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Nasopharyngeal carcinoma in childhood and adolescence: Analysis of a series of 32 patients treated with combined chemotherapy and radiotherapy

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Abstract

Standard therapy for nasopharyngeal carcinoma (NPC) in children has generally followed the guidelines established for adults. We report here, the treatment outcomes in 32 children and adolescents with NPC and we discuss treatment approaches. Between 1993 and 1997, 32 NPC patients aged $\leqslant$20 years (mean age 15 years) were treated in our institution; they represented 18% of all NPC cases seen during the same time period. 27 patients had no metastases at diagnosis; 26 of these were treated with primary chemotherapy combining epirubicin and cisplatin. Radiotherapy was then delivered to 22 patients at a mean dose of 70 Gy, either conventionally (6 patients) or bifractionated (16 patients). 5 patients had metastases at diagnosis and were treated with chemotherapy combining epirubicin, bleomycin and cisplatin before definitive radiotherapy. The objective response rate (OR) after chemotherapy was 90.9% at the primary site, with a 13.6% complete response (CR) rate. At nodal sites, the OR was 95.5% and the CR was 31.8%. Local control was obtained in all patients after definitive radiotherapy with a medium follow-up of 43.7 months. Late toxicity affecting quality of life was found in 26% of the children who were irradiated, especially among those under 15 years of age (skin fibrosis, 27%; trismus, 27%; hypothyroidism, 14%). No locoregional relapses were observed. Distant metastases occurred in 33% of cases, with a median delay of 4.7 months from the end of treatment. The 2- and 5-year overall survival (OS) rates were 76 and 56%, respectively. Disease-free survival (DFS) was 65% at 2 and 5 years. Therapeutic outcomes for childhood NPC were similar to those in adults, but with more radiotherapy-induced toxicity. New chemotherapeutic combinations and new radiotherapeutic techniques should be sought to improve both survival and quality of life.

Keywords: Nasopharynx; Carcinoma; Childhood; Toxicity; Survival

1. Introduction

The frequency of nasopharyngeal carcinoma (NPC) varies extensively with age, and ethnic and geographical origin [1–2]. Where there is a high risk for NPC (Southern China, Hong Kong, Singapore, Taiwan), the cancer is generally found in patients over 40 years of age and is uncommon in childhood (<1%) [2]. Where the risk is low (Europe, Japan and United States of America (USA)) or intermediate (North Africa, the Middle East, Turkey, Greece, Southern Italy), two peaks of frequency have been observed, the first between 10 and 20 years of age and the second between 40 and 60 years [1,3,4]. In North Africa, NPC constitutes 5–10% of childhood tumours [5].

Undifferentiated NPC is the most frequent histological type in childhood. It is classically associated with a more advanced locoregional stage and with more frequent distant metastases than in the adult [2,6–8]. However, the 5-year disease-free survival does not seem to differ from that of adult and varies from 30 to 60% [3–7].

Standard therapy for NPC in children has generally followed the guidelines established for adults and is based on radiotherapy. Successful randomised trials [9–11]

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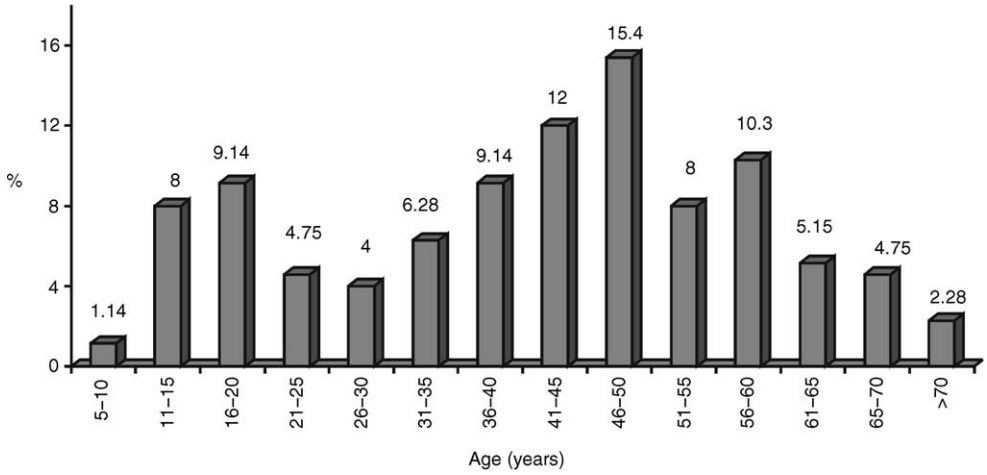

Fig. 1. Distribution of patients with nasopharyngeal carcinoma (NPC) according to their age (database from our institution, 1993–1997).

have led to the increased use of chemotherapy in combination with radiotherapy, but data on treatment outcomes in children are sparse. Therefore, we felt it important to examine specific survival and late toxicity in children treated for NPC.

2. Patients and methods

32 young patients (median age 15 years; range 8–20 years) with NPC were treated in our institution between January 1993 and December 1997. They represented 18% of all 175 patients with NPC treated during the same period. Fig. 1 shows the distribution of patients with NPC according to age. The gender ratio (male/female (M/F)) was 1.9. All patients presented with enlarged cervical lymph nodes.

Histological diagnosis was made according to the World Health Organization (WHO) classification on biopsies of the primary tumour; 18 patients (56.3%) had an undifferentiated carcinoma (WHO type 3) and the remainder had a non-keratinising carcinoma (WHO type 2).

All patients had a clinical history and examination, dental care with topical fluoride protection, computed tomography (CT) of the head and neck, a chest X-ray, abdominal ultrasonography, a bone scan, a full blood count, routine biochemical investigations and Epstein–Barr virus serology tests.

The TNM classification (International Union Against Cancer/American Joint Committee on Cancer (UICC/AJC) 1986) was used to define the extent of the disease; the TNM distribution of the patients is presented in Table 1.

All but 1 of the 27 patients with no metastatic disease were treated with three cycles of neoadjuvant chemotherapy every 21 days combining epirubicin (80 mg/m^2, day 1) and cisplatin (100 mg/m^2, day 1), followed by locoregional radiotherapy in only 22 patients (for reasons described below), monofractionated in six (2 Gy/fraction, five fractions a week) and bifractionated in 16 (1.6 Gy×2/day at 6-h intervals, 5 days a week) patients. Those given monofractionated radiation received a total dose of 70 Gy to the primary tumour and the cervical areas initially involved, and 50 Gy to the remaining cervical areas bilaterally. For those treated with bifractionated radiotherapy, the dose delivered was 70.4 Gy to the primary tumour and cervical areas initially involved, and 51.2 Gy to the remaining cervical areas bilaterally. A photon beam of cobalt-60 gamma rays was used. The guidelines for irradiation were as follows. Two lateral opposed fields and an anterior cervical field were used up to 44 Gy for the monofractionated modality and 38.4 Gy for the bifractionated. The remaining balance of irradiation was delivered via an anterior nasal field: 26 Gy for the classic modality and 31.6 Gy for the accelerated modality (after a week's break). Biological equivalent dosage was not used in patients in the bifractionated arm of the study.

For the 5 patients with metastatic disease at diagnosis, chemotherapy consisted of three cycles every 21 days of the BEC protocol (bleomycin, 12 mg intravenous (i.v.) bolus on day 1, followed by 15 mg/m^2 per day on days 1–5 by continuous infusion; epirubicin, 70 mg/m^2, day 1, and cisplatin 100 mg/m^2, day 1), followed

Table 1
UICC/AJC 1986 classification of patients under 20 years of age with nasopharyngeal carcinoma

	T2	T3	T4	Total
N1	3	1	0	4 (13%)
N2	1	4	15	20 (63%)
N3	1	1	6	8 (25%)
Total	5 (16%)	6 (19%)	21 (66%)	32

UICC/AJC, International Union Against Cancer/American Joint Committee on Cancer.

where there was a response to chemotherapy by locoregional radiotherapy delivered as described above.

In patients with relapses, a second-line of chemotherapy (the PBF protocol: cisplatin, 100 mg/m^2, day 1, bleomycin, 15 mg i.v. bolus on day 1 followed by 16 mg/m^2 per day on days 1–5 by continuous infusion; 5-fluorouracil: 650 mg/m^2 per day, on days 1–5 by continuous infusion) was administered.

Response to treatment was assessed after the third cycle of chemotherapy by head-and-neck examination and a CT scan of the nasopharynx; 2–3 months after the end of the radiotherapy a further head-and-neck examination, a biopsy and a new CT scan of the nasopharynx were performed.

Follow-up was every 3 months for the first 2 years, every 6 months the next 2 years, and then every year. The median follow-up was 43.7 months.

Toxicity and responses were evaluated according to WHO criteria.

A χ^2-test was used to detect statistically significant differences among potential prognostic factors between different groups. Overall survival (OS) and disease-free survival (DFS) were obtained according to the Kaplan–Meier method, and compared with the log-rank test.

3. Results

3.1. Response to treatment

Of the 26 patients who had no metastatic disease and were treated with neoadjuvant chemotherapy, only 22 completed three cycles of treatment and could be evaluated further. In 1 patient, chemotherapy was stopped after one cycle because of renal toxicity, another patient died of septic shock following a grade 3 neutropenia after the third cycle, and 2 were lost to follow-up after two cycles. An objective response (OR) at the primary site was found in 90.9% of cases (20/22), with a 13.6% complete response (CR) rate (3/22). For the cervical nodes, the OR was 95.5% (21/22) and the CR was 31.8% (7/22). Among patients who could otherwise have been evaluated further, 2 were then lost to follow-up and were not given radiotherapy. No information was available about the patients lost to follow-up.

After the therapy, 22 patients achieved complete locoregional remission, but 1 patient, whose tumour had been classified as T4N2M0, presented with bone metastases.

3.2. Treatment toxicity

Toxicity from chemotherapy was dominated by nausea/vomiting, grade 2–3 (92%), and alopecia, grade 3, (95%). One patient had grade 2 renal toxicity after the first cycle of chemotherapy and further chemotherapy was withheld. Grade 3 haematological toxicity complicated by septicaemia occurred in two patients, 1 of whom died from septic shock. The acute toxicity of radiotherapy was marked by mucositis, grade 1–2, in 73% of cases (16/22) and a skin reaction, grade 1–2, in 59% of cases (13/22). Mucositis, grade 3, was observed in 3 patients (14%), requiring an interruption of radiotherapy for 4 days in 2 cases. Late complications of radiotherapy were more frequent in patients under 15 years (69% versus 55%). They were dominated by xerostomia, grade 2 (12 patients; 55%); skin fibrosis, grade 2, was observed in 6 patients (27%); 6 patients developed trismus and 5 (23%) endocrine abnormalities: hypothyroidism (3 patients) and delayed puberty (2 among 11 girls). 2 patients (9%) had secondary dental damage. One patient presented with a basal-cell carcinoma requiring surgical treatment on the wing of the nose in an irradiated territory 4 years after radiotherapy. Late toxicity was judged to be affecting the quality of life in 26% of the patients who had been irradiated.

3.3. Evolution and long-term outcome

Within a median follow-up of 43.7 months (range 10–80 months), none of the 22 patients had a locoregional relapse. Among the 21 patients in CR, 7 (33%) eventually had distant metastases, with a median delay of 10.5 months (range 7–17 months) from the initial diagnosis of the primary and of 4.7 months (range 2–11 months) from the end of treatment. In 6 of these patients (86%), the metastases occurred within the 6 months following the end of the treatment. All patients with metastases had dissemination to bone, associated with liver invasion in 2 individuals. Pulmonary dissemination and involvement of axillary nodes were also observed in 2 patients. The PBF chemotherapy protocol was used for all patients in relapse. 2 patients with limited bony metastases were alive after six PBF cycles and local radiotherapy to the metastasis, with a delay of 36 and 49 months, respectively. For the 14 patients in CR, the median follow-up was 51.7 months (range 31–80 months).

For the whole population, the 2- and 5-year Overall Survival (OS) were 76 and 56%, respectively, and the DFS was 65% at 2 as well as at 5 years. Figs. 2 and 3 show, respectively, the OS and DFS of these children compared with those of 123 adults treated for NPC during the same period in our institution. No statistical difference in OS and DFS was found between children aged under or over 15 years.

Of the 5 children (16%) with bone metastases at diagnosis, 4 had tumours classified as T4N2 and one as T2N3. All these patients had three cycles of BEC followed by locoregional radiotherapy. 3 patients still had progressive disease at the end of treatment, with evol-

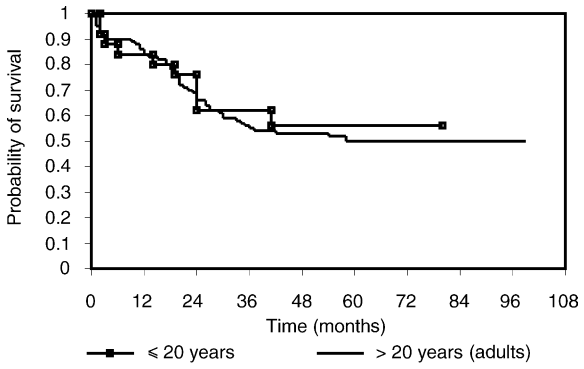

Fig. 2. Overall survival of 27 children with nasopharyngeal carcinoma compared with that of 123 adults treated in the same time period.

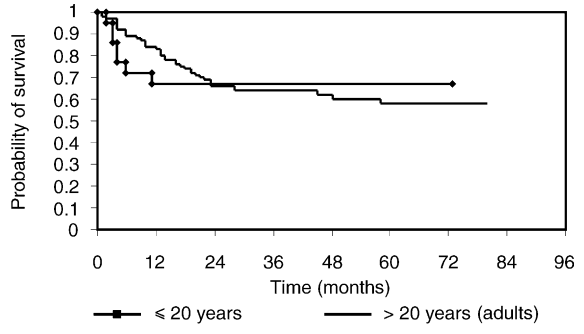

Fig. 3. Disease-free survival of 27 children with nasopharyngeal carcinoma compared with that of 123 adults treated in the same time period.

ving bone lesions in 2 and the occurrence of mediastinal nodes in the third; they died 6 months after the onset of treatment. The 2 remaining patients had had a single bony metastasis, which had been irradiated, and were alive 38 and 54 months after the end of treatment.

4. Discussion

NPC comprises 5–10% of all childhood tumours in Tunisia [5,6]. Its treatment follows the rules established for adults and is generally based on radiotherapy [12]. The prognosis for patients with locally advanced tumours is poor, owing to the frequency of locoregional relapse and/or distant metastasis [13–15]. Chemotherapy has proved efficacious in metastatic NPC [16–18], but its role in non-metastatic tumours remains controversial, especially in children.

In our study, the OR for neoadjuvant chemotherapy on the primary tumour (90.9%) and cervical nodes (95.5%) were high. In a previous study [19] of 19 adults with locally advanced NPC, we found an OR of 68% for the primary tumour, with a 16% CR; for the cervical nodes these rates were 100 and 53%, respectively. Another study [20] described a CR of 45% in a series of 11 children with stage IV NPC after three cycles of chemotherapy combining 5-fluorouracil, bleomycin and cisplatin. Another [21] recorded an OR of 90.8% in 22 children treated with three cycles of chemotherapy based on methotrexate, cisplatin and 5-fluorouracil. A CR of 50% was reported in a study of 12 children treated by three cycles of chemotherapy based on cisplatin, epirubicin and bleomycin [22]. The differences in CR among these studies could be due to differences in the assessment criteria.

Chemotherapy was generally well tolerated by the children in our study, although there was one death from toxic effects and a renal failure requiring the definitive interruption of treatment.

Local control had been successfully achieved after the end of radiotherapy in all of our patients, as in some other studies [20,22], but local control has varied from 66 to 91% in other series [4,12,23].

The acute toxicity of radiotherapy was dominated by oropharyngeal xerostomia in our series, as well as in others [15,22–24]. The late toxicity of radiotherapy can affect quality of life, and is dominated by cervical sclerosis, trismus and endocrine dysfunctions including hypopituitarism. These serious complications affected 25.5% of the children irradiated, but were seen in only 10% of patients in our adult series. In another series [20], 27% of young patients had primary amenorrhoea and 9% trismus and grade 2 cervical sclerosis. Hypothyroidism is a relatively frequent complication; it occurred in 12% of patients in one series [23], and in 14% in our study. These complications are much more frequent when children are irradiated under the age of 15 years (69% versus 55% in our study).

The occurrence of second malignancies has been reported in several relevant investigations. In our study, a basal-cell carcinoma appeared 4 years after the end of the treatment. We also reported 2 cases of second tumours in a previous study [26]. Others [14,25] have reported single cases of mandibular osteosarcoma that appeared 7 and 9 years after radiotherapy for NPC.

The 5-year OS ranged from 21 to 91% in earlier reports [2,20,22–24]; in the present study, it was 56%. In one previous study [2], 5-year OS was 21% for 53 children treated between 1964 and 1983 with radiotherapy alone, in other similar series, rates of 46% [22] and 64% [24] have been reported.

There were no locoregional failures in our study. This excellent local control can be explained by the high total dose of radiotherapy delivered and contrasts with the local failure rate (10.5%) observed in our adult series treated in the same way during the same time period. The 5-year locoregional relapse-free survival was 100% in the present series of children and 70% in the related series of adults ($P = 0.04$).

In a published series [24], a 5-year OS rate of 75% was reported for children who had been irradiated with

more than 65 Gy and 62% for those irradiated with lower doses; this difference was statistically significant. Similarly, others have shown [23] that locoregional control was significantly better for patients receiving more than 60 Gy than for those receiving 60 Gy or less ($P = 0.03$), with a better 10-year OS (76% versus 36%). These data suggest that de-escalation of doses may be followed by an increased rate of local relapse and a reduced survival. However, given the impact of the late toxicity of radiotherapy in patients younger than 15 years (69% in our study), a reduction in radiotherapy doses for good responders to first-line chemotherapy has been considered. Indeed, in an unpublished series of 50 children with NPC treated by neoadjuvant chemotherapy followed by 50 Gy in good responders and 65 Gy in poor responders, there was no suggestion of an increase in local relapses when using the lower dose (50 Gy), but the overall local relapse rate was relatively high for either dose level (J. Bourhis and F. Eschwege, Institut Gustave Roussy).

An alternative to improve the outcome of treatment could be to use new techniques of irradiation (conformational and intensity-modulated radiotherapy) [27], which might preserve good local control while decreasing the unwanted side-effects.

We found no difference in OS or DFS between the two arms of radiotherapy (mono- and bifractionated), either in the present children or in our adult series. Late toxicity was also similar between the two arms. Our results are in contrast to those [28,29] that have shown a benefit survival for bifractionated radiotherapy in head-and-neck cancer. Therefore, we intend to implement a randomised study comparing the two modalities of radiotherapy in advanced NPC.

In the present series of children, all of the failures had distant metastases (33%), these were less frequent and occurred later in our adult series (26%). Other series have reported rates of distant failure of 12% [15] and 29% [23]. New products, new combinations of chemotherapy, as well as intensification of the doses, need to be investigated further. The optimal timing for chemo- and radiotherapy also remains to be determined, since concomitant chemoradiotherapy has been tried with success in adults [11,30,31]. In a series of 33 children with NPC, there was a better survival for patients treated with concomitant chemoradiotherapy than for those treated with radiotherapy alone [23].

For patients with limited metastatic disease, aggressive treatment combining intensive chemotherapy, locoregional radiotherapy and radiotherapy for metastatic sites can be envisaged. In our study, 33% (4/12) of patients with metastatic disease are alive after intensive chemo- and radiotherapy for bone metastases. Others [32] have reported 20 long-term survivors in a series of patients with metastatic NPC treated between 1978 and 1996 with intensive chemo- and radiotherapy.

5. Conclusion

The therapeutic outcomes for NPC in children appear similar to those observed in adults, but with more long-term toxicity. A better rate of local control was obtained in children. Nevertheless, the important rate of metastatic failure in children, despite the use of a first-line chemotherapy, points to the need to develop new, more efficient and less toxic therapeutic strategies.

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