUCTION

Nasopharyngeal cancer (NPC) is a radiosensitive disease.[1] A recent series reported local control (LC) rates over 90% with intensity-modulated radiotherapy (IMRT) and chemotherapy (CC).[2–5] Alongside LC, acute and late treatment complications increase in a dose-dependent manner. Some studies have used dose reduction and contour modification for NPC to minimize side effects in adults. While tumor control is simi-

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lar using these treatment adjustments, according to the literature, results show a decrease in acute and chronic side effects.[6,7] In addition, IMRT reportedly decreases toxicity rates and provides better survival rates in NPC cases.[8–11] Therefore, current guidelines suggest IMRT for NPC.

NPC in childhood is rare, with an incidence rate of <1% among all childhood tumors.[12] When compared to adults with NPC, while treatment is similar, tumor LC and disease-free survival (DFS) are better for children.[13] However, toxicities such as dental caries, growth development abnormalities, endocrine irregularities, and secondary malignancies were observed more frequently in children than in adults.[1,14] Thus, dose reduction studies to reduce side effects without compromising LC have been performed.[4,15]

Our primary purpose in this study was to analyze the outcomes of different doses of radiotherapy (RT) by retrospectively reporting results from adolescent and childhood NPC cases treated with IMRT and 3D-conformal RT (3D-RT).

MATERIALS AND METHODS

Study Population
All children and adolescents ≤22 years old with NPC, treated at the Cerrahpasa Medical School Radiation Oncology Department between 2007 and 2021, were included in this retrospective study. Patients' medical records were reviewed for demographics, clinical presentation, laboratory results, radiology records, pathology data, treatment details, outcomes, and long-term sequelae. On admission, all patients underwent a thorough physical examination, nasopharyngeal endoscopy, and laboratory evaluation (complete blood count, liver and kidney function tests, and serum Epstein–Barr virus [EBV] DNA level, if possible). The standard diagnostic radiological assessment for all patients included nasopharyngeal and neck magnetic resonance imaging (MRI) on admission and after 3 courses of neoadjuvant CC. For those diagnosed after 2010, 18-fluorodeoxyglucose positron emission tomography-computed tomography (18-FDG PET-CT) was also performed as a routine part of the radiological evaluation. Tumor-node-metastasis was staged according to the 8th edition of the American Joint Committee on Cancer. Adverse effects were evaluated according to the Common Terminology Criteria for Adverse Events version 5. This study was approved by the local ethics committee (No: 404194).

CC
All but 2 patients (n=18) started treatment with neo-adjuvant CC followed by RT. Different induction chemotherapy (IC) regimens were administered every 3 weeks for 3–4 cycles during the study period. Patients diagnosed between 2007 and 2009 received cisplatin, 80 mg/m² on day 1 and 5-fluorouracil 800–1000 mg/m² for a 96 h continuous intravenous infusion (PF). From 2009 to 2019, patients received docetaxel 75 mg/m² on day 1 and cisplatin 75 mg/m² on day 1 with 5-fluorouracil 750 mg/m² for a 96 h continuous intravenous infusion (TPF). After 2019, gemcitabine 1 g/m² on days 1 and 8 and cisplatin 80 mg/m² on day 1 or 25 mg/m²/day on days 1–3 (GP) and concomitant chemotherapy (CCT) with RT consisting of cisplatin weekly 20 mg/m² by intravenous infusion were the preferred regimen. Two patients were administered only CCT with RT (no prior IC), one of whom had a diagnosis of cystic fibrosis and chronic lung disease. The other patient had early-stage disease (T2N1) and was >20 years of age.

RT
For RT, all patients were immobilized using a thermoplastic head and shoulder mask in a supine position. The planning CT was obtained with a 2.5 mm slice thickness from the head to the carina. Both PET-CT and MRI fusion with the RT planning CT were used to detect the primary tumor and metastatic lymph nodes. Organs at risk and target volumes were contoured according to radiation therapy oncology group (RTOG) guidelines.[16,17] The gross tumor volume of the primary tumor and metastatic lymph nodes were delineated according to clinical and radiological findings. Three clinical target volumes (CTV) were defined. The high-risk CTV was delineated as the primary tumor volume (according to pre-CT) and metastatic lymph nodes (according to post-CT) plus a 5 mm margin. The intermediate-risk CTV was defined as the high-risk CTV plus a 5 mm margin and was modified to include the entire nasopharynx and whole involved nodal level. The low-risk CTV had to cover the intermediate-risk CTV and the entire vomer, surrounding ethmoid sinus, sphenoid sinus (for T1-T2 stage tumors: Inferior part of sphenoid sinus, for T3-T4 stage tumors: Whole sphenoid sinus), cavernous sinus (for T3-T4 stage tumors: Whole ipsilateral cavernous sinus), skull base foramina (foramen ovale, foramen rotundum, and foramen lacerum), posterior nasal cavity, posterior maxillary sinus, clivus (if not involved: Anterior 1/3 part of clivus; clival involvement: Entire clivus), parapharyngeal space, and elective bilateral cervical lymph nodes. The planning target volume (PTV) was

defined by adding 3 mm in all directions for IMRT and 5 mm for 3D-RT to all CTVs. Field verification (anatomical match) for image-guided RT was carried out with daily cone-beam CT and kV images for patients with IMRT planning. The patients with 3D conformal planning were treated with portal imaging every day.

IMRT was used in 16 patients, while 3D-RT was used in 4 patients. The PTV 61.2 Gy/34 fr (complete or good partial response) and PTV 63 Gy/ 35 fr −70 Gy/ 35 fr (partial response or only concurrent chemoradiotherapy [CCRT]) were delineated as the high-risk volumes, while PTV 54 Gy/30 fr −60 Gy/33 fr was delineated as the intermediate-risk volume. For the low-risk volume, PTV 45 Gy/25 fr −54 Gy/30 fr was delineated for high-risk areas with the potential for microscopic spread and elective bilateral cervical lymph nodes. The treatment schedule is detailed in Table 1.

Response Criteria

Tumor response was assessed with 18-FDG PET-CT or MRI after IC and 12 weeks after the end of RT. A complete or good partial response was defined as the disappearance of the disease or >75% disease response. A partial response was defined as a tumor volume reduction between 75% and 50%, whereas a stable response was defined as a reduction of up to 50%.[18]

Follow-up

Follow-up time was calculated between the completion of RT to the last visit. All patients were re-evaluated with MRI at 1.5–2 months and with PET-CT at 3–4 months after completion of RT. Patients were followed up every 3 months during the first 2 years and every 6 months after that. Follow-up visits included a complete physical and fiber-optic head and neck examination and biochemical and hematological blood tests. A nasopharyngeal/neck MRI was performed every 6 months. All patients were assessed for chronic side effects such as skeletal growth retardation, bone necrosis, nasopharyngeal mucosa necrosis, radiation-induced trismus, cranial nerve palsy, aspiration, alopecia, xerostomia, hearing impairment, dental caries, hypothyroidism, fibrosis of the neck, hypopituitarism, esophageal stricture, and secondary malignancy. Toxicity was evaluated by the results of the patient's self-reported complaints, physical examination, hearing tests, and laboratory results.

Statistical Analysis

All analyses were performed with SPSS version 22.0 (IBM, NY, USA). Descriptive statistical methods were used to determine patient characteristics. The overall

Table 1 The treatment schedule

	n	%
Treatment modalities		
IC → CCRT	16	80
IC → RT	2	10
CCRT	2	10
Radiotherapy		
High-risk volume		
70 Gy	2	10
66 Gy	2	10
63 Gy	6	30
61.2 Gy	10	50
Intermediate-risk volume		
60 Gy	2	10
54 Gy	18	90
Low-risk volume		
54 Gy	2	10
45 Gy	18	90
Radiotherapy dose		
≤61.2 Gy	10	50
>61.2 Gy	10	50
Radiotherapy technique and dose		
3 DCRT+≤ 61.2 Gy	4	20
IMRT+≤ 61.2 Gy	6	30
IMRT+>61.2 Gy	10	50

IC: Induction chemotherapy; CCRT: Concurrent chemoradiation; RT: Radiotherapy; 3 DCRT: Three-Dimensional Conformal Radiation Therapy; IMRT: Intensity-Modulated Radiation Therapy

survival (OS), DFS, metastasis-free survival (MFS), and LC were defined from the completion of IMRT to the last visit. Survival analyses were made using the Kaplan–Meier method.

RESULTS

Twenty children and adolescents with NPC were evaluated. The median age at diagnosis was 16 years (range 11–22), and the male/female ratio was 3:1. Non-keratinizing undifferentiated carcinoma was the most common histopathology (n=19), as only one patient had keratinizing carcinoma. The tumor stage was T1-2 in 9 (45%) and T3-4 in 11 (55%). The nodal stage was N1 in 10 (50%) and N2 in 7 (35%) (Table 2).

Serum EBV DNA was detected in 1 of 5 patients and became non-detectable after IC.

Treatment Response

All patients were evaluated with MRI scans before and after CC; however, PET-CT scans were used in 14 patients for assessment.

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Table 2 Patient and disease characteristics		
	n	%
Median age (years)	16 (11–22)	
Sex		
Male	15	75
Female	5	25
T stage		
T1	4	20
T2	5	25
T3	3	15
T4	8	40
N stage		
N0	1	5
N1	10	50
N2	7	35
N3	2	10
TNM stage		
Stage 2	4	20
Stage 3	7	35
Stage 4	9	45
Pathology		
Keratinized	1	5
Undifferentiated	19	95

TNM: Tumor node metastasis

Table 3 Acute and chronic side effects of the doses				
	n	%	n	%
Treatment dose (Gy)	≤61.2		>61.2	
Acute side effects (grade 3)				
Mucositis	3	30	2	20
Dysphagia	3	30	2	20
Dermatitis	2	20	1	10
Chronic side effects				
Xerostomia (grade1-2)	2	20	5	50
Hearing impairment	0	0	4	40
Dental caries	4	40	6	60
Hypothyroidism	3	30	6	60
Fibrosis of the neck	0	0	1	10
Esophageal stricture	1	10	0	0

Eighteen patients received IC (TPF, PF, GP) before CRT (n=16) or RT (n=2). Two patients were treated with only CRT. After IC, 11 out of 18 patients achieved a complete or good partial response. The remaining 7 patients had a partial response (TPF n=6, GP n=1). All patients achieved a complete response after RT. The intended weekly CCRT could not be given regularly due to hematological toxicity in 3 patients treated with GP.

Treatment Outcome

The median follow-up time was 107 months (range: 6–168). No local or regional relapse was detected during follow-up. The 5-year LC, DFS, MFS, and OS were all 100%, while the 8-year LC, DFS, and OS were 100%, 90.9%, and 100%, respectively.

One patient developed single bone metastasis, which was confirmed with a biopsy 62 months after the primary diagnosis. He was treated with 6 cycles of CC followed by RT to the metastatic bone site and achieved a complete response. He is still well without any evidence of disease 26 months after completing treatment.

Toxicity

Grade 2 mucositis, dysphagia, and dermatitis were observed in the whole group. Grade 3 acute side effects observed were mucositis 25%, dysphagia 25%, and dermatitis 15%. There were no grade 4 acute side effects. Similar acute side effects were observed when ≤61.2 Gy and >61.2 Gy dose groups were compared.

Grade 2 chronic side effects of xerostomia 30%, hearing impairment 25%, dental caries 50%, and hypothyroidism 45% were observed. For hearing impairment, the cochlear doses for all patients (n=19) were within the dose limits (mean dose <50Gy) except for one patient. Fibrosis of the neck in one patient, hypopituitarism in one patient, and an esophageal stricture requiring endoscopic dilatation in another patient were also observed.

More chronic side effects were observed in the >61.2 Gy group compared to the ≤61.2 Gy group. Dental caries and hypothyroidism were observed in 60% of patients, and hearing impairment and tinnitus in 40% of patients in the >61.2 Gy group. However, in the ≤61.2 Gy group, the percentage of patients with dental caries was 40%, and hypothyroidism was 30%. Hearing impairment and tinnitus were not observed in this group (Table 3).

When we compared 3D-RT and IMRT groups who were treated with ≤61.2 Gy, the occurrence of dental caries and hypothyroidism was similar. On the other hand, hearing impairment was reported at 25% (n=1) with 3D-RT and 12.5% (n=2) with IMRT, and esophageal stricture (n=1) was also observed with 3D-RT.

DISCUSSION

The standard treatment for pediatric NPC is IC followed by definitive RT ± CC according to the current international guidelines.[12] Although dose reduction in RT is recommended for children, LC and OS were

better for children compared to adults with NPC. In this study, we reported the outcome of LC and OS in patients with pediatric NPC.

NPC is a chemosensitive malignancy, and several retrospectives and a few prospective studies have documented the efficacy of CC in pediatric cases.[12] Cisplatin-based CC protocols are now considered the standard of care in children and adolescents with NPC, but the optimal CC combination has not yet been determined. The current treatment plan for pediatric NPC is IC followed by CC with RT, but there are no comparative studies on the efficacy of different regimens. The treatment center usually determines the IC scheme.[4,12,19] In our center, cisplatin has been the main backbone of IC and CCRT for many years, and TPF has been the standard IC protocol since 2009. We had to choose an IC protocol with a shorter hospital stay. Due to a small study population, it is impossible to compare the efficacy of the 2 schemes, but 4 out of 5 patients treated with first-line GP achieved a very good or complete response before RT, whereas 5 out of 11 cases treated with TPF had similar responses. In our study, 55% (n=11) of patients had a near-complete response, and the remaining had significant responses to IC. However, it is noteworthy as a clinical observation that GP was more practical in terms of both duration and application and less toxic to use in resource-limiting settings like ours.

In our study, 2 patients were administered only CCRT without prior IC. Cystic fibrosis is a genetic disease affecting the lung and gastrointestinal tract with an immune function deficit failing to eradicate pathogens, so IC was omitted from this patient. The other patient had early-stage disease (T2N1) NPC and was >20 years of age. Their treatment protocol was similar to that for adult NPC.

The indication and efficacy of CCRT are still debatable in pediatric NPC. There are no randomized studies to compare RT with or without CC, and all information is based on retrospective data.[12] Some studies showed improved survival rates with CCRT with increased toxicity, and some suggest the omission of CC in the presence of a very good partial or complete response to IC.[1] Considering the toxicity, a response-based approach could be suggested in the future. Although some studies reported T classification and treatment response association with OS or DFS, only one distant metastasis was reported as the predominant pattern of failure in our study.[12,20] The study demonstrated that radiation dose reduction adapted to the CC response does not have a negative impact on OS and LC. Orbach et al.[15] treated 34 pediatric NPC patients according to their IC response. Of those patients, the overall response rate to neoadjuvant CC was 78%. The cervical nodal irradiation dose was reduced in 15 patients to the median dose of 47 Gy (range: 45–50). The high-risk volume was given 59.4 Gy (range: 45–66). The 5-year OS was 73±8%, and local and distant failure rates were 10% and 18%, respectively. A French multicenter study evaluated neoadjuvant platinum-based CC followed by tumor response-adapted CRT results. For the primary tumor, the dose was defined as 59,4Gy in patients with a CC response ≥50%, while in patients with a CC response <50% had a specified dose of 66.6 Gy. Involved and uninvolved neck nodes were prescribed reduced doses of 54 Gy and 45 Gy, respectively, after a favorable tumor response. After a median follow-up of 4.5 years, 13 (13.6%) relapses and 7 (7.3%) deaths were observed.[21] In the ARAR0331 study, patients with complete or partial response to IC received 61.2 Gy to the nasopharynx and neck, and patients with stable disease received 71.2 Gy. The 5-year event-free survival and OS estimates were 84.3% and 89.2%, respectively.[4] In our study, 10 patients with complete response to IC were treated with 61.2 Gy, whereas 6 patients with partial response to IC were treated with 63 Gy. The other 4 patients were treated at 66–70 Gy. Our standard treatment protocol for adults (70 Gy to high-risk volume) was administered to patients >18 years old. There was no relapse or death after the median follow-up of 5 years. This data supports the possibility of dose reduction for pediatric NPC patients responding to IC.

Another issue involves treatment volume. The guide recommended 2 volumes for primary tumors; one included the primary tumor, and the other included the sphenoid sinus-maxillary sinus and whole mucosa.[22] In another study using doses similar to ours, 2 RT volumes were defined as 61.2 Gy for the primary tumor and 45 Gy for the entire nasopharynx and cervical lymph nodes.[4] However, in our study, we determined 3 volumes: The first volume (high-risk) covered the primary tumor, the second volume covered the whole nasopharynx, and the third volume covered the sphenoid sinus-maxillary sinus and the whole mucosa with tumor spread risk. Although the whole mucosa was included in the low-risk volume, no recurrence was observed.

The side effects of RT were compared to our historical data.[23] There were varying degrees of acute mucosal and skin reactions, which were associated with weight loss in both series. No patient required hospitalization or tube feeding due to mucositis. On the other hand, chronic side effects such as skeletal growth retardation (15.6%), trismus (6.2%), and necrosis of the

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bone-nasopharyngeal mucosa (6.2%) were observed in historical data. In the present data from our clinic, radiation-induced trismus, cranial nerve palsy, aspiration, and alopecia were not observed; however, there was hearing impairment in 20% of patients. Ototoxicity depends on several factors, including cumulative cisplatin dose and RT dose as hearing impairment may be affected not only by the cochlear RT dose but also by cumulative cisplatin doses. In this study, over 60% of patients underwent IMRT with dose reduction, and chronic side effects decreased. In another study in which Sahai et al.[20] evaluated 41 pediatric patients for the outcome and treatment-related morbidity, 28 were treated with IC followed by CCRT with a dose of 65–70 Gy in 35 fractions, 8 were treated with IMRT, 18 with 3D conformal radiation therapy, and 14 with 2D simulation. Late side effects including xerostomia (88%), hypothyroidism (82%), dental caries (65%), neck fibrosis (59%), trismus (59%), dysphagia (47%), growth restriction (35%), and hearing impairment (29%) were reported. Only one patient was observed to have radiation myelitis. These side effects were observed less in our study. Xerostomia decreased with IMRT and dose reduction compared to our historical data. In a French study, 95 patients were evaluated with IC, followed by doses of adapted CRT to the IC response. Of those, 57 (60%) patients were treated with IMRT, while the remaining were treated with 3D-RT. Odynophagia was significantly reduced in patients treated by IMRT; however, 2 patients developed a second malignancy in the head and neck area.[21] These studies indicate that reduced-dose IMRT helps decrease side effects without compromising locoregional control.

Limitations

Our study has several limitations, including its retrospective design and small sample size. In addition, the enrolled patients had heterogeneous baseline characteristics. The brief follow-up period for chronic side effects and recurrence, when compared with the first historical data is also a study weakness.

CONCLUSION

In our study, over 60% of patients were treated with the reduced-dose IMRT technique. Although lower-dose RT was administered, local-regional control was 100%, and the rate of side effects was lower. Prospective multicenter studies are needed to confirm the safety of dose reduction, especially in patients with complete responses after IC.

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