

ORIGINAL ARTICLE

3D conformal radiotherapy in primary nasopharyngeal cancer: effectiveness and prognostic factors

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Summary

Purpose: To assess the efficacy and safety of using 3D conformal radiation therapy (3DCRT) to treat nasopharyngeal cancer (NPC) in a Caucasian cohort and evaluate factors with prognostic value.

Methods: Between September 2001 and November 2012, 44 NPC patients with a mean age of 57 years underwent 3DCRT at the University Hospital of Ioannina. Nineteen patients (43%) presented with WHO type 1 and 2 histology. Thirty two patients (73%) had advanced-stage disease (stage III/IV). Thirty-one patients (70%) received chemotherapy. The mean total radiotherapy dose prescribed to the planning target volume (PTV) was 67.2 Gy. The daily dose was 1.8 Gy.

Results: With a median follow up of 43 months (range 8.4-125), the 4-year local relapse-free (LRFS), nodal relapse-free (NRFS), distant metastases-free survival (DMFS), disease-free survival (DFS) and overall survival

(OS) were 90, 87, 91, 80 and 82%, respectively. Histology was a significant prognostic factor concerning overall survival, with worst prognosis in patients with WHO type 1/2 compared to type 3. Age <70 years, absence of retropharyngeal lymph node metastasis, complete response after treatment and the completion of ≥ 4 cycles of concurrent weekly cisplatin favored overall survival. Fifteen patients (34%) developed grade 3 late side effects (xerostomia: 6, soft tissue fibrosis: 6, hearing loss: 2, brachial plexus neuralgia: 1).

Conclusion: 3DCRT in our Caucasian cohort, characterized by predominantly advanced-stage disease, combined with chemotherapy, is an effective treatment modality approach in patients with NPC with excellent tolerance.

Key words: 3D-conformal radiotherapy, nasopharyngeal carcinoma, prognostic factors

Introduction

NPC is a rare disease among Caucasians [1]. Radiotherapy (RT) is considered the first choice and main treatment method for newly diagnosed and nonmetastatic NPC. In recent randomized trials, chemoradiotherapy has shown significant survival benefits over radiotherapy alone, improving both local and distant control, and overall survival [2-5].

Various prognostic factors have been considered to influence survival in NPC, like WHO histology type, with favorable prognosis in undifferentiated WHO type 3 [6,7]. It is also considered

that patients of Asian origin have improved survival when compared to non-Asians [8, 9].

The aim of this retrospective study was to assess the outcome and toxicity profile of 3DCRT with chemotherapy in our Caucasian patients with predominantly advanced-stage disease and to evaluate factors with prognostic value.

Methods

Study population, disease and staging characteristics

Between September 2001 and November 2012, 44

NPC patients underwent definitive 3DRT in our Department. The disease was staged according to the 2002 American Joint Committee on Cancer (AJCC) staging classification [10].

Pretreatment evaluation included a complete history and physical examination, direct flexible fiberoptic endoscopy, magnetic resonance imaging (MRI) scans of the nasopharynx, skull base and neck, chest computed tomography (CT) or X-ray, laboratory studies and dental evaluation. Bone scans and CT scans of the abdomen were obtained when clinically indicated.

Treatment characteristics

Radiation therapy

Patients were immobilized from head to shoulders with commercially available thermoplastic masks. CT images (4mm slice thickness) were acquired from the level of the anterior clinoids down to the level of the carina parallel to the orbitomeatal line.

The target volumes were drawn on each axial planning CT slice, based on diagnostic CT images, supplemented with fused diagnostic MRI and/or PET-CT scans. The treatment volume was determined on the basis of the extent of disease at presentation and was not influenced by the response to chemotherapy.

The patients were treated by a linear accelerator (6MV) with two lateral opposed fields to irradiate the nasopharynx and upper neck, followed by the shrinking-field technique with multiple beam arrangements to limit the dose to the spinal cord. An anterior field was used to treat the lower neck and supraclavicular fossae. The prescribed dose delivered to the PTV of the primary disease was 70.2 Gy (1.8 Gy/fraction) in 18 and 66.6Gy (1.8 Gy/fraction) in 26 patients. The prescribed dose encompassed at least 95% of the PTV. No more than 20% of any PTV would receive >110% of its prescribed dose, while no more than 1% of any PTV would receive <93% of the desired dose.

The high risk and the low risk lymph node areas received 60 Gy and 45 Gy respectively, while the supraclavicular fossae received 45-50.4Gy. The mean total treatment time was 50.7 days (range 37-65).

Organs at risk were outlined in three dimensions with an estimated planning organ at risk volume (PRV)-margin of 2-10mm. The maximum spinal cord dose was 45 Gy; the maximum brainstem and optic chiasm dose was 54 Gy.

Chemotherapy

Twenty-six patients (59%) received 2-3 cycles of neoadjuvant chemotherapy with cisplatin (100mg/m² i.v, day 1) and 5-fluorouracil (1000mg/m² continuous infusion, days 1-4), every 4 weeks (modified Head and Neck Intergroup protocol 0099) [2]. Twenty-eight patients (64%) received cisplatin (40mg/m² i.v weekly), concurrently with RT. Nineteen of these patients (68%) completed 5-7 chemotherapy cycles. Thirty-one out of

44 patients (70%) received chemotherapy (neoadjuvant and concurrent chemotherapy, N=23; concurrent chemotherapy only, N=5; neoadjuvant chemotherapy only, N=3).

Follow up

Posttreatment patient assessment included physical examination with additional fiberoptic nasopharyngoscopy at our Department approximately every 3 months in the first and second year of follow up, every 6 months in the third to fifth year, and annually thereafter. A baseline MRI scan of the nasopharynx and neck was obtained within 6 months and then yearly or when clinically indicated. Suspected findings were clarified with PET-CT.

Normal tissue effects were graded according to the Radiation Therapy Oncology Group (RTOG)/ European Organization for Research and Treatment of Cancer (EORTC) radiation morbidity scoring criteria [11].

Statistics

Statistical calculations were performed using StatView® program (Abacus Concepts Inc., CA). p values ≤0.05 were considered statistically significant. LRFS, NRFS, DMFS, OS and DFS curves were constructed using the Kaplan-Meier method and compared with log-rank test. To assess the effect of prognostic factors univariate Cox proportional hazards method was performed.

Results

Treatment outcome and patterns of failure

Analysis was based on follow up data available as of May 2014. At a median follow up time of 43 months (range 8.4-125), 7 (16%) patients developed local failure. In 7 (16%) patients regional nodal failure was observed, and in 6 (14%) patients distant metastases developed. The actuarial 4-year LRFS, NRFS, DMFS, DFS and OS rates were 90, 87 91, 80 and 82%, respectively (Figure 1).

Patient, disease and staging characteristics

Patient and disease characteristics are listed in Table 1, while TN staging results are outlined in Table 2.

Prognostic factors

Univariate analysis was performed to examine the impact of various prognostic factors. Histology was a significant prognostic factor concerning OS, with worst prognosis in patients with WHO type 1/2 compared to type 3 (median survival 25.6 vs 56.2 months) (p=0.011). Patients

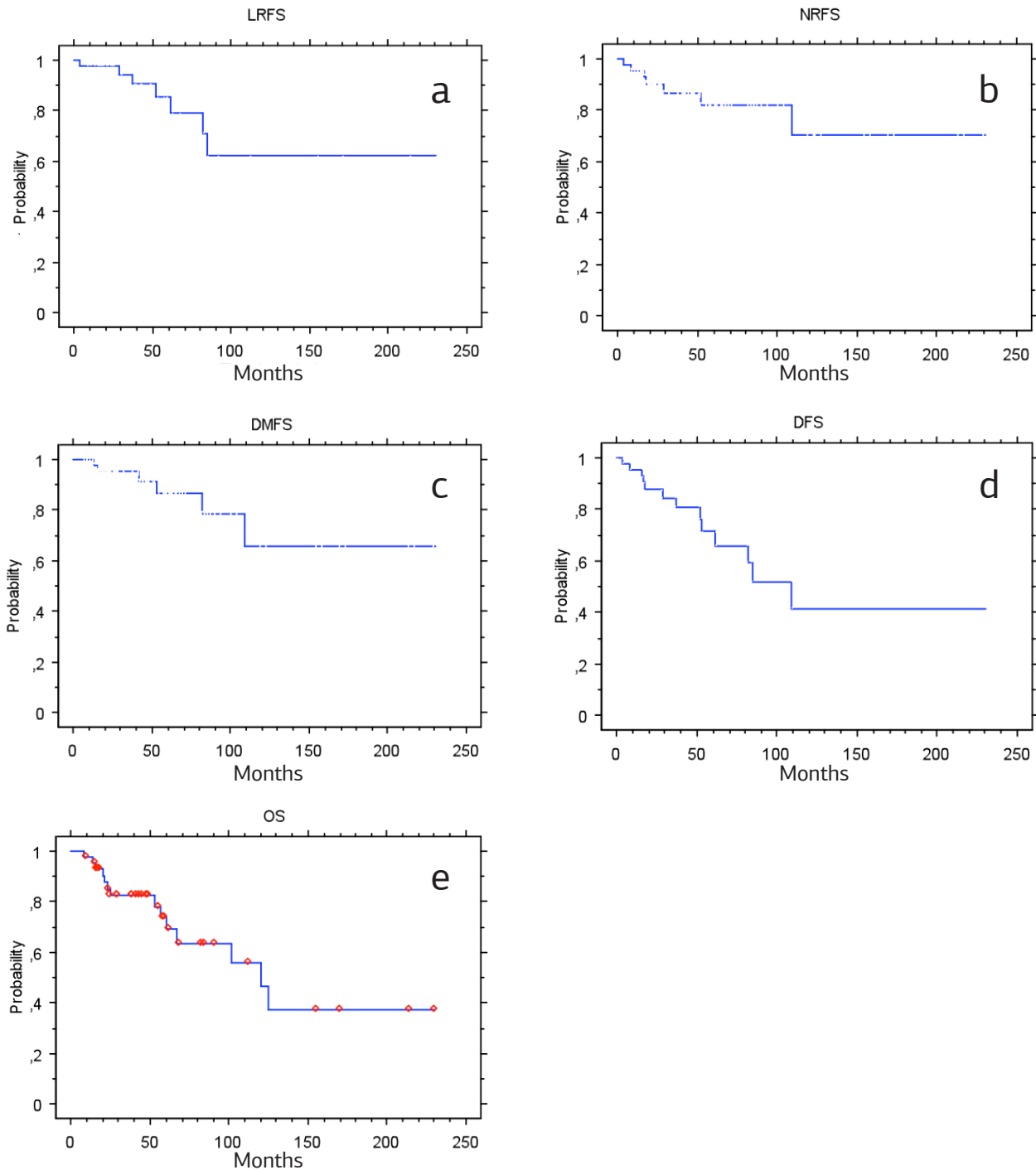


Figure 1. Kaplan-Meier estimates of actuarial 4-year. **a)** Local relapse free survival (LRFS); **b)** Nodal relapse free survival (NRFS); **c)** Distant metastasis free survival (DMFS); **d)** Disease free survival (DFS); **e)** Overall survival (OS).

aged >70 years had worse prognosis regarding OS ($p=0.04$) and DFS ($p=0.05$).

The presence of retropharyngeal lymph nodes metastasis (RLN) was a significant prognostic factor with worse OS ($p=0.04$) and DMFS ($p=0.016$). The incidence of RLN metastasis in this study was 43%.

After completion of chemoradiation, 22 (50%)

patients were in complete remission (CR), on the basis of clinical evaluation and MRI/CT examination. CR favored OS ($p=0.003$) and DFS ($p=0.01$)

The addition of neoadjuvant chemotherapy did not confer any statistically significant benefit regarding OS. The completion of ≥ 4 cycles of concurrent weekly cisplatin favored OS ($p=0.023$) (Figure 2).

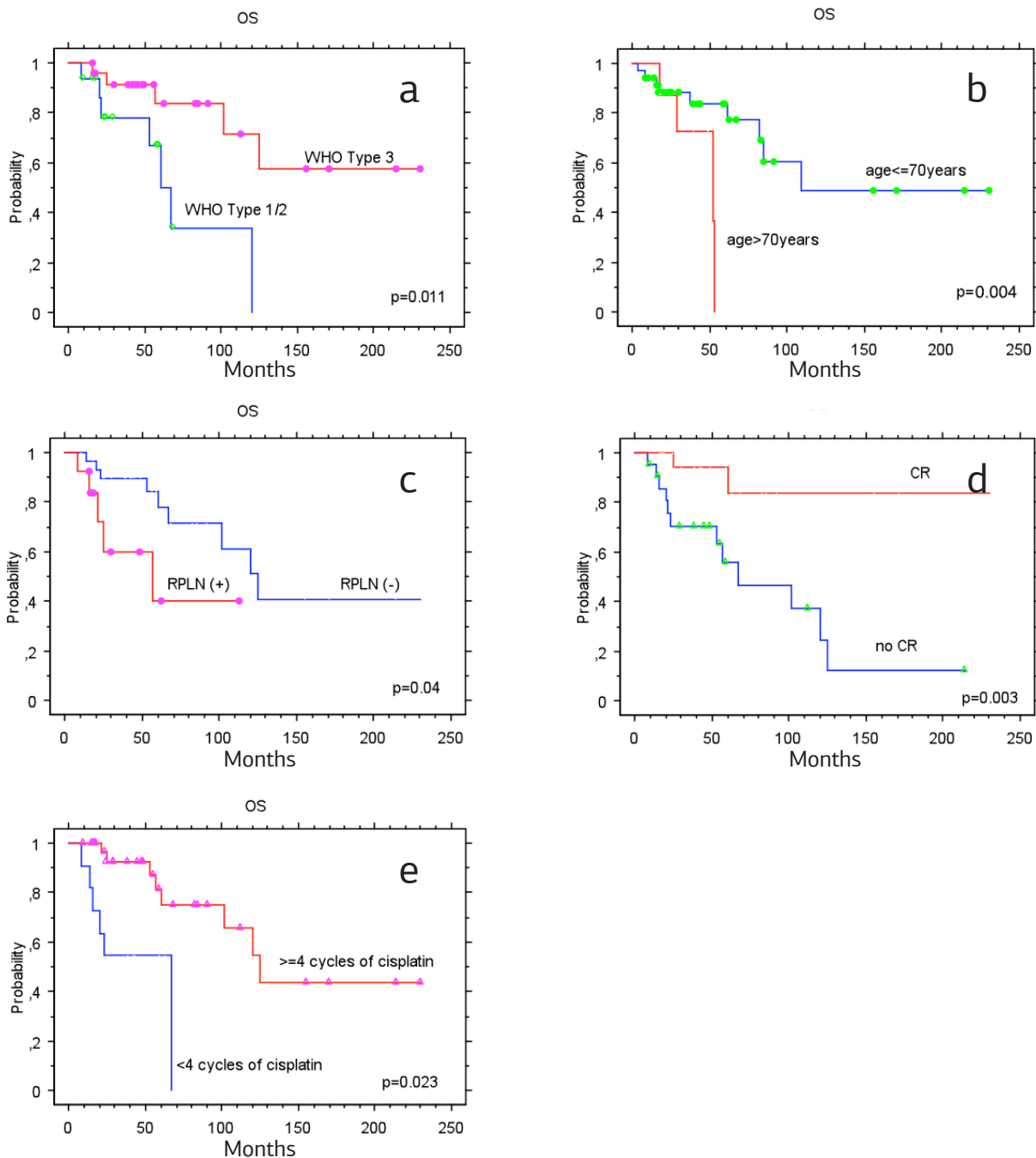


Figure 2. Overall survival (OS) of patients by (a) histology WHO type, (b) age, (c) presence of retropharyngeal lymph nodes, (d) complete response (CR), and (e) completion of ≥ 4 cycles of concurrent cisplatin-based chemotherapy.

Toxicity

Acute grade 3/4 myelotoxicity was observed in 3 (7%) patients, with one patient experiencing febrile neutropenia. Acute grade 3 mucositis was observed in 7 (16%) patients, while 4 patients (9%) experienced grade 3/4 skin toxicity. One patient with T2N1 disease showed cognitive disorders and aphasic symptoms during chemoradiation, without any proof of skull base involvement or liver metastasis.

No grade 4 late toxicity was observed. The most common late effect was xerostomia. At the 12-month postirradiation follow-up, grade 3 xerostomia was noticed in 10 patients (23%), a symptom that insisted in 6 patients (14%).

Six patients (14%) developed soft tissue fibrosis, while 2 patients (5%) presented with subcutaneous submental tissue edema. Two patients experienced grade 3 hearing loss; one of them had received 3 cycles of neoadjuvant cisplatin-con-

Table 1. Patient and disease characteristics

Characteristics	No of cases	%
Age, years, median (range)	57 (38-80)	
Gender (male: female)	31:15	70:30
Ethnicity (Caucasian: Asian)	44:0	100:0
WHO/ECOG PS		
0	31	70
1	13	30
WHO histology		
Type 1/2	19	43
Type 3	25	57
Grade		
G1	2	5
G2	10	23
G3	32	72
Stage III/IV	32	73
T3/4	25	52

WHO: World Health Organization, ECOG: Eastern Cooperative Oncology Group, PS: performance status

taining chemotherapy and concurrent chemoradiation. These patients had no clinically apparent hearing impairment before treatment, although baseline audiometry was not performed. One patient presented with brachial plexus neuralgia at the 18-month clinical evaluation, which resolved partially 6 months later.

In summary, persistent grade 3 late effects were observed in 15 (34%) patients. There were no cases of temporal lobe necrosis, clinical optic neuropathy, or clinical hypopituitarism.

Discussion

NPC is a highly chemo and radiosensitive tumor, and excellent disease control can be achieved using combined chemoradiation even in patients with locoregionally advanced disease [4]. In our study, the locoregional control as well as DFS and OS rates were in the range of NPC-3DCRT series published so far, describing similar results, despite the fact that our cohort included only patients of Caucasian origin (100%), with a relatively great proportion of patients with stage IV disease (74%).

The acute and late toxicity using 3DCRT combined with concurrent chemotherapy was acceptable. No grade 4 late adverse effects were observed. Xerostomia was the main documented late toxicity. As it has been estimated that parotid tolerance is likely a stepwise function [12], dose reduction at any dose level may improve the prob-

Table 2. TN stage distribution in all 44 patients

	N0	N1	N2	N3	Total
T1	0	0	1	0	1
T2	5	8	6	1	20
T3	7	3	0	0	10
T4	9	2	2	0	13
Total	21	13	9	1	44

ability of parotid function, which may better be achieved with intensity modulated radiotherapy (IMRT). Considering the favorable tolerance profile in our patient cohort, a careful dose increase may be possible, beside of other theoretical ways to biologically increase effectiveness [13].

NPC has a high propensity of cervical lymph node metastasis, which appears to occur in an orderly fashion with a rare incidence of skip metastasis, ranging from 0.5 to 7.9% [14]. The retropharyngeal lymph nodes and cervical level II lymph nodes have been reported to be the most commonly involved nodal regions [15-17].

Our study confirmed the reported results from other studies [16,18], demonstrating that the presence of retropharyngeal lymph nodes metastasis is a significant prognostic factor concerning OS and DMFS.

According to our results, complete response after chemoradiation was a prognostic factor concerning DFS and OS rates. This could imply the significance of close disease monitoring, aiming to achieve complete response [19,20]. Hence, if the therapeutic effect can be predicted at the early course of the treatment, it is possible either to modify the therapeutic strategies for the remaining treatment or add novel therapeutic alternatives for patients likely to be resistant to conventional treatment.

Regardless of the advances in radiation therapy technique, adding chemotherapy has been a major step towards improved survival in NPC as shown by randomized trials and meta-analyses [2-5,21,22]. Our study confirmed the role of concurrent chemotherapy, with statistical significance regarding OS in patients completing ≥ 4 cycles of weekly cisplatin, while induction chemotherapy failed to statistically benefit the patients. This would suggest the importance of meticulous care of the patients, in order to complete at least 4 cycles of concurrent chemotherapy.

In our cohort, histology was confirmed to be a significant prognostic factor with better prognosis in patients with WHO type 3 disease [6].

Patients aged >70 years showed inferior survival, which could arise concerns in older patients, as the combination with performance status and comorbidities could lead to a substantial impact on morbidity [23].

It seems that the prescribed doses were considered adequate for cases with T1-T2 tumors, given that there was no local recurrence observed in these patients [24]. Higher doses may be required for locally advanced disease, as it has been shown in a radiation dose escalation study for patients with T3-T4 disease with promising locoregional control and survival rates [25].

Patients included in this retrospective analysis received 3DCRT. This treatment modality has the potential of tailoring the isodose surfaces to the shape of the PTV. Of note, IMRT can improve

dose conformity for complex tumor targets and is able to obtain a better protection of adjacent organs [26,27]. IMRT also offers the opportunity to increase the fractionation dose inside the boost area using an integrated boost concept, while keeping the single dose below 2 Gy in most organs at risk at the same time [26,28]. It is likely that IMRT will become the standard technique employed for nasopharyngeal tumors.

In conclusion, our study confirms that chemoradiotherapy in our non-Asian NPC patients presenting with predominantly advanced-stage disease, represents the standard treatment. 3DCRT with neoadjuvant/concurrent platin-based chemotherapy resulted in encouraging rates of local and distant disease control, DFS and OS with very satisfactory treatment tolerance.

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