



Adapted strategy to tumor response in childhood nasopharyngeal carcinoma: the French experience

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Abstract

Purpose The aim of this study was to retrospectively study survival and long-term morbidities of children with nasopharyngeal carcinoma (NPC) treated by induction chemotherapy and concurrent chemoradiation (CRT). The total dose of radiation was adapted to the response following neoadjuvant chemotherapy.

Methods Children with non-metastatic NPC treated in France between 1999 and 2015 were retrospectively included in the study. The strategy combined neoadjuvant platinum-based chemotherapy, followed by adapted CRT to tumor response.

Results In total, 95 patients (median age 15 years [range, 7–23 years], male-to-female ratio 1.8) with undifferentiated NPC were included; 59% of patients had TNM stage IV. Intensity-modulated radiotherapy (IMRT) was delivered to 57 patients (60%), while the other patients were treated with conformal RT (3D-RT). After a median follow-up of 4.5 years [range, 3.6–5.5 years], 13 relapses and seven deaths had occurred. The 3-year overall and relapse-free survival (RFS) were 94% [95% CI, 85–97%] and 86% [77–92%], respectively. The locoregional failure rate was 6% [95% CI, 2–14]. Long-term treatment-related sequelae of grade 2+ were reported by 37 (50%) patients; odynophagia was significantly reduced treated by IMRT vs. conventional 3D-RT (7% vs. 55%, $p=0.015$). Using a reduction dose of 59.4 Gy, 54 Gy, and 45 Gy, respectively, to the primary, involved, and uninvolved neck nodes, after a favorable tumor response, was not associated with an increased locoregional failure rate.

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Conclusions The survival rates for NPC have been considerably improved by means of multimodal therapy, but long-term locoregional morbidity remains common. Use of IMRT may induce less residual odynophagia. Radiation dose reduction adapted to chemotherapy response does not have a negative impact on outcome. These findings support the use of an RT protocol adapted to the tumor response to neoadjuvant chemotherapy for a long-lasting improvement in the patient's quality of life.

Keywords Nasopharyngeal carcinoma · Radiotherapy · Chemotherapy · Adolescents—young adults · Long-term sequelae

Auf die Tumorreaktion angepasste Behandlungsstrategie beim Nasopharynxkarzinom in der Kindheit: Erfahrungen aus Frankreich

Zusammenfassung

Zielsetzung Retrospektive Analyse der Überlebenszeit und der Langzeitmorbidity von Kindern mit Nasopharynxkarzinom (NPC), die mit neoadjuvanter Chemotherapie und zeitgleicher Chemoradiotherapie (CRT) behandelt wurden. Die Strahlendosis wurde an die Reaktion auf die neoadjuvante Chemotherapie angepasst.

Methoden Kinder mit nichtmetastasiertem NPC, die zwischen 1999 und 2015 in Frankreich behandelt wurden, wurden retrospektiv in die Studie eingeschlossen. Die Behandlungsstrategie bestand aus einer Kombination von neoadjuvanter platinbasierter Chemotherapie, gefolgt von einer an das Ansprechen auf Chemotherapie angepassten Strahlentherapie.

Ergebnisse Fünfundneunzig Patienten (mittleres Alter 15 Jahre, Spanne 7–23 Jahre; Verhältnis Männer/Frauen 1,8) mit NPC vom Typ III konnten in die Studie eingeschlossen werden; 59 % der Patienten hatten ein TNM-Stadium IV. Bei 57 Patienten (60 %) wurde eine intensitätsmodulierte Strahlentherapie (IMRT) verabreicht, während die anderen Patienten mit einer konformen RT (3D-RT) behandelt wurden. Nach einer medianen Nachbeobachtungszeit von 4,5 Jahren (Spanne 3,6–5,5 Jahre) traten 13 Rückfälle und 7 Todesfälle auf. Die 3-Jahres-Gesamtüberlebensrate und die rezidivfreie Überlebensrate (RÜR) betragen 94 % (95 %-Konfidenzintervall [KI] 85–97 %) bzw. 86 % (95 %-KI 77–92 %). Die regionale Rückfallrate betrug 6 % (95 %-KI 2–14). Langzeitfolgeerscheinungen von Grad 2 oder höher traten bei 37 Patienten (50 %) auf; Odynophagie war bei Patienten, die mit IMRT behandelt wurden, im Vergleich zu herkömmlicher 3D-RT signifikant reduziert (7 % vs. 55 %; $p=0,015$). Die Verwendung einer Reduktionsdosis von 59,4 Gy, 54 Gy bzw. 45 Gy für die primären, betroffenen und nichtbetroffenen Halsknoten nach günstiger Tumorantwort war nicht mit einer erhöhten lokoregionalen Ausfallrate verbunden.

Schlussfolgerung Die NPC-Überlebensraten konnten durch eine multimodale Therapie erheblich verbessert werden; eine lokoregionale Langzeitmorbidity besteht jedoch nach wie vor. Das IMRT-Verfahren kann zu einer Verringerung der Odynophagie führen. Die an das Ansprechen auf Chemotherapie angepasste Dosisreduktion hat keinen negativen Einfluss auf die Überlebensraten. Diese Ergebnisse unterstützen die Verwendung eines RT-Protokolls, das an das Ansprechen auf neoadjuvante Chemotherapie angepasst ist, um die Lebensqualität des Patienten nachhaltig zu verbessern.

Schlüsselwörter Nasopharynxkarzinom · Strahlentherapie · Chemotherapie · Jugendliche – junge Erwachsene · Langzeitfolgen

Introduction

Nasopharyngeal carcinoma (NPC) is rare in children, but nevertheless represents the most common of the very rare pediatric tumors, accounting for about 1 % of all pediatric malignancies in France. The incidence worldwide may vary strongly according to geographical differences [1]. The median age at diagnosis in the pediatric population is between 12 and 15 years [2–4]. Tumor stage is often locally advanced (>40–55 % of TNM stage IV) at diagnosis, although distant metastases are rare (<5–10%; [3, 5–9]).

Sensitivity to radiotherapy (RT) and chemotherapy (ChT) has been established for a long time. Irradiation

of the nasopharynx and cervical nodes therefore remains the standard local treatment with total radiation doses between 50 and 70 Gy. In recent series, based on multidisciplinary strategies, 5-year overall survival (OS) is higher than 75 % [3, 5, 10–12]. Other factors, such as age at onset and RT doses delivered, do not constitute prognostic factors in most pediatric studies [3, 5, 6, 13].

Distant metastasis is the predominant mode of tumor failure in pediatric NPC and occurs within the first 2 years of follow-up. Neoadjuvant ChT was initially used in children to reduce metastatic tumor spread and RT field volume. Although no prospective study has compared outcomes for pediatric patients receiving RT, with or without ChT, the OS

was higher with the RT/ChT combination currently used suggesting that neoadjuvant ChT should be administered systematically in all cases of NPC in childhood and therefore it remains the standard treatment in childhood NPC [3, 5, 7, 14].

Locoregional relapse is also rare, with local control rates of up to 90–95% in the most recent studies [5, 7, 13, 15, 16]. Long-term head and neck sequelae, mainly related to irradiation, are nevertheless commonly observed in NPC in childhood [3, 5, 7, 11, 12]. In order to improve long-term locoregional control and reduce sequelae, several groups have therefore proposed the use of more conformal RT techniques with adaptation of the radiation dose to the response to neoadjuvant ChT, by decreasing the total dose and radiation volume in the case of a favorable response to neoadjuvant ChT [3, 5, 7, 10, 16].

This retrospective multicenter national study was designed to analyze therapeutic aspects and long-term toxicity data with the current systematic use of conformal RT, and to analyze an adapted strategy based on tumor response to neoadjuvant ChT in pediatric patients with NPC.

Patients and methods

This study retrospectively reviewed the medical charts of all patients with NPC treated from 1999 to 2015 in seven large French pediatric and adult oncology centers (Institut Curie, Paris; Gustave Roussy, Villejuif; Centre Oscar Lambret, Lille; Centre Léon Bérard, Lyon; Centre Paul Straus, Strasbourg; Institut Claudius Regaud, Toulouse; Institut Jean Godinot, Reims), satisfying the following inclusion criteria: biopsy-proven NPC (World Health Organization [WHO] type II or III, non-keratinizing and undifferentiated carcinoma), diagnosis before the age of 25 years, nonmetastatic disease, treated with conformal RT (3D-RT) or intensity-modulated radiation therapy (IMRT) in combination with ChT \pm maintenance therapy. This study was approved by the Lille IRB (Institutional Review Board) and CCTIRS agreement of the 9.1.2016 (Advisory Committee on Information Processing in Material Research in the Field of Health).

Patients were staged according to the 5th edition of the American Joint Committee of Cancer staging system (2010; [17]). Staging and routine assessments at diagnosis included ear–nose–throat specialists using clinical examination, upper endoscopy, and head and neck magnetic resonance imaging (MRI) with ultrasound of cervical nodal regions. Radiological assessment by head and neck MRI was recommended after two or three courses of ChT [3]. Complete response (CR) to neoadjuvant ChT was defined as no evidence of residual disease; partial response (PR) was defined as a decrease of $\geq 50\%$ and no evidence of new lesions;

stable disease (SD) was defined as minor changes that did not meet criteria for PR or progressive disease (PD); very good PR (VGPR) was defined as no evidence of measurable disease, but persistent asymmetry of the nasopharyngeal tumor region or contrast enhancement or a decrease of $\geq 90\%$ of the sum of the greatest dimensions of target lesions; and PD was defined as an increase of $\geq 25\%$ of target lesions or the appearance of new lesions [18]. Favorable response was considered in the case of CR, VGPR and PR, while other cases were considered to be an unfavorable response.

Initially, ChT regimens and dosing schedules were heterogeneous, as they were based on physician decisions and initial tumor response. Patients with NPC diagnosed after 2011 were systematically registered after parents/guardians' consent in a database set up by the French very rare tumor group (FRACTURE group; [19]). Therapeutic guidelines propose neoadjuvant ChT regimens comprising three courses of 5 FU-cisplatin, followed by nasopharyngeal and cervical node RT using doses adapted to the initial response to ChT, with concurrent ChT using cisplatin (optional for patients in VGPR) followed by optional maintenance beta-interferon (IFN- β ; Rebif®) therapy for 6 months [10]. One patient was previously included in a trial [15]. Severe (\geq grade 2) long-term locoregional toxicities (fibrosis, xerostomia, trismus,odynophagia, xerostomia, ototoxicity, dental caries, endocrine disorders, etc.) were retrospectively graded according to the worst Common Terminology Criteria for Adverse Events v4.0 (<https://evs.nci.nih.gov/ftp1/CTCAE/>), and compared after IMRT and 3DRT. The Brock grading scale was used for assessment of hearing loss [20].

Radiotherapy guidelines

Optimal immobilization of patients was recommended in a supine position with a thermoplastic mask covering the head to the shoulders. The primary lesion and lymph node involvements were defined at diagnosis by conventional scan with contrast, axial contrast-enhanced MRI with thin slices (< 3 mm), and endoscopy examination. Another axial contrast-enhanced MRI with thin slices (< 3 mm) was recommended again after two or three cycles of induction ChT, to evaluate the ChT response, in order to allow for RT dose adaptation. It was recommended to combine at least the second MRI with computed tomography (CT) planning.

Briefly, gross tumor volume (GTV) included the extent of disease in the primary tumor (GTV T) and cervical lymph nodes (GTV N), as observed on pre-radiation MRI or CT after neoadjuvant ChT. The clinical target volume (CTV1) included primary tumor region (GTV T and N), the whole nasopharynx, the parapharyngeal lymph nodes, as well as all sites of potential subclinical disease and all visible, and enlarged (> 1 cm) cervical lymph nodes, usually with a 0.5-1-

Table 1 Radiotherapy doses scheduled for patients with NPC according to response after induction therapy (French FRACTURE group proposal)

	PTV of residual tumor following induction ChT	PTV of macroscopic tumor and nodes prior to induction ChT	PTV of uninvolved nodal areas
Standard dose Complete response (CR), very good partial response (VGPR), or partial response (PR) [50–90%]	59.4 Gy	54.0 Gy	45.0 Gy
High dose Response <50%, stable or progressive disease	66.6 Gy	66.6 Gy	45.0 Gy

PTV planned tumor volume, Gy Gray, ChT chemotherapy

cm safety margin. A second clinical target volume (CTV2) included lymph node levels III, IV, and V as well as the supraclavicular regions, even if not involved at diagnosis. Margins from CTV to PTV were between 3 and 5 mm, depending both on the physician's choice and RT technique. A daily dose of 1.8–2.2 Gy was delivered 5 days/week by conventional fractionation. Details of RT doses according to tumor response to neoadjuvant ChT proposed by the FRACTURE group are reported in Table 1. The total duration of RT was reviewed and considered to be non-optimal in the case of premature RT discontinuation or RT delayed by more than 15% with respect to the initially scheduled dates. The main critical organs to be delineated and to be spared as much as possible were the cochlea, parotid glands, brain stem, spinal cord, pituitary gland, eyes, lens, chiasma, optic nerves, larynx, and brachial plexus.

Statistical methodology

Survivals estimates were calculated using the Kaplan–Meier method [21]. Overall survival was defined as the time interval from the date of biopsy to the date of death from any cause and relapse-free survival (RFS) was defined from the date of biopsy until the date of first relapse (localized and/or metastatic), tumor progression, or death from any cause. Patients with no events were censored on the date of the last follow-up. For univariate analysis, the statistical significance of each variable was first tested by the log-rank test. A stepwise variable selection procedure was applied to the covariates with a p value ≤ 0.10 in univariate analysis. Variables with $p < 0.10$ were entered into multivariate analyses and considered significant if $p \leq 0.05$. Prognostic factors for RFS were analyzed using a Cox model. Associations between two variables were analyzed with Fisher's exact test or the Wilcoxon Mann–Whitney test. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated according to the Wald method. Stata software

v13.1 (StataCorp LP, Stata Statistical Software: Release 11, College Station, TX, USA) was used for statistical analysis.

Results

Patient and tumor characteristics

This study included 95 patients with a median age at diagnosis of 15 years (range, 7–23). Clinical and tumor characteristics are detailed in Table 2. Two thirds of patients were treated in a pediatric department (online supplemental Fig. 1). One patient had a family history of nasopharyngeal carcinoma (father and uncle). The diagnosis was based on cavum biopsy for 33 patients (52%), on cervical lymph node biopsy for eight patients (12%), or on both for 23 patients (36%), with missing data on the biopsy site for 31 patients. The main histological type was WHO type III for 93 patients (99%) and the presence of Epstein–Barr virus (EBV) antigen or DNA in tumor tissue (EBER probe) was positive in almost all patients for whom this information was available (43/44 patients). Only three patients (3%) had stage II disease, while the remaining 91 patients (97%) had stage III or IV disease.

Treatment characteristics

In total, 90 patients (95%) received neoadjuvant ChT, but five patients did not receive neoadjuvant ChT for various reasons: stage II disease (two cases) and patients treated in an adult medical oncology department (two cases), physician's decision (one case; online resource 1). Details of the therapy are listed in Table 3. Neoadjuvant ChT consisted of cisplatin and 5-fluorouracil for 82% of patients and was cisplatin-based in 99% of cases. Docetaxel was added in 27% of cases (TPF regimen). Overall, 70 of 87 patients (80%) received at least three cycles of neoadjuvant ChT (median 3; range: 1–6).

Table 2 Patients with nasopharyngeal carcinoma: tumor characteristics at diagnosis

	Number of patients	%	Median	Range	Missing data (number of cases)
Patient characteristics					
<i>Age at radiotherapy (years)</i>	–	–	15	7–23	5
<i>Gender</i>					
Male	61	64	–	–	0
Female	34	36	–	–	
<i>Geographic origin</i>					
Europe/France	46	55	–	–	12
North Africa	21	25	–	–	
West Indies/Reunion Island	8	10	–	–	
Central Africa	6	7	–	–	
Other	2	3	–	–	
Tumor characteristics					
<i>Time to management (months)</i>	–	–	3.9	0–29	7
<i>Presenting symptoms (possibly multiple)</i>					
Cervical adenopathy	53	58	–	–	4
Unilateral hearing loss	27	30	–	–	
Rhinology symptoms	27	30	–	–	
Headache	20	22	–	–	
Neurologic	10	11	–	–	
Other	8	9	–	–	
<i>Histology WHO type</i>					
Type II	1	1	–	–	1
Type III	93	99	–	–	
<i>Positive EBV immunostaining</i>	43/44	98	–	–	51
<i>TNM staging:</i>					
<i>T stage</i>					
T1	5	5	–	–	2
T2	21	23	–	–	
T3	30	32	–	–	
T4	37	40	–	–	
<i>N stage</i>					
N0	8	9	–	–	1
N1	12	13	–	–	
N2	49	52	–	–	
N3	25	26	–	–	
<i>Stage</i>					
II	3	3	–	–	1
III	36	38	–	–	
IV-A	31	33	–	–	
IV-B	24	26	–	–	

Tumor response

Response to neoadjuvant ChT based on imaging (CT and/or MRI) was assessed after two cycles in 41 patients (65%), after three cycles in 21 patients (33%), and after four cycles in one patient (2%; missing data for 21 cases). In six patients, evaluation was available but the timing of this eval-

uation was not specified. Among the 69 patients for whom tumor response was available based on local assessment, 24 patients (35%) achieved CR or VGPR, 36 patients (52%) achieved PR, eight patients (12%) presented SD, and one patient (1%) presented PD of the primary tumor. Overall, the primary response rate—RR = (CR + PR + VGPR) / total

Table 3 Treatment characteristics for pediatric patients with nasopharyngeal carcinoma (95 patients)

Characteristics	Number of patients	%	Median (range)	Missing data
Induction chemotherapy	90	95	–	0
<i>Duration (days)</i>	–	–	46 (10–116)	16
<i>Number of courses</i>	–	–	3 (1–6)	3
<i>Type of courses</i>				0
Cisplatin-based	89	–	–	
Other regimens	1	–	–	
Radiotherapy	95	100	–	0
<i>Type</i>				0
3D-RT	38	40	–	
IMRT	57	60	–	
<i>Real duration (days)</i>	–	–	50 (29–75)	6
<i>Theoretical duration (days)</i>	–	–	46 (35–53)	4
<i>Duration of RT >8 weeks</i>	16	18	–	6
<i>Number of fractions</i>				
Primary	–	–	33 (25–38)	4
Nodal area	–	–	30 (25–37)	17
<i>Dose per fraction</i>				
Primary	91	–	2 Gy (1.7–2.3)	4
Nodal area	82	–	2 Gy (1.8–1.9)	13
<i>Interruption</i>	16	–	–	10
Reasons: mucosal toxicity/infection/other	14/1/1	–	–	
<i>Number of days</i>	–	–	5 (3–19)	
<i>Doses delivered</i>				
Primary	–	–	65 Gy (45–74)	–
Nodal area	–	–	60 Gy (45–72)	–
Concurrent ChT/RT	55	59	–	2
<i>Type of courses</i>				5
Cisplatin-based regimens	45	–	–	
CBP/cisplatin-based regimens	4	–	–	
Other regimens	1	–	–	
<i>Number of courses</i>	–	–	3 (1–7)	6
<i>Duration (days)</i>	–	–	36 (1–52)	15
Maintenance therapy	29	31	–	0
<i>Type of therapy</i>				
Interferon	17	–	–	0
Conventional ChT	11	–	–	0
Unknown	1	–	–	–
<i>Duration (months)</i>	–	–	5.8 (0.7–6.6)	6

ChT chemotherapy, RT radiotherapy, 5FU fluorouracil, CBP carboplatin, SD stable disease, PD progressive disease, PR partial response, VGPR very good partial response, Gy Gray, IMRT intensity-modulated radiation therapy, 3D-RT three-dimensional conformal RT

number of patients—to neoadjuvant ChT was 87%, and the cervical node RR was 89%.

All patients received external RT (Table 3), consisting of conformal RT in 38 patients (40%) and IMRT for 57 patients (60%). Median radiation dose to the primary tumor

was 65 Gy (range: 45–74 Gy) in 25–38 fractions (median: 33) and 60 Gy (range: 45–72 Gy) in 25–37 fractions (median: 30) to involved cervical lymph nodes. Among the 95 patients, based on medical decisions, 14 had a lower dosage and 28 a higher dosage than the recommended

Table 4 Patient outcome after therapy

Relapse or progression	Number of cases	
–	14/95	–
<i>Metastatic relapse</i>	10	–
Bone	–	5
Visceral	–	4
Bone and visceral	–	1
<i>Cervical regional nodal relapse (in radiotherapy fields)</i>	1	–
<i>Local relapse (primary)</i>	2	–
<i>Locoregional and metastatic progression</i>	1	–
Status at last follow-up		
<i>Death</i>	7/95	–
From disease	–	6
From disease and toxicity	–	1
<i>Alive</i>	88/95	–
Relapse-free	–	85
On therapy	–	2
With disease without treatment	–	1

Fig. 1 Overall and relapse-free survivals for the population of patients with nasopharyngeal carcinoma. OS overall survival, RFS relapse-free survival



	Number of events/total	3-years rate (95%CI)
OS	7/95	94% (85-97%)
RFS	14/95	86% (77-92%)

guidelines. The distribution of patients according to total dosage to primary is detailed in the online supplemental resource 2. Median doses to the primary tumor was 60.0Gy (range: 50.0–70.0) in the case of favorable response (CR/VGPR) vs. 64.0Gy (50.4–70.0) after a PR and 66.6Gy (59.4–70) in the case of SD or PD ($p < 0.01$). Overall, 55 patients (59%) received concurrent platinum-based single-agent ChT (with cisplatin in 45 cases, cisplatin/carboplatin combination in four cases, other regimen in one case, and missing data in five cases). Amifostine was added in eight cases.

Maintenance therapy after completion of ChT and ChT/RT was received by 29 patients (31%): 17 patients

received IFN- β and 11 patients received conventional ChT (treatment not specified in one case) for a median duration of 5.8 months (range: 0.7–6.6).

Outcome

All but one of the patients who presented early locoregional and metastatic progression had been considered to be in remission at the end of initial therapy. After a median follow-up of 4.5 years (range: 0.6–18), 14 patients had experienced relapse or progression at a median follow-up of 8 months (range: 1–102; Table 4), and 7 seven had died from progression despite salvage therapy. The tumor status

Table 5 Univariate analysis of prognostic factors for relapse-free survival

Factor	Number of events	HR (95% CI)	<i>p</i> Log-rank test
Population description			
Age			
<14 years	7/23	3.5 (1.2–10.5)	0.02
≥14 years	6/67	1	–
Gender			
Female	2/34	1	–
Male	12/61	3.8 (0.9–17.0)	0.08
Stage			
Stage II-III-IVA	7/70	1	–
Stage IVB	6/24	3.1 (1.03–9.4)	0.04
Time to diagnosis			
≤5 months	5/53	1	–
>5 months	9/42	2.6 (0.9–7.7)	0.09
Induction therapy			
No	1/5	1.7 (0.2–12.8)	0.63
Yes	13/90	1	–
Tumor response after neoadjuvant ChT			
CR or VGPR	1/24	0.19 (0.02–1.5)	0.12
PD, SD, or PR	9/45	1	–
Median dose delivered to primary tumor			
≤60 Gy	3/32	1	–
>60 Gy	11/63	1.9 (0.5–7.0)	0.31
Median dose delivered to cervical lymph nodes			
≤60 Gy	5/50	1	–
>60 Gy	9/35	2.9 (0.98–8.8)	0.05
RT technique			
Conformal	7/38	1	–
IMRT	7/57	0.9 (0.3–2.6)	0.81
Concurrent ChT			
No	8/38	1	–
Yes	5/55	0.5 (0.2–1.5)	0.21
Interferon maintenance therapy			
No	14/78	–	–
Yes	0/17	–	0.08

HR hazard ratio, CI confidential interval, ChT chemotherapy, RT radiotherapy, Gy Gray, CR complete response, VGPR very good partial response, PD progressive disease, SD stable disease, PR partial response

at the end of follow-up, for the whole cohort, is indicated in Table 4. The 3-year OS was 94% (95% CI: 85–97%) and RFS was 86% (95% CI: 77–92%); (Fig. 1). The locoregional failure rate was 6% (95% CI: 2–14); two local relapses, one cervical nodal relapse (in RT fields), and one locoregional progression. Among the 13 patients with relapses, only one had favorable response (VGPR), seven had PR and three SD/PD (missing data in three cases). Median total dose to primary for these 13 patients was 66 Gy (range: 54.8–72 Gy).

Prognostic analysis

The only significant prognostic variables for RFS on univariate analysis were median age at onset (<14 vs. \geq 14 years), and stage of disease (Table 5). No difference was shown in survival between patients receiving a median dose over or under 60 Gy on the primary tumor. Concurrent ChT did not appear to influence survival, but maintenance therapy with interferon tended to have a favorable impact on outcome. The 3-year RFS and OS rates among patients treated by IMRT were 89% (77–95%) and 93% (80–98%), respectively, and were not different when compared with conformal RT. In multivariate analysis, only time to diagnosis of >5 months remained prognostic (HR 1.2 [95% CI: 1.01–1.35]; $p=0.03$) but not gender, stage, median dose to cervical nodes, or interferon administration.

Long-term morbidities

The incidence of long-term toxicities of any grade was 95% (69/73 patients with data on long-term follow-up), including 37 patients (50%) with \geq grade 2 toxicity. Main head and neck sequelae were neck fibrosis, xerostomia, or caries (online resource 3). The residual odynophagia rate of grade 2+ was significantly higher in the group treated with 3D-RT compared with the group treated with IMRT (55% vs. 7%; $p=0.015$, Fisher's exact test). Hypothyroidism was observed in 64% of cases, and trismus was observed in 43% of cases. Two patients developed a second malignancy: A 13-year-old girl diagnosed with NPC developed squamous cell carcinoma of the tonsils 6 years after treatment of the NPC (including RT with a total dose of 63 Gy), and is currently in remission 5 years after surgery; a 17-year-old girl diagnosed with NPC developed squamous cell carcinoma of the tongue 8 years after treatment of the NPC (including RT with a total dose of 70 Gy), and is currently in remission 7 years after surgery and brachytherapy.

Discussion

This series confirms the very good long-term tumor control and survival in pediatric patients with NPC currently obtained with multimodal strategies comprising ChT and concurrent chemoradiation using a dose reduction of 10% in the case of response following induction ChT. The 3-year OS in the present cohort was satisfactory at 94% (85–97%). Overall survival rates with combined strategies are fairly satisfactory (around 80% and sometimes up to 95%, as in the present cohort) with local tumor failure rates of less than 10% [10–12, 16]. Most tumor events therefore correspond to early distant metastatic relapses mainly occurring during the first 2 years of follow-up, systematically raising the question of medical therapy in addition to locoregional irradiation. Notably, in this series, despite RT dose reduction (<60 Gy) for patients with a favorable response, RT adaptation did not appear to have any negative impact on outcome [3, 10, 14, 22]. To date, there have been some prospective pediatric NPC studies adapting RT by response to induction ChT. In the study by Buehrlen et al., the radiation dosage to the primary tumor was reduced from 59 to 54 Gy in patients with tumor who showed a complete response after three cycles of ChT by MRI [10]; the approach seemed to be feasible as none of the patients treated with a reduced total dose relapsed. In the other study by Rodriguez-Galindo et al., the radiation dosage to the primary tumors was increased from 61.2 Gy to 71.2 Gy in patients who did not have a CR or PR after three cycles of ChT. Event free survival for all patients was 92% in the first study (after a median follow-up of 30 months) and 85.5% in the latter one. Based on the two prospective NPC-91-GPOH [14] and NPC-2003-GPOH [10] studies, a German group (GPOH) published treatment guidelines [23]. In these studies, the majority of patients received dosages below 60 Gy. Moreover, in the GPHO experience, patients in CR after three cycles of ChT received a lower dose to the primary of 54 Gy.

Pediatric NPC frequently presents as advanced locoregional disease (59% of our patients had stage IVA or IVB disease), but distant metastases are rare at diagnosis (<5–10%; [15]) and are difficult to treat in this setting (5-year DFS 18% for stage IV_c [metastatic patients]; [24]). Overall, pediatric NPC patients appear to have a better prognosis despite more advanced disease compared with adults [8, 13, 25]. Treatment regimens currently remain highly heterogeneous throughout the world. In most series, patients receive cisplatin-based neoadjuvant ChT, often in combination with 5-FU. Heterogeneous RT doses were used, both within studies and between series, with median doses to the cavum ranging from 59 to 72 Gy. Therapy remained heterogeneous in the present study, despite official national pediatric guidelines proposed by the very rare tumor group. These differences can be explained by

the absence of strong prospective comparative randomized trials precisely defining the role of concurrent ChT, the possibility to reduce the primary irradiation dosage in the case of a favorable response to neoadjuvant ChT, the role of maintenance therapy, and the best dosage of locoregional RT.

Patients were exclusively treated with IMRT in two series [7, 12]. The German series treated patients with NPC exclusively with 3D-RT [10]. The other seven series, including the present series, report the results of patients treated by both techniques. Optimum total dose to the primary tumor region remains controversial with some studies in favor of high RT doses (>60 Gy; [26–29]), while others are not [6, 12, 30]. It should be noted that some patients in the series by Orbach et al. and Liu et al. were treated with 2D-RT [3, 31].

In the present cohort, 95% of patients experienced at least one late toxicity, as commonly reported in the literature. In addition, long-term sequelae might be underrepresented as the long-term follow-up was not specifically structured. In this tumor, long-term effects are mainly due to head and neck RT and some appear to be correlated to the type of RT. The most frequent toxicities after head and neck irradiation are locoregional sequelae, with xerostomia, neck fibrosis, hypothyroidism, ototoxicity, and dental abnormalities. Cheuk et al., in their retrospective series of 59 patients under the age of 20 treated in the United States before 2004, reported a cumulative incidence of late morbidities of 84% after a 15-year follow-up [30]. Laskar et al. showed that patients treated with IMRT had significantly less acute grade 3 odynophagia, grade 3 mucositis, and grade 3 dermatitis than patients treated with conventional RT. They also showed that the median time to onset of all acute toxicities was significantly longer in patients treated with IMRT compared with those treated with 3D-RT [32]. In our series, significantly fewer patients experienced odynophagia in the IMRT group (7%) compared with the conformal RT group (55%, $p < 0.01$). In addition, Cheuk et al. reported four cases of secondary malignancies: two cases of basal cell carcinoma of the neck and head region 23 and 27 years after the first diagnosis, one case of parotid muco-epidermoid carcinoma 2 years after NPC treatment, and one case of brain stem tumor 24 years after diagnosis. One patient also presented with multiple carcinomas including colorectal adenocarcinoma, maxillary squamous cell carcinoma, and esophageal adenocarcinoma in a context of a germline *P53* mutation [30]. Secondary head and neck cancers are common after treatment of pediatric NPC with an incidence of 0–8.5% [5, 13, 30, 33, 34]. Two patients in the present series developed secondary malignancies in irradiated volumes 6 and 8 years after treatment, respectively. All these findings argue strongly in favor of reduction of head and neck RT

doses in children with NPC after a favorable response in an attempt to reduce long-term sequelae.

The long recruitment period (1999 to 2015) associated with the changing management of this disease may have impacted the quality of diagnostic imaging (with the advent of PET scanning and improvement of MRI), and RT techniques have also improved with the development of IMRT. However, our inclusion criteria required patients to be recently treated by conformal RT or IMRT and had therefore systematically undergone CT planning. Intensity-modulated radiotherapy is a time-consuming technique for delineation and treatment, but RT planning and delineation are crucial when margins are small, with a risk of under-coverage of target volumes or a risk of toxicity due to coverage of critical organs. Treatment planning is effectively assisted by contrast-enhanced CT/MRI fusion to delineate targets and critical organs, which cannot be reliably performed on CT only (especially without contrast; [35]). The major advantage of CT/MRI fusion is better delineation of CTV [31]. The potential benefit of IMRT in NPC children compared with other conventional RT techniques is the possibility to substantially reduce long-term toxicity while maintaining excellent tumor control and thereby improving quality of life in the individual child and young adult. No comparative study in pediatric NPC has been published. Nevertheless, recent large retrospective studies have confirmed the benefit of IMRT in terms of local control (+9%) and survival (+14%; [16, 32, 33]). A randomized trial in adults showed better local control (+6 to 11%) and DFS/OS (+5 to 12%) due to better target coverage using IMRT [36–38]. The role of proton therapy in pediatric NPC has not been clearly defined. The sharp dose fall-off results in high radiation doses to the tumor with a minimal exit dose ensures improved sparing of normal tissues. However, very few data are available concerning the clinical impact of proton therapy in NPC, and no series of pediatric NPC has been published. Dosimetric comparisons showed similar target coverage to that obtained with IMRT. This technique should therefore be the subject of clinical trials owing to the significantly lower doses to the parotid glands, cochlea, maxillary, and larynx, although it does not appear to have any clinical impact on thyroid function [39–41]. Moreover, the potential value of new imaging modalities, such as RT adapted to PET scan changes, may allow for a potential reduction of tumor volume, and metabolic activity also needs to be prospectively assessed throughout treatment.

Despite the large size of this cohort, we acknowledge that the major limitation of this study is represented by its retrospective nature and the biases associated with this type of methodology, particularly selection and monitoring biases. The main selection bias arises from the fact that patients were recruited by radiotherapists of the French Pediatric Radiotherapy Group (GFRP), which means that all

patients in our study come from a referral center and the vast majority (91/95) were derived from the five French RT centers treating the largest number of children in France, which may not be strictly representative of the general population with NPC. In addition, this was a multicenter study, but the overall characteristics of the study population were similar to those described in the literature, which limits the risk of selection bias. In this study, 67% of patients were treated in a pediatric department and 33% were treated in an adult medical oncology department. The majority of young adults (18–25 years) were treated in an adult medical oncology department. However, many studies have shown that adolescents and young adults (AYA) have improved survival when treated for certain diseases in a pediatric department [42], as AYAs are less often included in clinical trials and therefore do not benefit from progress in pediatric oncology or adult medical oncology [43, 44]. Many pediatric oncology departments have set up specific medical and psychosocial care for this population. One study in the United States specifically focused on the survival of AYAs with rare tumors, particularly NPC (25 patients), and did not demonstrate any significant difference in terms of 10-year OS according to the site of management (adult medical oncology vs. pediatric oncology; [45]). However, it seems to be important that these patients are being treated in specific structures used to take care of young patients. Moreover, significant late toxicities require specialized long-term follow-up.

The exact role and type of neoadjuvant ChT have not been clearly determined. In adult NPC, patients treated by induction ChT followed by radiochemotherapy had a better survival than patients treated by immediate radiochemotherapy (3-year failure-free survival: 80% vs. 72%, $p=0.034$; [46]). The only available phase 2 comparative prospective randomized study in children with NPC showed that the addition of docetaxel to cisplatin-5-fluorouracil induction therapy did not provide any benefit in terms of local control rate and outcomes in children and adolescents with NPC [15]. In addition, the role of concurrent chemoradiotherapy in NPC remains unclear in children. Since a beneficial effect of concurrent radiochemotherapy has been shown in adults, this principle of therapy has been introduced in prospective trials on NPC in children and adolescents [10, 15]. Meta-analyses showed that the greatest benefit of ChT in adults with NPC was obtained when ChT was delivered concurrently to RT [47, 48] with an absolute 5-year survival benefit of 6%. Recently, a meta-analysis of 20 randomized trials concluded in favor of systematic usage of ChT to RT with better locoregional and distant tumor control for protocols including induction ChT. Protocols with adjuvant ChT always ranked better than those with concomitant ChT alone [49]. Nevertheless, schedules containing more than one timing of ChT generally resulted in more toxicity

than the use of only one timing [49, 50]. Finally, the place of maintenance therapy after RT has never been scientifically defined. Most patients in the various studies, except in the German series [10], did not receive systematic adjuvant therapy. However, treatment comprising neoadjuvant ChT, concurrent RT/ChT followed by 6 months of interferon therapy was associated with a 3-year OS of 97% [10]. In the present series no relapse was observed in patients who received interferon maintenance therapy. No multivariate analysis could be performed because of the small number of events in this series. According to this analysis, the FRACTURE group has updated their national guidelines for NPC in childhood and adolescence to ensure more homogeneous treatment (online resource 4). Overall prognosis remains dismal for patients with initially metastatic tumor or after relapse. For those patients, owing to the specific immune environment of EBV-associated NPC, rational targets for immunotherapy seem promising and need to be developed for pediatric patients [51].

Conclusion

The survival rates for NPC have been considerably improved by means of multimodal therapy, but locoregional morbidity remains common and needs long-term follow-up. Treatment with IMRT may induce less residual odynophagia compared with 3D-RT treatment. Radiation dose reduction adapted to ChT response has no negative impact on outcome. These findings support the use of an RT protocol adapted to the tumor response to neoadjuvant ChT in order to lastingly improve the patient's quality of life. Authors recommend an adapted protocol with dose reductions after favorable tumor response to induction ChT. For patients with tumor in CR or VGRP, recommended dosages are for PTV-T1 54Gy, PTV-N1 54Gy, and PTV N0 45Gy; for patients with PR, PTV-T2/N2 59.4Gy, PTV-T1/N1 54Gy, and PTV-N0 45Gy; and for patients with poor tumor response (SD/PD), PTV-T2/N2 66.6Gy, PTV-T1/N1 54Gy, and PTV-N0 45Gy.

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