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Weight Loss in Nasopharyngeal Cancer is Mainly Associated with Pre-Treatment Dental Extraction, a European Single-Center Experience

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Abstract

Background: The treatment of nasopharyngeal carcinoma (NPC) consists of radiotherapy alone (stage I) or radiotherapy concomitant with chemotherapy (stage II-V). Acute side effects management forms a major challenge for practitioners. Substantial literature is available from endemic areas, whereas data from Europe is scarce. This study examines clinical characteristics, therapeutic results, acute and late side effects of patients treated at the Jules Bordet Institute.

Materials and Methods: Twenty-two consecutive non-metastatic NPC patients treated between May 2012 and September 2015 were retrospectively analyzed. All patients were treated by Intensity Modulated Radiation Therapy (IMRT) with or without chemotherapy (CT).

Results: Thirteen patients have North-African ancestry while nine are of European origin. Seventy-three percent had a non-keratinizing carcinoma and 90% had an advanced stage disease (III-IVb). Ninety-five percent of the patients received concomitant CT. After a median follow-up time of 31 months, overall survival was 77%. Local, regional and distant control rates were 95%, 86% and 73%. Main acute grade 3 toxicities were swallowing disorders (91%), vomiting (82%), oropharyngeal mucositis (64%) and dermatitis (23%). Only one patient developed grade 4 dermatitis, requiring treatment discontinuation in the sixth week. In the seventh week of treatment, 86% of the patients had lost more than 10% of their starting weight. Univariate analysis identified three factors driving the weight loss: grade 3 mucositis of the soft palate (p=0.027), vomiting (p=0.019) and pre-treatment dental extraction (p=0.006). In multivariate analysis, weight loss is only linked to dental extraction (p=0.042, Odds Ratio 1.62, [95% CI: 1.16-2.80]). Late toxicities were xerostomia (68%), auditory symptoms (55%), hypothyroidism (45%) and swallowing disorders (23%).

Conclusion: Our clinical characteristics outcome and toxicity are comparable to published data from endemic regions. Interestingly, weight loss of >10% is correlated to pre-treatment dental extraction. This finding should be confirmed and analyzed in a prospective manner.

Keywords: Nasopharyngeal cancer; Weight loss; Dental extraction; Carcinoma; Oropharyngeal mucositis; Chemotherapy

Introduction

NPC is an uncommon disease in Belgium following its geographical and ethnic distribution. Dr. John Ho was a pioneer in the epidemiological study, carcinogenesis, staging (Ho's Classification) and the development of radiotherapy techniques for this particular cancer [1]. Regarding carcinogenesis, his observations in the 1970s on boat people in southern China led him into the search and identification of salted fish as a carcinogen [1].

In 2012, 86.691 cases (0.6% of all cancers) were reported worldwide, of which 71% in endemic areas (i.e. South-East and South-Central Asia, North and East Africa) [2]. Belgium NPC is uncommon, only 76 cases (0.0008% of NPC, M/F ratio: 3.2) were diagnosed in 2012 [3].

The etiology is multifactorial, the Epstein-Barr virus (EBV) is the most studied association [4]. Family history accounts for 10% of the cases [5]. The environment, especially the nitrosamines found in cured and smoked foods, contributes to the carcinogenesis [4]. Since 2012, Cantonese salted fish is among the 119 agents which is classified in group 1 carcinogenic substances by the International Agency for Research on Cancer [5,6].

Regarding the pathogenesis related to alcohol consumption and smoking habits (tobacco or marijuana), links are inconsistent between studies and even when they are present, they are weaker than that seen for salted fish [4,6,7].

Advances in radiation therapy (RT) have revolutionized the treatment of this cancer [8]. With the emergence of the Computerized-Tomography (CT-scan) [9], RT has evolved from two-dimensional over conformational three-dimensional RT into the intensity-modulated irradiation (IMRT) era [10].

This evolution allowed for a more conform treatment of the tumor while better saving the surrounding healthy tissues. Therefore, IMRT resulted in a significant decrease in side effects, including the risk of permanent xerostomia [11-13]. Peng et al., also found an improvement of local-recurrence-free survival especially in late-stage NPC [13].

Currently, the concomitant administration of CT to radiotherapy (CRT) is the standard of care for locally advanced disease [8,14-16].

In endemic areas, recent meta-analysis shown a benefit on overall

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survival and progression free survival with the addition of induction CT to CRT for patients with locally advanced disease [8]. However, long-term follow-up is necessary to assess the efficacy and toxicity of induction CT in this setting [16]. In Europe, only one phase III study was recorded (NCTNCT00828386), but it ended due to insufficient accounting.

Regarding adjuvant CT more evidence is needed, the low compliance (around 55-75%) is a major problem [4]. For recurrent or metastatic NPC, new systemic therapy are emerging as a promising treatment according to early clinical data [4,17]. Patients with NPC can have very specific needs, due to both the location of their diseases and the impact of the treatment. This cancer can interfere with vital activities such as eating, speaking and breathing.

The objectives of this study are to analyze the epidemio-clinical characteristics, therapeutic results, acute and late side effects of the NPC patients treated at the Jules Bordet Institute.

Materials and Methods

Design of study

Twenty-two consecutive non-metastatic NPC patients treated between May 2012 and September 2015 were retrospectively analyzed. All patients were treated by IMRT with or without chemotherapy. The study was approved by the Jules Bordet Hospital Ethics Committee (Protocol_v1_20160727).

Methods

The pretreatment evaluation included an anamnesis and a complete physical examination, a nasopharyngo fibroscopy with biopsies (with an **in situ** hybridization to evaluate the abundant EBV-encoded small RNAs transcripts), a renal clearance, an ophthalmologic assessment, an audiogram, a dental evaluation and a magnetic resonance imaging (MRI) of the head and neck (HN). Screening for distant metastases was done by CT-scan and positron emission tomography-CT (PET-CT). The 7th edition of the TNM Classification of Nasopharyngeal Cancers has been used for staging (The International Union Against Cancer [UICC]/American Joint Committee on Cancer [AJCC]) [18].

Patients were immobilized with a thermoplastic HN mask to ensure reproducible positioning. CT-scan simulation with a 3 mm slice thickness with and without intravenous contrast was performed. Then CT images were electronically transferred to the treatment planning system (TPS) for target and critical organs contouring. Radiotherapy has given with 2- 2.12 Gy per fraction with five daily fractions per week for 7 weeks, using the 6 MV photon beam of a linear accelerator planned with simultaneous integrated boost technique.

The cumulative radiation doses were 70 Gy to the primary tumour and the involved neck area and 56 Gy to the elective neck area and potential sites of peritumoral microscopical invasion. All patients but one got concurrent CRT, i.e. three weekly cisplatin (80–100 mg/m^2) in 19 patients and weekly cisplatin (40 mg/m^2) in two patients. Moreover, a 17-year-old patient also received neoadjuvant CT (two cycles of cisplatin and 5-FU) and two other patients got adjuvant CT (three cycles of cisplatin or carboplatin and 5-FU) on top of their CRT.

Patients were seen weekly during treatment and every 2-3 months for the first 2 years, every 3-6 months in 3rd, 4th and 5th years and then yearly further on after (C)RT. A MRI and PET-CT were performed three months (median time 11 weeks) after the end of the (C)RT. Toxicity was graded according to the criteria of RTOG (Radiation Therapy Oncology Radiation) [19]. Nutritional counseling (NC), oral nutritional supplements (ONS), percutaneous endoscopic gastrostomy (PEG) or nasogastric tubes (NGT) feeding, laser phototherapy have been applied when clinically indicated.

Statistics

Survival and control rates (local, regional and distant) were calculated from the end of the RT to the last consultation or event (death or recurrence) using Kaplan-Meir curves. Mantel-Cox tests were used to identify independent variables significantly related to distant control.

In order to compare the weight-loss percentage we performed clinical characteristics a univariate analysis with comparison tests (Student's or Wilcoxon-Mann-Whitney test) and a linear regression to characterize the impact of the number of extracted teeth on weight loss. Finally, the variables were analyzed in a multivariate analysis (multiple linear regression). We also performed Statistical analysis were performed by GraphPAd Prism® software version 7.0a and R® version 3.3.2. A $p<0.05$ was considered as a significant result.

Results

Patient and tumour characteristics

The median time between the first symptoms and the histological diagnosis was 5.1 months (20 days-36 months). On average, patients presented at the clinic with three symptoms (1-4). Auditory symptoms (tinnitus, hearing loss, otalgia) were present in 86% of cases (19 patients), followed by lymphadenopathy in 59% (13 patients), 23% of which were bilateral, nasal symptoms (congestion, rhinorrhea, epistaxis) in 50% of cases, oral symptoms (hemoptysis, dysgeusia, hyposialia, retro-pharyngeal abscesses, dental pain) in 36% of cases, neurological symptoms (headache, cranial nerve [5th, 6th] palsy, ptosis, neck pain) in 27% of cases, visual symptoms (diplopia) in 14% of cases, swallowing disorders 14% of cases and trismus in 1 patient. The median duration between the first consultation and the start of (C)RT was 21 days (8-35). The patient characteristics and treatment parameters for the twenty-two patients are presented in Table 1 and Figure 1.

Therapeutic results

After a median follow-up of 31 months (5-39), the actuarial three-year survival rate is 77% (Figure 2) and the local control is 95% (Figure 2A). One cT3N3M0 patient developed clinical characteristics a out-of-field (geographic miss) local failure (Figure 2B). Regional control is 86% at 3 years (Figure 2B). Three patients presented with lymph node progression (Figure 2B). Distant control is 73% at 3 years (Figure 2B). Six patients presented an immediate distant recurrence (4 cases in bone, 1 case in liver and 1 patient in lung), diagnosed at the first PET-CT. One cT2N1M0 patient developed one late bone metastasis (45.5 months), this patient had a complete local response but an incomplete regional response at the first PET-CT (Figure 2B).

Distant control analysis by stage AJCC-7th edition reports a significant difference between stages ($p=0.009$). Similarly, there is a significant difference in the distant control as a function of nodal status ($p=0.008$). There is no significant difference with T stage ($p=0.658$).

Acute toxicity

Dermatitis: Figure 3A, details the incidence of dermatitis which appeared during (C)RT. Only one patient developed grade 4 dermatitis requiring treatment discontinuation in the sixth week.

Mucositis: The evolution of oral and/or oropharyngeal mucositis

Variable	No. (%)
Age (years)	
Min-Max	17-75
Median	46.5
Gender	
Male	18 (82)
Female	4 (18)
Ethnicity	
Maghreb	13 (59)
Mediterranean basins	3 (14)
Other	6 (27)
Alcohol consumption	
Yes	12 (55)
No	10 (45)
Smoker (tobacco)*	
Yes	13 (59)
No	9 (41)
Family history of NPC	
Yes	3 (14)
No	19 (86)
EBV	
Positive	17 (77)
Unknown	5 (23)
Histological type (WHO 2005)	
Keratinizing squamous cell carcinoma	1 (4.5)
Differentiated non-keratinizing carcinoma	1 (4.5)
Undifferentiated carcinoma	15 (68)
Basaloid squamous carcinoma	5 (23)
Chemotherapy	
Concurrent	18 (81.9)
Concurrent + adjuvant	2 (9.1)
Induction + concurrent	1 (4.5)
Not given	1 (4.5)
Radiation therapy	
70 Gy-33 fractions	7 (32)
70 Gy-35 fractions	15 (68)
Median follow-up, months (range)	31 (5-59)

NPC: Nasopharyngeal Carcinoma; WHO= World Health Organization; EBV=Epstein-Barr Virus. *Two patients smoked marijuana and tobacco.

Table 1: Patient characteristics and treatment parameters.

cTNM	T0	T1	T2	T3	T4	Total:
N0	0	0	1	0	3	4
N1	0	1	0	1	1	3
N2	1	3	3	0	3	10
N3	0	2	0	1	2	5
Total:	1	6	4	2	9	22

The 7th édition of the AJCC/UICC staging system:

Stage II (n= 3). Stage III (n=7). Stage IVA (n=8). Stage IVB (n=5).

Figure 1: Tumor and lymph node staging (The 7th edition of the [AJCC/UICC] staging system).

during the seven weeks of (C)RT is depicted in Figure 3. In case of mucositis, soft palate was involved in 100 % of case, 52.6% (n=10) was seen in the oral cavity. Furthermore, we noted grade 3 mucositis of the soft palate was more prevalent when the tumor was in close contact with the palate soft.

Swallowing disorders: At diagnosis, two patients suffered from odynophagia, none had dysphagia. During (C)RT, 2 (9%), 8 (36%), 3 (14%), and 9 (41%) of the 22 patients had Grade 0, 1, 2, and 3 swallowing disorders, respectively. Swallowing disorders were not significantly related to weight loss during (C)RT (p=0.2836). Six months after (C) RT, 5 patients (23%) still had dysphagia while none suffered from odynophagia.

Evolution of weight during treatment: At the seventh week of (C)RT, 86% of patients had lost more than 10% of their initial weight (Figure 4). One cT1N3M0 patient with an active tobacco addiction (60 pack-year) had lost 26.76% of his initial weight during CRT. Due to his poor oral hygiene, he had 13 teeth pre-therapeutic extraction. CRT was initiated within 4 weeks and 3 days after his first RT consultation. He continued to smoke during his treatment. At the beginning of the 3rd week, he developed Grade 3: dermatitis, mucositis of all the soft palate, swallowing disorders, vomiting and loss of taste. He had prophylactic NC and ONS and a therapeutic PEG at the beginning of the 4th week of his CRT.

Regarding prophylactic nutritional interventions, 7 patients had NC and ONS if indicate, and 1 patient had PEG. Fourteen patients had accepted a therapeutic intervention (7xNC and ONS, 2xPEG, 5xNGT) between the 2nd-6th week of their (C)RT.

Two patients refused therapeutic PEG and NGT. One cT4N3M0 patient had to be hospitalized for peritonitis due to a gastric perforation following the insertion of a therapeutic PEG. Therefore, he benefited from a jejunostomy. He stayed in the intensive care unit for 5 days and had his RT discontinued for 7 days.

Concerning upper gastrointestinal toxicity during (C)RT, 4 (18%), 10 (46%) and 8 (36%) of the 22 patients had Grade 0, 2, and 3 vomiting respectively. No patients developed protracted vomiting after (C)RT.

Univariate analysis of the mean difference in weight loss identified three significantly variables. The average weight loss of patients who had grade 3 mucositis or vomiting or dental extraction before radiotherapy during (C)RT was significantly higher than those who did not have this intervention or side effects (Table 2).

In multivariate analysis weight loss, as a percentage of weight at the first RT consultation is solely related to tooth extraction (0 tooth vs 1 or more teeth, p=0.042), Odds Ratio: 1.62, [95% CI: 1.16-2.80]. Vomiting (p=0.996) and Grade 3 mucositis (p=0.069) are not significantly related to weight loss. In addition, the number of teeth extracted per patient is correlated to the weighting loss independently of Grade 3 mucositis and vomiting (p=0.0001, R^2=0.53).

Late side effects

On average, sixth months after (C)RT patients accumulated 4 symptoms (1–6). Xerostomia accounted for 68% of cases (15 patients), followed by auditory complaints (tinnitus, otitis media, hearing loss) in 55% of cases (12 patients), biochemical peripheral hypothyroidism in 45% of cases (10 patients), nasal symptoms (rhinorrhea, rhinitis, epistaxis, anosmia) in 41% of cases, dental problems (dental pain,

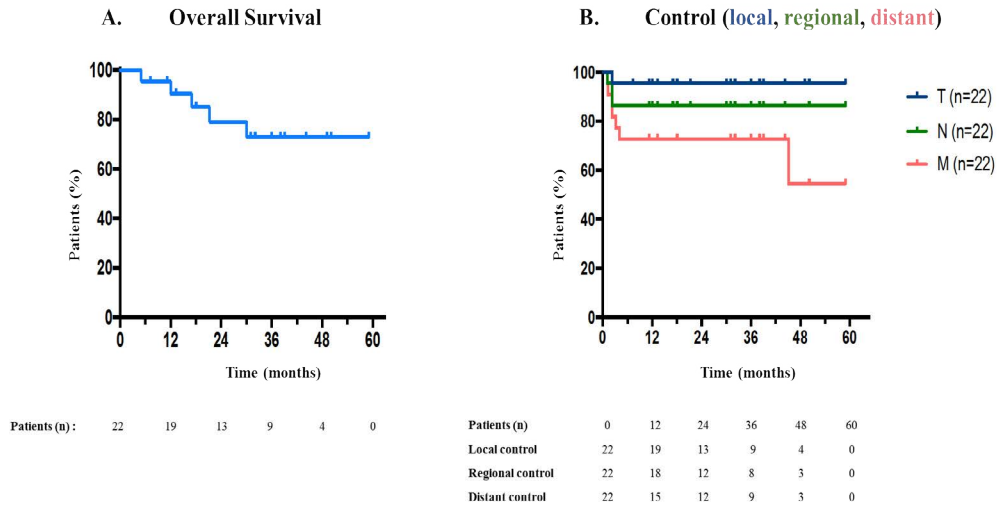

Figure 2: Overall survival curve (A) and Kaplan-Meier curve showing local (blue curve), regional (green curve) and distant (red curve) control (B).

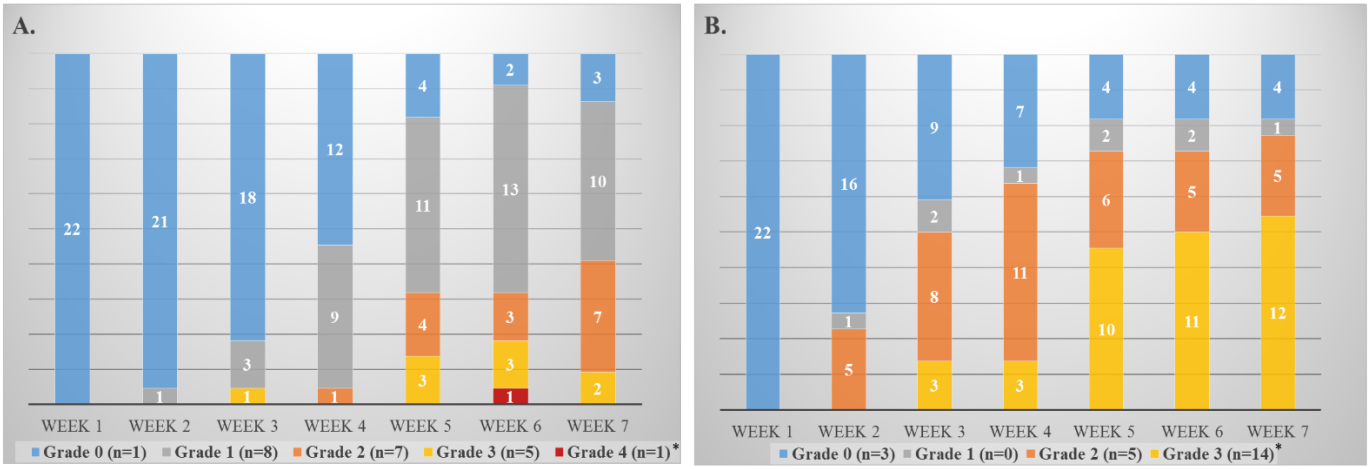

Figure 3: Incidence of dermatis (A) and mucositis (B) during (C)RT.

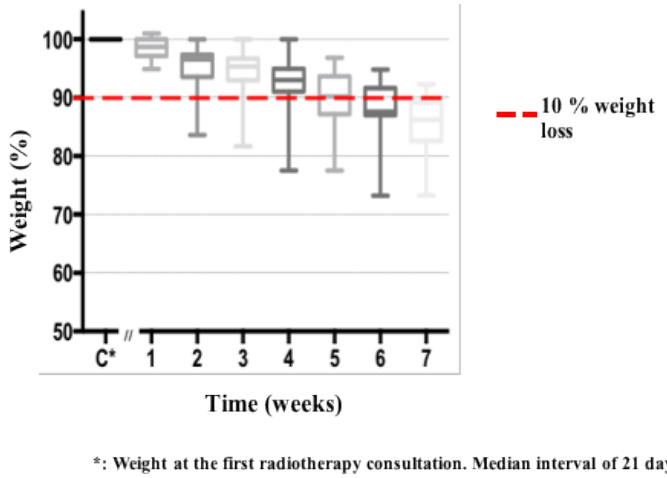

Figure 4: Evolution of the initial weight (First radiotherapy consultation [C*]) up to the last week of radiotherapy.

Analysis	Yes	No	Univariate analysis	Multivariate analysis
Grade 3 mucositis				
N (%)	14 (63.6%)	8 (36.4%)	--	--
Weight loss % median (Q2)	14.9%	10.4%	p=0.027*	p=0.069
Interquartile % of weight loss (Q1-Q3)	(12.6%-18.8%)	(8.1%-15.1%)	--	--
Vomiting				
N (%)	18 (81.8%)	4 (18.2%)	--	--
Weight loss % median (Q2)	14.9%	10.4%	p=0.019*	p=0.996
Interquartile % of weight loss (Q1-Q3)	(11.7%-18.8%)	(8.4%-11.4%)	--	--
Pre-treatment dental extraction				
N (%)	14 (63.6%)	8 (36.4%)	--	--
Weight loss % median (Q2)	16.25%	11.0%	p=0.006**	p=0.042*
Interquartile % of weight loss (Q1-Q3)	(12.8%-19.1%)	(8.4%-12.6%)	--	--

Table 2: Univariate and multivariate analysis of factors influencing weight loss during (C)RT.

fracture) in 41% of cases, neurological symptoms (fatigue, headache, cranial nerve [5th] palsy, muscle tension, Lhermitte sign) in 23% of cases (5 patients), swallowing disorders in 23% of cases, visual symptoms (exophthalmia, cataracts, periorbital pain) in 18% of cases and trismus in 14% of cases.

Discussion

Non-keratinizing carcinomas represented 73% of our population, which is the most common profile in endemic areas (>95%) [4,6]. This is explained by the proportion of NPC patients from Northern-Africa and the Mediterranean Basin living in Brussels and who have been referred to our Institute for (C)RT.

We find the three predominant symptoms (auditory symptoms, lymphadenopathies and nasal symptoms) described in the literature [4,6,20,21]. Physicians confronted with patients having a combined or chronic history of these symptoms without relief by conventional therapy (antibacterial or anti-allergic) should be on alert for more detailed investigation at early stage. According to Chan the screening of NPC (EBV DNA in plasma) can significantly detect early NPC and lead to better outcomes but the true benefit (lead-time-bias) is still uncertain [22].

The 3-year rate of regional progression-free, distant metastases-free and survival were 86%, 73%, and 77% respectively. In the literature, these rates varied between 91-98%, 66-100% and 83-100% [5,12,20,23]. The comparison between different studies is difficult given the heterogeneity of populations and treatment regimens. However, our results are explained by our case mix, as 90% presents with a stage III to IVB.

We attribute late diagnosis of NPC to the non-specific clinical presentation in combination with the lack of awareness of general practitioners in our country due to the low frequency of NPC in Belgium. Unfortunately, early NPC is relatively asymptomatic, 80% of the patients with NPC present with locally advanced disease or distant metastasis at diagnosis [22].

In addition, the undifferentiated carcinoma group (68% of our patients) and the EBV positive patients (77% of our patients) have a higher propensity for distant dissemination despite better local control [4,21].

In our series, distant control is significantly influenced by N stage and AJCC stage, well-established data [21]. The local (95%) control rates at three years are comparable to those obtained in the studies of Kam [12], Wolden [20] and Lee [23].

Nutritional management during (C)RT for NPC is fundamental. However, there is not sufficient evidence to determine the optimal type of intervention (NC and ONS, PEG or NGT) [24,25]. In our population, univariate analysis identified three factors significantly influencing weight loss: Grade 3 mucositis, vomiting and pre-therapeutic dental extraction.

Mucositis is the culmination of a complex biological mechanism [26]. They are a source of alterations in the quality of life, increase in the cost of care and compromise the effectiveness of treatment plans [26].

Secondly, vomiting was present in 82% of the patients. This can be caused by cisplatin who is one of the most highly emetogenic agent [27] as well as by irradiation of emetogenesis-associated regions [27]. The strategy should always focus on prevention rather than treatment, physicians can optimize their patients' outcomes by ensuring that therapy is tailored according to each patient's individual risk profile [28].

Thirdly, pre-treatment dental extraction had the greatest impact on weight loss during (C)RT. The number of teeth extracted is correlated to weighting loss during CRT but was poorly predictive (R^2=0.53).

To our knowledge, no study has illustrated this association between weight loss and the teeth extracted before (C)RT. Our hypothesis on the role of pre-therapeutic extraction is focused on a multifactorial etiology evolving over time. Between extraction and the first session of RT, discomfort due to pain and edema leads the patient to reduce his dietary intake.

This is followed by a difficulty in chewing, which correlates with the number and location of the extracted teeth. Edentation can also lead to significant psychosocial distress. Multidisciplinary cancer teams are positioned to implement effective distress screening programs and treatment to their patients' psychological and medical vulnerabilities. Furthermore, the number of extracted teeth reflects the oral hygiene, addictions (alcohol and tobacco) and socio-economic status (cost of dental care, therapeutic compliance, type of diet) of the patient. It is important for stomatologists to be conservative during tooth extraction. Currently, there are no randomized controlled trials on what to do as dental care prior to RT [29-31]. The damage caused by RT on the dentition is known [32]. We recommend a close collaboration between the radiation oncologist and the stemmatologist during the dental evaluation before RT. The first indicating the dose predicted to the different teeth, the latter taking care of the teeth most at risk of long-term release, according to clinical examination and panoramic radiography. In our center, every patient receives a thorough pre-therapeutic assessment by a stemmatologist who gives preventive advice

and performs extractions and filings when indicated. If extractions are performed, it is important to allow sufficient healing time prior to the start of RT without unduly delaying it. Therefore, the benefit-risk ratio of pre-therapeutic dental extraction has to be considered and evaluated for each patient. In our population swallowing disorders were not significantly related to weight loss during treatment, 41% of our patients developed grade 3. This can be explained by the fact that 32% have benefited from enteral nutrition (NGT or PEG) between the 2nd and 6th week of their (C)RT.

Patients who survive NPC can have several late complications, many of them resulting from RT. The use of CT further adds to these side-effects, e.g. cisplatin-associated ototoxicity [21]. Our study confirms the main late side effects found in the literature, xerostomia being the most prominent of them [4,21,23].

Our 45% post-RT hypothyroidism confirms the incidence of 20% to 50% found in different reports [33-35]. Comparable to the studies of Zhai [34] and Lee [35] no patient was found to have a central hypothyroidism due to excessive irradiation to the pituitary gland. However, as HT may not become evident but/unless for many years after RT, physicians should be aware of this complication. One patient who had a Grade 4 dermatitis during CRT developed a Lhermitte sign at six-month post-RT, suggesting hypersensitivity to the RT. We did not see any temporal lobe necrosis, carotid artery stenosis or cognitive disorders. For all these reasons surveillance for late side effects is crucial in the follow-up of NPC survivors.

The authors are aware of the weaknesses of this study. Its retrospective nature, the small size of the population and the short-term follow-up are important limitations. Nevertheless, we are convinced of its value generating hypotheses. The impact of mucositis and pre-therapeutic dental extraction on weight loss surprised us a lot and deserves to be examined in prospective study.

Conclusion

The epidemiological-clinical profile of NPC patients referred to our institution corresponds to that of endemic areas. Our therapeutic results and toxicities are comparable to the data from the literature. Improving distant control and prevention of side effects are key elements for future clinical trials. Careful dental evaluation and treatment before radiation therapy are crucial as tooth-loss directly relates to weight loss. Therefore, we recommend a dental practitioner with experience in HNC to be included in the HNC multidisciplinary team. Guidelines for prevention and management of pre-radiotherapy dental assessment have to be developed.

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