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Original research article

Improved long-term results of intensity-modulated radiotherapy for a non-endemic European nasopharyngeal carcinoma cohort: single-center retrospective study

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ABSTRACT

Purpose: Report our matured outcomes of European nasopharyngeal carcinoma (NPC) treatment from a non-endemic region in the IMRT era.
Methods: We reviewed 109 consecutive patients with biopsy proven NPC treated between 2009 and 2013. All received IMRT as per RTOG 0615. Toxicity was scored accordingly to CTCAE 4.03. Platinum-based chemotherapy was delivered following the Intergroup 0099.
Results: Median age of 53 years; 97% Caucasian; 74% male; 72% WHO grade III; 43% T1; 14% T2; 18% T3, 25% T4; 17% N0; 17% N1; 39% N2; 27% N3. Compliance to adjuvant chemotherapy was 88%. With a median follow up of 56 months, the 4-year local control was 90.2% (88.6% for T1; 100% for T2; 85% for T3; and 91.7% for T4), the 4-year distant metastases-free survival was 86% and an overall survival rate was 77%. Local control and survival were better in G3 ($p < 0.001$ and $p = 0.032$, respectively). Xerostomia was the most frequent late toxicity in 55% ($n = 60$). Hypothyroidism requiring hormonal reposition occurred in 15.5% ($n = 17$). From the 36 deaths, 20 were due to distant metastases, 3 grade 5 toxicity, 2 from local progression, 5 non-cancer deaths and unknown cause in the remaining 6. On multivariable analysis, age ($p = 0.017$), local recurrence and distant metastases were associated with death ($p < 0.001$, both).
Conclusion: Our matured data from the IMRT era showed a major improvement from our 3D cohort series reaching excellent local and regional control, even in T4. Local recurrences, despite few, and distant metastases were correlated with the risk of death.

1. Introduction

Nasopharyngeal carcinoma (NPC) is an enigmatic cancer that poses challenges to the scientific community.[1–4] Its etiology lies on an exquisite balance between EBV infection, environmental factors and host susceptibility. Despite its sensitivity to radiation and chemotherapy, distant metastasis is still a challenge and represents the main cause of death. Although 80% of cases occur in Asia, the remaining 20% are spread all over the world in non-endemic areas. According to the Globocan, Portugal has 1.4 cases per 100.000 habitants-year of NPC, one of the highest incidences in the European continent.[5] Our 3D conformal radiotherapy cohort (3DCRT) has already been published with an overall survival of 65.1%.[6] Thereafter, in 2009, we implemented IMRT for head and neck cancer and reported our preliminary results in NPC.[7] There is robust literature from Asian and North American NPC cohorts treated with intensity modulated radiation therapy (IMRT).[8–12] Since data on long-term outcomes of European non-endemic NPC are still scarce in the IMRT era,[13–18] we report our matured long-term results.

2. Methods

After approval from the Institutional Review Board and Ethics Committee, we retrieved clinic, image and laboratory data from 109

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consecutive patients with biopsy-proven non-recurrent nasopharyngeal carcinoma treated between February 2009 and December 2013.

2.1. Patient evaluation and staging

All patients were evaluated with complete medical history, physical examination with optic nasopharyngoscopy, computed tomography (CT) and/or magnetic resonance (MR) scans of the head and neck were performed as part of the pretreatment evaluation, unless there was a contraindication. Chest staging consisted of plain film radiograph or CT scan. Positron emission tomography (PET) scans were performed as part of the standard staging, except for Stage I and II, during the period. A pathological review of all cases according to the WHO classification was done for this manuscript. All patients were staged accordingly to AJCC/UICC 7th Edition, the current edition during the cohort era.

2.2. Treatment and follow up

Intensity-modulated radiotherapy (IMRT) was implemented in February 2009 and was delivered as per RTOG 0615, with a simultaneous-integrated boost of 69.96 Gy in 33 daily fractions to the primary and nodal GTVs, 59.4 Gy to the areas at risk and

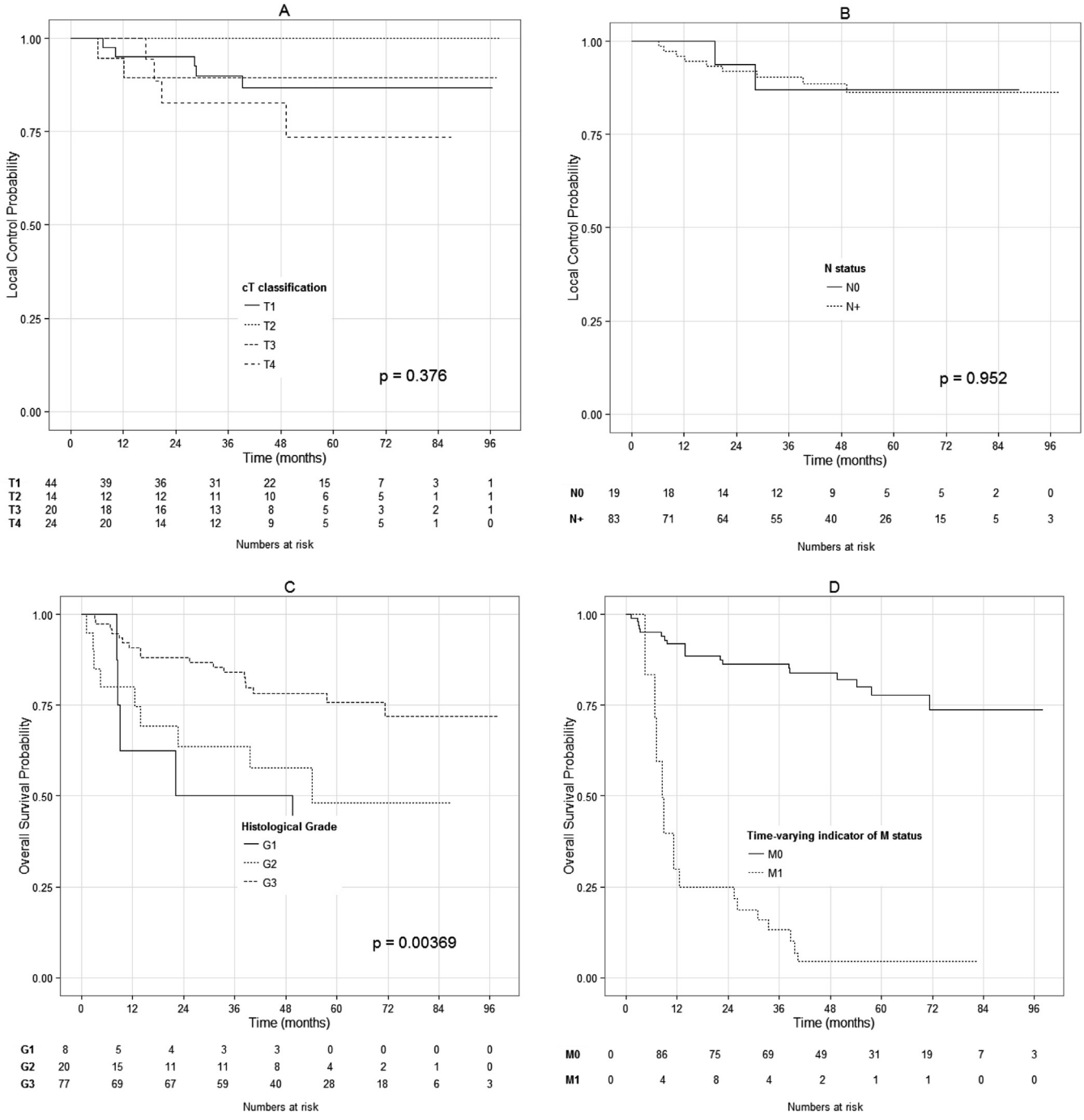

Fig. 1. a) Local control by T-Stage (p = 0.376); b) Regional control by N-Stage (N0 vs. N+, p = 0.952); c) Overall survival by pathology WHO grade (p = 0.003); d) Overall survival by metastases status (M0 vs. M1, p < 0.001).

involved neck levels and 54 Gy to the uninvolved lower neck.[19] Organs at risk were spared by RTOG 0615 recommendations until 2010. After that, QUANTEC tables were added whenever applicable.[20,21] A 5-mm PTV margin was used until 2011, and 4 mm thereafter since we performed a quantitative study of margins already documented.[22] Concurrent and adjuvant platinum-based chemotherapy was delivered according to the Intergroup 0099 trial fashion. Induction chemotherapy was performed for M1 patients and definitive radiation or chemoradiation was added in 3–6 cycles depending on response. Post treatment neck dissection was performed in the presence of worrisome clinical or imaging features. Patients were followed every 3 months with consults and routine blood tests including thyroid function, with ENT, Medical Oncology and Radiation Oncology for the first 2 years with endoscopy and MRI or CT image. Similar follow up was continued every 6 months until 5 years, and yearly thereafter. Toxicity was scored using CTCAE v. 4.03 whenever possible. Audiogram was not available for our patients, so ototoxicity was scored following CTCAE recommendations for non-enrolling patients in audio monitoring.

2.3. Statistical analysis

Endpoints comprised time to local, regional and distant recurrence and overall survival (all evaluated from the first day of treatment). These were calculated using the Kaplan-Meier method and log-rank test for group comparison. Cox regression was used for multivariable analysis to identify the variables independently associated with overall survival. The independent variables of interest defined a priori were age at diagnosis, T and N classification, histological grade and the time-dependent variables: local recurrence and distant metastasis (backward selection; exit criterion $p > 0.15$). All tests were two-sided and a significance value of 0.05 was considered (R version 3.1.2 http://www.R-project.org). Outcome data was calculated as per April 6th, 2018.

3. Results

Median follow up in surviving patients was 56 months with 77 patients reaching a minimum follow up time of 24 months. Almost 74% were male. WHO grade III was present in 73% of cases. Most patients were Caucasians (97%), with a few other ethnicities. Patients and tumor characteristics are displayed on Table 1.

The 4-year overall survival for the whole cohort was 77%. The 4-year local control was 88.5% (86.9% for T1; 100% for T2; 89.5% for T3; and 82.6% for T4). From 102 patients evaluable for local control, we found 11 local relapses: 5 on T1; 0 on T2; 2 on T3; and 4 on T4 patients. Seven out of 11 occurred before 2 years of follow up. All 11 local recurrences occurred within the PTV70Gy volume. There was no difference in local control regarding T stage ($p = 0.376$; Fig. 1a).

The 4-year regional control (neck) rate was 95% (100% for N0; 91% for N1; 94% for N2 and 96% for N3). Nodal failure occurred in 6 of the 102 patients: 1 on N1; 4 on N2; and 1 on N3 patients. Three out of 6 regional recurrences occurred less than 2 years after treatment. There was no difference in regional control regarding N-stage ($p = 0.434$) even after dichotomizing N0 versus N-positive groups ($p = 0.276$) (Fig. 1b). Only one patient shared both local and regional relapses.

Five patients (5%) had distant metastasis at diagnosis and were treated with both concurrent radical treatment to the primary site and metastatic disease. Fourteen patients had distant metastasis diagnosed during follow-up; of these 11 occurred within 2 years after treatment completion. The 4-year distant metastasis free survival was 79.8% and median time to distant metastasis was not reached.

Table 1
Patient, tumor and treatment characteristics (n = 109).

Variable		N (%)
Age, years	Median (range)	51 (12–89)
Gender	Male	81 (74%)
	Female	28 (26%)
Histological grade	I	9 (8%)
	II	20 (18%)
	III	79 (73%)
	Missing	1 (1%)
Clinical T Stage	T1	47 (43%)
	T2	15 (14%)
	T3	20 (18%)
	T4	27 (25%)
Clinical N Stage	N0	19 (17%)
	N1	19 (17%)
	N2	42 (39%)
	N3	29 (27%)
Clinical M Stage	M0	104 (95%)
	M1	5 (5%)
Stage	I	7 (6%)
	II	10 (9%)
	III	36 (33%)
	IVA	25 (23%)
	IVB	26 (24%)
	IVC	5 (5%)
BMI	20–25	40 (37%)
	< 20	3 (3%)
	25-30	22 (20%)
	>30	15 (14%)
	Missing	29 (27%)
ECOG performance status	0	81 (74%)
	1	23 (21%)
	2	2 (2%)
	3	2 (2%)
	4	1 (1%)
Ethnic Group	Caucasian	106 (97%)
	African	1 (1%)
	Asian	2 (2%)
Birth Place	Portugal (Europe)	105 (96%)
	Ukraine (Europe)	1 (01%)
	Macau Region,	1 (01%)
	China (Asia)	1 (01%)
	Angola (Africa)	1 (01%)
	Cabo Verde (Africa)	
Native Language (language spoke at home)	Portuguese	108 (99%)
	Russian	1 (01%)
Smoking habits	0 to ≤10	69 (63%)
	pack-year-units	38 (35%)
	>10	2 (2%)
	pack-year-units	
	Missing	
Treatment	RT	12 (11%)
	CCRT	28 (26%)
	CCRT + aCT	59 (54%)
	iCT + CCRT	1 (1%)
	iCT + RT	3 (3%)
	Missing	6 (6%)
Radiotherapy Technique	IMRT-SIB	103 (94%)
	3D	6 (6%)
Adjuvant Chemotherapy Compliance	3 Cycles	52 (88%)
	2 Cycles	4 (7%)
	1 Cycle	3 (5%)
Overall Treatment Time (CCRT)	< 49 days	65 (60%)
	> 49 days	41 (38%)
	Missing	3 (3%)
EBV EBNA & serum load pre treatment	Undetected	24 (22%)
	Detected	36 (33%)
	Missing	49 (45%)

IQR-Interquartile range; SD-standard deviation; BMI-body mass index; CCRT ± aCT-Concurrent chemoradiation ± adjuvant chemotherapy; RT - Radiotherapy alone; iCT ± CCRT-Induction chemotherapy ± concurrent chemoradiation.

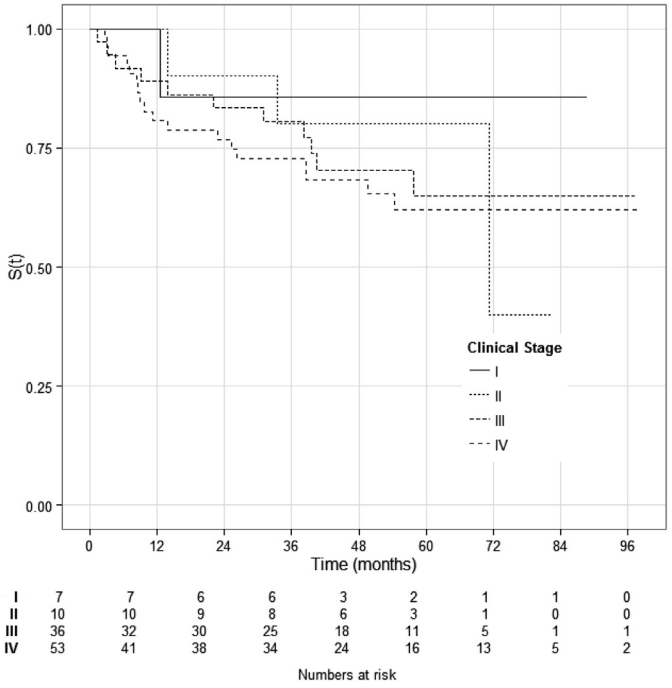

Fig. 2. Overall survival for the whole cohort by clinical stage at presentation (p = 0.753).

Table 2
Long-term toxicity profile.

	Grade ≤ 2 (%)	Grade 3–4 (%)
Hearing loss	–	9 (8%)
Xerostomia	60 (55%)	–
Hypothyroidism	17 (15.5%)	–
Peripheral Neuropathy	5 (4.5%)	–
Skull Base Radionecrosis	–	1 (1%)
Temporal Lobe Radionecrosis	1 (1%)	–
Renal	1 (1%)	–
Pituitary dysfunction	1(1%)	–
Any	85 (77%)	10 (9%)

Treatment outcomes stratified by T-, N-category, WHO pathological grade and metastases (M1) are presented on Fig. 1(a–d). Overall survival for the whole cohort by clinical stage at presentation is presented on Fig. 2.

Patients with WHO grade III had a significantly better local control and survival (p = 0.001 and p = 0.004 respectively, overall comparison).

Local relapses occurred within the PTV70Gy volume covered by the prescribed dose as per protocol. For that purpose, the authors matched a follow up MR scan with the initial planning CT with visual evaluation.

Regional control was 90% and N stage did not affect local or distant failure, even though 59 patients were N2 or N3 (66%).

From the 36 deaths, 20 were due to distant metastases, 3 to grade 5 toxicity, 2 from local progression, 5 were not cancer or treatment related. In 6 cases, the cause of death could not be determined.

Long-term toxicity profile is presented on Table 2. Xerostomia was the most frequent late toxicity 55% (n = 60), but no patient developed grade >2. Hypothyroidism requiring hormonal replacement occurred in 15.5% (n = 17) with no other clinical hormonal deficit in this cohort. With a mean cochlear dose of 49 Gy, grade 3 hearing loss or need of aid occurred in 8% (n = 9). Persistent peripheral neuropathy was seen in 4.5% (n = 5). One patient developed grade 2 renal toxicity, 1 had asymptomatic temporal lobe necrosis and another had skull base osteoradionecrosis requiring hyperbaric oxygen therapy, although none with re-irradiation.

Only 60 patients (55%) had documented EBV DNA and viral copy load and 36 (60%) of those with titles above the detection level (600 copies).

4. Discussion

NPC has a strong relation to ethnical groups and series usually report the percentage of patients from endemic areas. Arnold et al., reporting a higher incidence of non-keratinizing carcinoma in the Netherlands, concludes that this increase may be related to higher immigration from higher incidence areas.[15] Other series from non-endemic regions treated with IMRT have already been reported. Setton et al., who also published long-term results from the MSKCC (n = 177), had 31% of patients of Asian origin. Colaco et al. reported an UK-based NPC cohort treated with 2D and 3D conformal RT (n = 128 patients from 1992 to 2005). The series of Ruuskanen et al. recently published (n = 207 from 1990 to 2009) had 96% of patients originated from Finland. The Toronto data (n = 107) accounted for 81% of patients born in Asia. Our series has 96% of patients born in Portugal with very few other ethnicities.

The 4-year outcomes in the present report represent an improvement from our previous published data from the 3DCRT era[6] and are consistent with our preliminary reports.[5,6,23] Others have already documented the generational difference in outcomes with IMRT.[16]

D'Espiney Amaro series have reported a 5 year overall survival of 65.1% in 2009 using 3DCRT, while the present study shows an overall survival of 77% for all stages (Fig. 2). This cannot be attributed solely to the technique, since the previous data included a large number of patients (80%, n = 117) treated with neoadjuvant chemotherapy followed by radiotherapy with or without chemotherapy.[6] At the present series, 80% of patients received concurrent chemoradiation and 54% required adjuvant chemotherapy as per Intergroup 0099. Induction chemotherapy was used only for 4 patients.

Among 109 patients, we observed similar 4-year actuarial local or regional control rates of 90%, almost the same as the 2-year rate previously reported by our group in a preliminary abstract. By 2015, after a median follow up of 22 months, 2-year local control was 95.9%, regional control 98%, freedom from distant metastases 88% and overall survival 79.8%.[7]

The present series show distant metastases-free survival of 86% and an overall survival rate of 77% for all stages similar to other series with IMRT.[24–27]

Others have reported a poorer local control rate for T4 patients.[28] In fact, we found no statistical difference in local control between T1 to T4 (Fig. 1a) or any stratified comparison of T4 vs. other T stage. Xue et al. reported a series of 41 T4 patients effectively treated with induction chemotherapy and IMRT even with dosimetric inadequacies.[29]

In our cohort, local relapses occurred within the PTV70 volume covered by the prescribed dose as per protocol. Among these 11 local relapses, 5 (50%) were previous T1 patients, 0 on T2, 2 on T3 and 4 on T4 stages. From these, 8 were successfully salvaged either with fractionated stereotactic re-irradiation or radiosurgery as described in the literature.[30]

Regional control was also excellent (90%). In fact, N stage did not affect local or distant failure, even considering that more than half (n = 59) of our cohort was N2 or N3 (66%) and it is similar to what has already been described by others.[28]

WHO grade III patients (73%) experienced a much more favorable prognosis with significantly higher local control and survival

Table 3
Variables independently associated with overall survival (multivariable Cox regression analysis).

	Hazard Ratio (HR)	95% Confidence Interval	p-value
Local recurrence[a] Yes vs. No	7.52	2.64 – 21.45	<0.001
Distant metastasis[a] Yes vs. No	32.99	12.95 – 84.08	<0.001
N status at diagnosis N + vs. N0	3.03	0.69 – 13.27	0.141
Age at diagnosis Per additional year	1.08	1.04 – 1.11	<0.001

[a] time-dependent variables.

(p = 0.000 and p = 0.032, respectively, Fig. 1c) as well as in other Eastern and Western series.[2,8,10]

Surgery was indicated for persistent neck enlarged nodes after treatment or clinical/imaging worrisome features (i.e. unhealed neck ulcer on tumor site) in 13 patients. With median number of 13 nodes dissected (range 5–32), only 1 patient had persistent metastatic disease after combined modality. This patient was planned to receive adjuvant CT but indication was withdrawn due to toxicity. All others had fibrosis and post treatment findings in nodes up to 4 cm. As in other head and neck sites, before 2016, PET-CT was not used to select patients for neck dissection.[31]

Five patients with stage IVC (AJCC/UICC 7th Edition) were included in this analysis since they received concurrent chemoradiation as part of the initial approach. Data from Asian and Western cohorts have already been published confirming that intensive treatment incorporating concurrent chemoradiation yields superior results.[16,32,33,34]

From the 36 deaths, 20 were due to distant metastases confirming this feature as the most important cause of death in agreement with other Eastern and Western reports.[2,3,9–11]

On multivariable Cox regression analysis (Table 3) distant metastases had the greatest impact on overall survival (p < 0.001; HR = 32.99; 95% CI 12.95-84.08). Nevertheless, even though salvage reirradiation has been able to successfully rescue 8 out of 11 local relapses, local recurrence was also correlated with increased risk of death (p < 0.001; HR 7.52; 95%CI 2.64–21.45). When analyzed as a single variable, nodal involvement was not predictive of regional or distant relapse nor was it associated with death (p = 0.141; HR 3.03; 95%CI 0.69–13.27). No other factor (PS, overall treatment time, ethnicity or smoking habits) had an impact on outcomes.

Treatment with radiation alone was an option for patients with severe comorbidities or frail elderly patients (n = 12). CCRT with or without adjuvant CT was the standard treatment for the majority of patients. N-stage was the most frequent reason for this strategy since N2 or N3 patients accounted for 66% (n = 71) of all patients. Although controversial, adjuvant chemotherapy was performed with 3 cycles in 52 patients and a high compliance with 88% of patients receiving 3 adjuvant cycles. Only 7 (12%) patients who had planned adjuvant CT did not receive it due to toxicity, a percentage equal or superior to other series.[8,16] Induction chemotherapy was used instead of upfront CCRT in only 4 patients due to problematic RT planning, immediate treatment (e.g. bleeding) or initial M1 disease. Since 80% of our patients were uniformly treated with CCRT, it is not possible to compare results with a residual percentage of patients that received induction CT.

Our acute toxicity profile have already been presented.[35] Late toxicity is displayed in Table 2. Xerostomia was the most frequent late toxicity. Our results are comparable with other published data confirming dry mouth as the most frequent late complication from treatment.[8–10,17,25]

Thyroid function was accessed during routine analysis on follow up. Hypothyroidism requiring hormonal replacement (grade 2) was present in 17 patients (15.5%). This is lower than expected, considering the recent extensive data published by McDowel et al. with 69% patients having hypothyroidism.[8] Nevertheless, a large number of their patients had hypothyroidism as a precondition. In our series, long-term hormonal reposition need was lower, specially taking into account that all patients received lower neck irradiation and thyroid (as an OAR) was not optimized at planning on this cohort between 2009 and 2013. Only one other survivor has pituitary dysfunction requiring medication. Since thyroid function is the only hormonal deficit regularly accessed during follow-up, other subclinical deficits may have been underdiagnosed. Two patients developed radiation necrosis, one asymptomatic temporal lobe necrosis and another skull base necrosis requiring hyperbaric oxygen therapy.

Audiogram was not available for our patients prior to treatment, so hearing was accessed by CTCAE v. 4.03 recommendations without enrolling in a monitoring program. With a median cochlear dose of 49 Gy for the whole cohort, 9 patients (8%) developed hearing impairment requiring aid devices (at least grade 3). This is lower than other series reporting the need for hearing aid of up to 70%[21] and approaches data from series that report less than 10% grade 3 hearing impairment.[36] The MSKCC group have already reported lower toxicity with an average cochlear dose of 43 Gy with more than one fashion of boost prescription.[36] However, enrolling patients in audio monitoring is an important follow up tool to detect early hearing impairment that was underestimated in our series and may long affect patients' quality of life.

This report has several important limitations such as its retrospective single-centered nature. Proper serum EBV EBNA and viral copy loads data before and/or after treatment was not available in nearly half of the patients which prevents us to draw conclusions and comparisons to other endemic and non-endemic cohorts. The authors decided to keep the initial staging according to the AJCC UICC 7th edition since all patients were staged and treated between 2009 and 2013.

In conclusion, we present the largest matured data from a Portuguese-based cohort confirming excellent loco regional control, regardless of T-Stage, in the IMRT era. It represents a major improvement from our previous 3DCRT cohort, especially considering that local recurrence was also correlated with the risk of death. As in endemic and other non-endemic cohorts, distant metastases are a challenge and desperately need more investigation.

Conflict of interest

None.

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None.

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