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Nasopharyngeal carcinoma in children: a challenging disease in a middle-income country, Tunisia

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Abstract

Background: This study aimed to assess the epidemiological, clinical, and therapeutic aspects and prognosis of juvenile nasopharyngeal carcinoma in Tunis country.

Materials and Methods: This study included 68 patients, younger than 18 years of age. All the patients had a clinical and para-clinical tumoral assessment. The study of survival and prognostic factors was done after a descriptive analysis. These prognostic factors were studied through uni and multivariate analysis.

Results: The median age was 14.7 years and the sex ratio was 2 male to 1 female. The average time to first consultation was 4 months. Rhinological signs were the most frequent symptom for consultation (n= 41). The T3-T4 tumors accounted for 78% of patients and there was a lymph node invasion stage N2-N3 in 63% of cases. Non-metastatic patients had radiotherapy associated with chemotherapy in 97% of cases. Metastatic patients received hypofractionated radiotherapy on bone metastasis, and first-line chemotherapy followed by radiotherapy on the primitive tumor and lymph node areas in case of good response to chemotherapy (n= 2). The mean follow-up was 94 months; 78% of these patients were alive and in complete remission, 19% were in therapeutic failure, and 16% of them had metachronous metastases. The five-year-overall survival was 95%. Hyposialia and skin dystrophy were the most frequent late complications.

In univariate analyses, significant prognostic factors were cranial nerve invasion, intracranial invasion, and infra-temporal fossa invasion. In multivariate analysis, the most parsimonious model associated extension to the infratemporal fossa, endo-cranial extension, and initial therapeutic modality (treatment failures were less frequent with neoadjuvant chemotherapy (p= 0.22)).

Conclusion: Treatment of nasopharyngeal carcinoma in children consists of chemotherapy and radiotherapy. Synchronous or metachronous metastases are common in this patient population. Modern radiotherapy techniques, including conformal radiotherapy with intensity modulation, are promising and could overcome toxicities in long-term survivors.

Keywords: Chemotherapy, Children, Disease-free Survival, Nasopharyngeal Cancer, Radiotherapy

Introduction

Tunisia is considered an intermediate risk area of nasopharyngeal carcinoma (NPC). The standardized incidence was estimated at 3.6 new cases per 100,000 inhabitants according to the Cancer Registry of Northern Tunisia, based on data between 2004 and 2006 (1). NPC is distinguished, in its undifferentiated form: Undifferentiated Nasopharyngeal Carcinoma Type (UCNT type), by its close association with the Epstein-Barr virus (EBV), but also by its deep basi-cranial location on the borders of the upper aero digestive tract (2). The main treatment is, therefore, radiotherapy. The intermediate-risk countries of UCNT are characterized by a bimodal distribution with a first peak between 15 and 20 years old and a second peak between 50 and 55 years old (2). In Tunisia, pediatric nasopharyngeal carcinoma diagnosed before the age of 18 represents about 5% of nasopharyngeal cancers and represents the most common epithelial malignancy in pediatric oncology (2). Nasopharyngeal carcinoma

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in children is frequently diagnosed at advanced stages with bulky cervical lymph nodes, large tumors, and a high rate of para neoplastic syndromes (3). Their evolution is marked by the frequency of metastatic failures and the risk of long-term sequels after chemotherapy and radiotherapy. The treatment of pediatric NPC remains a dilemma due to the lack of prospective studies devoted to this population. We aimed to describe the epidemiological profile and the clinical characteristics of NPC in the young population, to describe the therapeutic management of our patients, and their prognosis, as well as to analyze their prognostic factors.

Materials and Methods

This was a retrospective study, which involved 68 patients under the age of 18 years treated for undifferentiated (UCNT type) or poorly differentiated nasopharyngeal carcinoma from January 1, 2004, to December 31, 2014, at Salah Azaiez Institute of Cancer. The data collected from the records were the age, sex, geographical origin, pathological history (personal and family), the reasons for consultation, tumor characteristics given by posterior rhinoscopy and/or by nasofibroscopy, and cervical lymph node characteristics (size of the lymph nodes, their location, number, and mobility). We also collected the neurological examination data including the examination of the cranial nerves and the complete Oto-rhino-laryngological physical examination findings. The pre-treatment assessment included computed tomography (CT) and/or magnetic resonance imaging (MRI) of the nasopharynx for locoregional extension assessment and a chest x-ray, abdominal ultrasound, and bone scintigraphy for the distant extension assessment. According to these data, the disease was classified according to the Tumor Nodes Metastases TNM 2010 classification. The pre-therapeutic assessment also included a complete blood count (NFS), and a study of renal function before each course of chemotherapy; as well as audiometric and ophthalmological examinations with measurement of visual acuity. Before treatment with radiation therapy, patients underwent also the treatment of dental caries and the manufacture of fluoridated miniplastsplints. At the end of the treatment, the patients were examined with a nasofibroscopy and an MRI or a nasopharyngeal CT scan. They were followed at the consultation every three months during the first two years, every six months during three years then annually from the 5th year. A biological assessment and an endocrinology consultation were carried out on patients presenting clinical and biological signs evoking a hormonal disorder. Therapeutic failure was associated with loco-regional and distant disease progression and recurrences (diagnosed 6 months after the end of treatment).

Statistical analysis

All statistical analyses were performed with IBM SPSS 24 and Microsoft Excel 2013 software. Kaplan-Meier test was used to estimate survival rates. Overall survival (OS) was calculated from the date of histological diagnosis until the date of the last news or the date of death. A patient lost to follow-up in poor general condition (progressing or relapsing) was considered dead on the date of the last consultation or last treatment. Those lost to follow-up in good general condition were not counted in the survival study. The statistical test used to compare different survival results was the Log-Rank test. In multivariate analysis, a Cox regression model was constructed. The variables introduced into this model had a level of significance p less than 0.3 in univariate analysis. The method used in this regression model was of the descending Wald type, making it possible to determine a parsimonious

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model. However, the results reported in the form of hazard ratios and their confidence intervals were those of step 1 in the summary table and of the most parsimonious model in the text. The retained significance cut-off was p=0.05.

Results

Study population

The median age of our patients was 15 years (8-18ans) and the sex ratio was 2. Seventy-four percent of patients were originated from the North of Tunisia. Ninety-three percent of patients consulted within 6 months of the appearance of the first symptoms with an average consultation time of 4 months (20 days-12 months). Lymph node tumor syndrome and rhinological signs were the main reasons for consultation. On initial examination, cervical lymph nodes were palpable in 90% of patients. They were unilateral in 20 patients (29%) and bilateral in 41 patients (60%). Forty-nine patients had multiple lymph nodes (72%), and it affected the upper cervical chains (upper jugular-carotid chain (IIa) and/or the upper spinal chain (Va) in 58 cases. Cranial nerves were affected in 11 patients (16%). The trigeminal and common oculo-motor nerves were the most commonly, cranial pairs affected. Histologically, the biopsy revealed an undifferentiated carcinoma in 65 patients (96% of cases) and a poorly differentiated carcinoma in 3 cases. As for radiological assessment, 59 patients (87%) had a nasopharyngeal CT scanner while only 8 patients had MRI, and one patient had done both MRI and CT scanner. At imaging (CT and/or MRI), a tumor invaded the base of the skull in 49% of patients, the infra-temporal fossa in 34% of patients and an intra-cerebral invasion was noted in two patients (Figure 1). According to the TNM 2010 classification, 78% of patients were classified as T3-T4 and 63% N2-N3. Two patients were metastatic at diagnosis: one to the iliac bone and the other to the mediastinal lymph node (Table I). All patient files were discussed in a multidisciplinary consultation meeting where therapeutic decisions were made.

Treatment

As for treatment protocols for non-metastatic patients, 50 have received neoadjuvant chemotherapy followed by radiotherapy. The most commonly used chemotherapy protocol was AC (Adriamycin-Cisplatin), given in 32 patients (64% of patients who received neoadjuvant chemotherapy). While 11 patients received concurrent chemoradiotherapy and only 4 patients had neoadjuvant chemotherapy followed by concurrent chemoradiotherapy (Table II).

Only one patient classified as T2aN0M0 had exclusive radiotherapy. Radiotherapy was delivered at a dose of 70 to 74 Gy to the nasopharynx and cervical lymph node areas initially involved and 50 to 54 Gy to the other cervical lymph node areas. The fractionation was classic: 2Gy per session, 5 sessions per week for all irradiated patients. Fifty-seven patients (88%) have received conventional radiotherapy (2D), while, six patients (9%) have received conformal radiotherapy (3D), and only three patients (5%) have received IMRT (intensity modulated radiotherapy). The average duration of radiotherapy was 56 days (50-120 days). Two patients did not complete treatment, the first had died of febrile aplasia after the third course of chemotherapy (Adriamycin-Cisplatin (AC) protocol) and did not have been irradiated; the second one interrupted radiotherapy twice, because of radio mucositis. He died in the progression of his tumor within 5 years of diagnosis. Radiotherapy was performed by a Cobalt 60 machine or by a linear accelerator. A simulation of the irradiation fields with the taking of two-dimensional images preceded each

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irradiation. A first series of rays was delivered up to a dose of 42Gy by two opposite and equally weighted cervicofacial lateral beams set up in Tumor Source Distance (DST) with the target volume of the nasopharynx and the upper cervical lymph nodes. The boundaries of the fields were drawn according to bony landmarks, and an anterior cervical bundle in Distance Source Skin (DSP) targeted the middle, lower, and supraclavicular cervical lymph node areas. Personalized lead covers were put in place for the protection of healthy tissues, in particular the oral cavity, the eyeballs, the larynx, etc. During the second series of radiotherapy, starting at 42Gy, a medullary block was used to exclude the spinal cord, and then, additional irradiation of the spinal ganglion areas by direct electron beams was used. Patients who were metastatic at diagnosis have received first-line chemotherapy such as AC for the first one and Taxotere + PF for the second, followed by locoregional radiotherapy for the first patient and concurrent chemoradiotherapy for the second patient. The second patient had also hypofractionned radiotherapy on bone metastasis (8Gy in 2 fractions). During loco-regional relapses, salvage chemotherapy was indicated, whether or not associated with re-irradiation of the nasopharynx at a dose of 40 Gy if the general condition of the patient allowed it. We decided to change chemotherapy protocol in case of metastatic relapses, so 8 patients received Capecitabine as a monotherapy and 2 patients received Cispaltinum associated to 5 fluouracil. After the end of the treatment, the patient was seen every three months with a nasofibroscopy and an MRI or a scan of the nasopharynx.

Survival

The mean follow-up was 94 months (3-170 months). Fourteen patients deceased and 4 were lost to follow-up. The overall survival (OS) was 84%, and 74% at 5 years and 10 years respectively. OS after recurrence was 30% at 5 years ($p<10-3$) (figure 2). Disease-free survival (DFS) was 81% and 72% at 5 years and 10 years, respectively (figure 3). The mean time to recurrence was 16 months (6-24 months). For non-metastatic patients, 2 patients had a synchronous locoregional and metastatic recurrence and 10 patients had isolated metastatic recurrences. We have considered loco-regional and metastatic recurrences as treatment failures. We reported different ways of relapsing depending on the initial treatment modality in Table III.

Prognosis Factors

OS was correlated with the occurrence of treatment failure, so we have considered that prognostic factors for recurrences are those of OS. Treatment failure events vary by the treatment protocol, thus we noted 4 (36%) recurrences in the concurrent chemoradiotherapy group; 5 (10%) recurrences in the neoadjuvant chemotherapy followed by the radiotherapy group, and 1(25%) recurrence in the neoadjuvant chemotherapy followed by concurrent chemoradiotherapy group of patients, but the difference was not statistically significant. In univariate analyses, significant prognostic factors were: cranial nerve invasion, intracranial invasion, and infra-temporal fossa invasion. Patients aged more than 14 years old, male, staged T3-4 TNM, who have interrupted radiotherapy, and who haven't received neoadjuvant chemotherapy had more risk of recurrence but without significant difference (Table IV). In multivariate analysis, the most parsimonious model associated extension to the infratemporal fossa, endo-cranial extension, and initial therapeutic modality (treatment failures were less frequent with neoadjuvant chemotherapy). Thus, at step 5 of the Cox regression model, the adjusted HRs and their confidence

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intervals were respectively 4.65 [1.15-18.7], 5.27 [1-27] and 2.6 [0.73-9.15].

Toxicity

Acute toxicity from chemotherapy: Acute toxicities due to chemotherapy were observed in 45 patients (66% of patients), with the particular frequency of digestive toxicity (diarrhea/vomiting) observed in 42 patients (62% of patients) and the hematological toxicity in 32 patients (47%). Unfortunately, a 16-year-old patient died from febrile aplasia after the third course of chemotherapy (adriamycin-cisplatin protocol). As for nephrotoxicity, 3 patients had acute renal failure due to cisplatinum that was reversible by hyperhydration. No other toxicities (hepatic, cardiologic, or neurological) due to chemotherapy were reported.

Acute toxicity from radiotherapy: Acute toxicities from radiotherapy were observed in 65 patients (96% of cases). The most common toxicities were hyposialy, radiodermatitis, and radio mucositis in 90%; 84%, and 77% of patients respectively. They were classified as grade 1 or grade 2 toxicities.

Late toxicities: Late toxicities were essentially due to radiotherapy. They were assessed on data from medical records of living patients at the time of data collection (50 patients). For these patients, radiotherapy was performed by 2D or 3D technique. No late toxicity related to chemotherapy was reported (figure 4).

Table I: Patients' characteristics with nasopharyngeal carcinoma

Characteristic	N (%)
Sex	
male	46(67%)
female	22 (32%)
Age	
Median	15 years
average	14 years
Presenting complaint	
Neck swelling	61(90%)
epistaxis	41(60%)
Blocked nose	36 (54%)
Headache	1928%)
Hearing loss	11(16%)
Neurological symptoms	11 (16%)
Histological type	
UCNT	65 (66%)
SC poorly differentiated	3 (4%)
T classification	
T1	6 (9%)
T2	9(13%)
T3	20 (29%)
T4	33 (49%)
N classification	
N0	7 (10%)
N1	18 (26%)
N2	25(37%)
N3	18(26%)

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M classification	
M0	66(66%)
M1	2 (2%)
TOTAL	68 (100%)

N: number of patients, %: percentage of patients, T: tumor, N: lymph node extension, M: metastases, SC: squamous cell carcinoma, UCNT: Undifferentiated Nasopharyngeal Carcinoma Type

Table II: Details of induction chemotherapy (drugs, doses, intervals, and number of patients per Protocol)

Chemotherapy Protocol	Drugs, doses, intervals	Patients' number
AC (Adriamycin-Cisplatin)	Doxorubicin (Adriamycin) : 70-90 mg/m2 SC (J1) + Cisplatin (Platinol) : 100 mg/m2 SC (J1).	34
AC+ Bleomycin	Doxorubicin+ Cisplatin+ Bleomycin : 15 mg in bolus (J1) than 12 mg/m2 SC (J1-J5).	1
Cisplatin+ Epirubicin	Cisplatin :100 mg/m2 SC (J1)+ Epirubicin : 80 mg/m2 SC (J1)	1
Cisplatin as amonochemotherapy	One cycle every21days: 100 mg/m2 SC (J1). Or 1 cycle/ week : 40 mg/m2 SC.	1
PF (Cisplatin-5-fluorouracil)	Cisplatin : 100 mg/m2 à (J1) + 5-FU : 1 000 mg/m2 (J1-J5)	8
TPF (Taxotere + PF)	Taxoter: 75 mg/m2 (J1) + Cisplatin: 75 mg/m2 (J1) + 5-fluorouracil: 750 mg/m2 (J1-J5).	5
Total		50

SC: Body surface area, J1: first day of chemotherapy course, J5: fifth day of the beginning of chemotherapy course, SC: squamous cell carcinoma

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Table III: Number of patients with relapses depending on initial treatment modality

	Exclusive RT	Concurrent CT-RT	Neoadjuvant CT followed by RT	Neoadjuvant CT followed by CT-RT	Total
Metasatatic relapse	0	4	3	1	8
Locoregional and metastatic relapse	0	0	2	0	2
Total	0	4	5	1	10

RT: radiotherapy, CT: chemotherapy, CT-RT: Concurrent chemoradiotherapy

Table IV. Factors influencing the occurrence of treatment failure (univariate and multivariate analysis).

Factors	n	N	HR_b	CI	P	HR_a	CI	p
Age at diagnosis					0,07			0,42
- **≤14 years old**	3	31	0,35	0,1-		0,55	0,13-	
- **>14 years old**	10	37	Ref.	1,18		Ref.	2,34	
Sex					0,19			0,41
- **Male**	11	46	2,6	0,6-		1,92	0,39-	
- **Female**	2	22	Ref.	10,8		Ref.	9,34	
Time to consultation					0,46	-	-	-
- **≤90days**								
- **>90 days**	9	41	1,48	0,5-4,3				
	4	27	Ref.					
Neural invasion					0,029			0,65
- **yes**	5	11	3,2	1,3-8		1,67	0,18-	
- **No**	8	57	Ref.			Ref.	15,39	
ITF invasion					**0,007**			0,06
- **yes**	9	23	4,4	1,5-		4,07	0,91-	
- **No**	4	45	Ref.	12,7		Ref.	18,12	
Intracerebral invasion					**0,034**			0,4
- **Yes**								
- **No**	2	2	6	3,5-		3,23	0,21-	
	11	66	Ref.	10,3		Ref.	49,37	
T stage (TNM 2010)					0,26			0,77
- **T1-T2**								
- **T3-T4**	1	15	0,29	0,04-2		0,72	0,07-	
	12	53	Ref.			Ref	6,67	
N stage (TNM 2010)					0,75	-	-	-
- **N0-N1**								
- **N2-N3**	4	25	0,76	0,26-				
	9	43	Ref.	2,2				
M stage (TNM 2010)					0,34	-	-	-

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- **M0** - **M1**	12 1	66 2	0,36 Ref.	0,08- 1,5				
Staging - **Stage I, II et III** - **Stage IV**	5 8	27 41	0,94 Ref.	0,34- 2,6	0,9	-	-	-
Treatment protocol - **RT (+/-CT concurrent)** - **Neoadjuvant CT**	4 9	12 56	2 Ref.	0,76- 5,6	0,22	2,3 Ref.	0,6- 8,83	0,22
Time between diagnosis and treatment - **≤30 days** - **>30 days**	6 7	37 31	0,71 Ref.	0,27- 1,9	0,5	-	-	-

n: number of failures; N: number of patients; Ref. : reference group; RT: radiotherapy CT: chemotherapy; ITF: infratemporal fossa; CI: confidence interval, HR_b: Hazard Ratio brut; HR_a: Hazard Ratio adjusted.

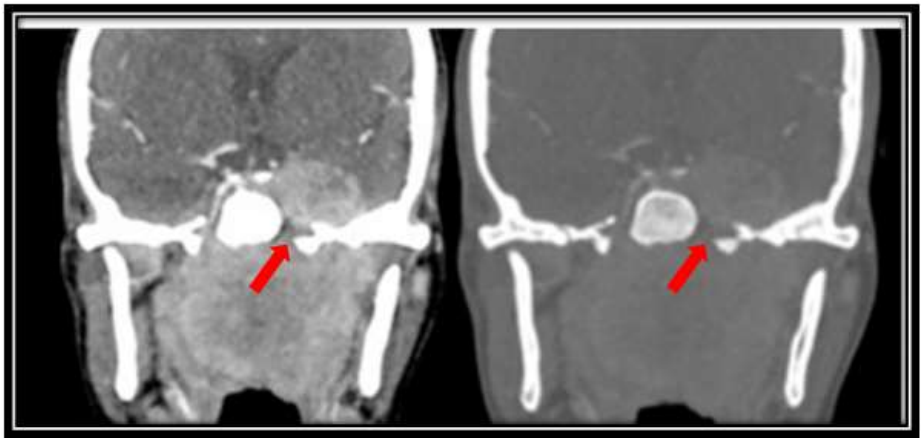

Figure 1.Nasopharyngeal carcinoma: cerebral scan showing an intracranial invasion in a 10-year-old boy.

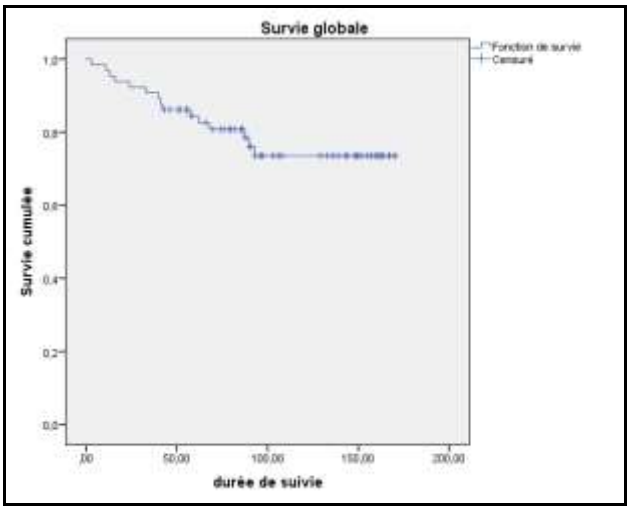

Figure 2. The overall survival in 68 patients treated for a nasopharyngeal carcinoma Disease-free survival (DFS) was 81% and 72% at 5 years and 10 years, respectively (figure 3). The mean time to recurrence was 16 months (6-24 months).

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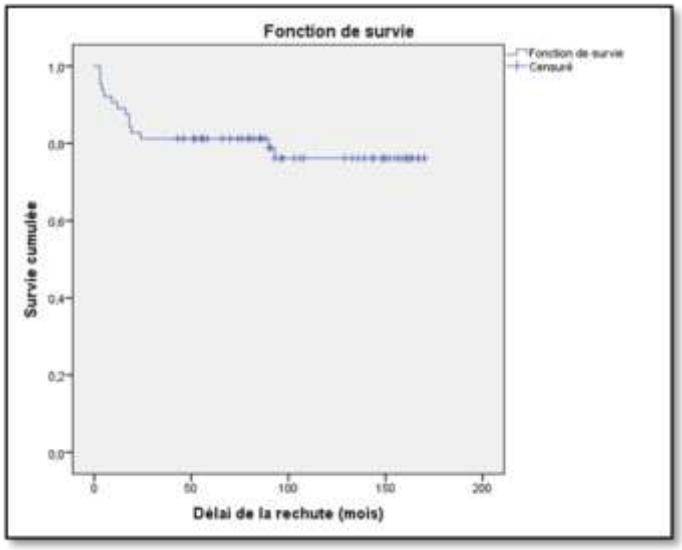

Figure3. Disease-free survival in 68 patients treated for a nasopharyngeal carcinoma

Figure 4: A survivor patient treated for an UCNT at the age of 10 in 1993 (Sequential CT and RT): cervical cutaneous sclerosis, hypoacusis with hearing aids

Discussion

The epidemiology of nasopharyngeal carcinoma is variable with age, race, geographic origin, dietary habits, genetic predispositions, and rate of Epstein - Barr virus infection. It's well known that there is a geographical distribution in 3 areas of different incidences of NPC: countries with a high incidence of NPC like Japan and China, countries with a low incidence of NPC like Europe and North America, and a middle incidence area such as the region of North Africa. In this region, a bimodal distribution is common with a particular peak of occurrence in children (3). Our series included 68 patients under 18 during a period of 11 years, another Tunisian series included 40 pediatric cases under 17 during 10 years (4). Commonly, the pediatric population is poorly represented in trials of NPC (3-5). Moreover, a male predominance was

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reported by the majority of series of NPC (5-9) regardless of age (adult, child) and geographical origin (5). Our study supports these results, as, the sex ratio was 2 (48 patients were male). The most frequent presenting symptom is cervical lymph nodes (63% of cases in our series), as reported in other series in 32 to 92% of cases (10-15). The majority of patients were staged T3-T4: 53 patients (78% of patients).

Advanced lymph node involvement (N2-N3) was noted in 63% of cases (43 patients) with involvement classified as N3 in 27% of cases (18 patients). Two patients (3% of patients) were metastatic at the initial assessment. Grouping by TNM stage showed that the majority of our patients were at stage IVA (39 patients: 57%) and III (22 patients: 32%). It is largely reported that locally advanced tumors are frequent in the juvenile form of NPC; tumors classified T3/T4 represent between 30% and 92% (5-6, 16-20). Lymph node involvement is frequently observed. It varies between 32 and 93% depending on the study and the country (20-25). The incidence of metastases at the time of diagnosis of juvenile NPC varies between 1.5 % and 15%. Commonly, bone is the first metastatic site.

As for treatment, to our knowledge, there are few published randomized trials (26, 27, 28), so for a long time, the management of juvenile NPC followed the therapeutic guidelines established in adults; but recently, new guidelines were published (29). Radiation therapy is the cornerstone in the treatment of NPC (30). The first studies carried out on juvenile NPC, between the years 1981 and 1999, included patients treated either by exclusive radiotherapy at variable doses (35-85 Gy) or (rarely) by chemoradiotherapy (31-33). The local control rates were satisfactory (61% to 94%) but the results in terms of overall survival at 5 years were disappointing (20 to 60%), mainly for locally advanced forms with frequent metastatic failures, which suggested the need for the adjunction of chemotherapy (26, 34-36). A meta-analysis published in 2006 confirmed that the addition of chemotherapy (adjuvant, neoadjuvant, or concurrent to radiotherapy) to external radiotherapy improves significantly disease-free survival and overall survival at 5 years (37). Nowadays, it is recognized that treatment should be based on radiotherapy in combination with chemotherapy. However, the optimal treatment regimen is still unclear as opting for sequential or concomitant treatment remains a subject of debate in the absence of randomized pediatric trials comparing these two treatment options. A sequential regimen consisting of 3 cycles of chemotherapy followed by radiotherapy was the treatment modality most commonly used in our series (75%).

Neoadjuvant chemotherapy aims to eradicate micro-metastases and diminish the initial tumor burden before the beginning of radiotherapy (38). Given the results reported in adults in terms of disease-free survival, pediatric series have adopted neoadjuvant chemotherapy followed by loco-regional radiotherapy in the treatment of locally advanced forms. Most of the protocols used are based on Cisplatin combined with other molecules (4, 39-42). The protocol combining Cisplatin with 5-fluorouracil (PF) as a neoadjuvant chemotherapy has been reported by several authors with an overall 5-year survival of 70 to 80% (3, 27, 28, 43, 44). For example, in Jmal's series, 48 children (less than 16 years old) with NPC were treated with neoadjuvant chemotherapy combining Cisplatin and Adriamycin (AP) followed by locoregional radiotherapy (45). The 5-year overall survival and disease-free survival rates

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were 79.1% and 68.9%, respectively. In our series, 50 patients (74%) had neoadjuvant chemotherapy. Cisplatin-adriamycin (AP) protocol was the most used (received by 32 patients). Neoadjuvant chemotherapy followed by radio-chemotherapy seems to be one of the optimal treatment regimens in terms of survival but with high toxicity (46). In our series, only four patients were treated by neoadjuvant CT followed by concomitant radio-chemotherapy. The risk of acute toxicity and the absence of evidence of better efficacy of concurrent chemoradiotherapy in the young population justified our reluctance to prescribe this treatment plan in children. Therefore, we often, opt for sequential treatment in children to guarantee better adherence and tolerance of patients.

On the other hand, the optimal dose of radiation in juvenile NPC is still controversial (4). Thus, old series have shown that low doses (below 50 Gy) were associated with high rates of local relapses (5). A multicentric retrospective study that included 165 patients aged less than 18 years, found that irradiation at doses greater than or equal to 66 Gy led to better loco-regional relapse-free survival at 5 years (90% versus 73% at 5 years; p=0 .01) (47). The limiting factor of irradiation in the young population is mainly late toxicities.

The overall survival (OS) was 84%, and 74% at 5 years and 10 years respectively, in our series; this result was comparable to the series of Zrafi and al where the 5-year overall survival rate was 77.7% (4). Factors influencing survival were as follows: the occurrence of recurrence (p<0.001), a cranial pair invasion (p=0.029), the involvement of the infratemporal fossa, and intracranial extension (p=0.007). Other prognostic factors have been reported in retrospective pediatric series, in particular advanced TNM stage like in the study of Jenkin (48), which reported a significant difference in overall survival at 5 years between tumors classified as T1-T2 (75 %) and tumors classified as T3-T4 (37%), the extent of lymph node involvement as in the series of Laskar (49) and Bakkal (50) which showed a significant influence of lymph node involvement on overall survival and disease-free survival. Laskar even reported that a lymph node greater than 6 cm in size, significantly, influences overall survival (p=0.007) and disease-free survival (p=0.004) (49).

In general, acute toxicities related to treatment, are acceptable and resolve under symptomatic treatment. Authors often reported mucositis, vomiting, or bone marrow aplasia (51). In Daoud's series, 92% of children complained about nausea and vomiting in grades 2 and 3 (20). Late toxicities were dominated by hyposialia (86%) and cervical cutaneous sclerosis (68%). Late toxicities are rarely reported in published series because of the scarcity of this tumor in children but also the lack of follow-up in different published populations.

Conclusion

In conclusion, it seems difficult to deduce definitive conclusions from our results because of multiple reasons such as the relatively low number of patients included, and the retrospective nature of the study. But it seems clear that it is one of the largest series published about pediatric NPC, particularly in North Africa. Treatment is challenging in this particular young population and more trials especially randomized ones are mandatory to improve survival rates and reduce the risk of late toxicities.

Ethics approval

Ethics approval is not required for case reports or case series deemed not to constitute research in our institution (Salah Azaiez Institute of cancer). All the data

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were used following the Helsinki Declaration of 1975.

Author's Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted.

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Conflict of interests

There is no conflict of interests.

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