Cerrahpaşa Med J 2023; 47(2): 150-155 ORIGINAL ARTICLE

The Evaluation of Nodal Tumor Volume in Nasopharyngeal Carcinoma

Halil Cumhur Yıldırım, Sevda Kanat, Emine Sedef Akovalı, Meltem Dağdelen, Songül Çavdar Karaçam, Ömer Uzel

Department of Radiation Oncology, İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, İstanbul, Turkey

Cite this article as: Yıldırım HC, Kanat S, Akovalı ES, Dağdelen M, Çavdar Karaçam S, Uzel Ö. The role of nodal tumor volume in nasopharyngeal carcinoma. *Cerrahpaşa Med J.* 2023;47(2):150-155.

Abstract

Objective: The aim of this study is to evaluate the value of nodal tumor volume in predicting distant metastasis in nasopharyngeal carcinoma and to investigate the feasibility of nodal tumor volume-guided patient selection for induction chemotherapy.

Methods: Eighty-eight patients with nasopharyngeal carcinoma treated with intensity-modulated radiotherapy ± chemotherapy between 2010 and 2016 were reviewed. Nodal tumor volume was calculated in radiotherapy planning computed tomography fused with the initial magnetic resonance imaging and positron emission tomography and computed tomography. Survival analysis was made by the Kaplan–Meier method.

Results: Median follow-up time for surviving patients was 76 months. Sixteen (18.2%) patients developed distant metastasis. Nine (10.2%) patients developed locoregional recurrence. Five-year overall survival, locoregional recurrence-free survival, and metastasis-free survival rates were 71.5%, 87%, and 79.4%, respectively. In multivariate analysis, nodal tumor volume > 45 cc [hazard ratio: 7.160 (95% CI: 2.560-20.024), $P < .001$] and advanced T stage [hazard ratio: 3.419 (95% CI: 1.238-9.442), $P = .018$] were found as predictive parameters for metastasis-free survival, whereas only age ≥50 [hazard ratio: 2.939 (95% CI: 1.182-7.308), $P = .020$] was found to be a negative independent factor of overall survival.

Conclusion: Nodal tumor burden has a predictive role for distant metastasis in nasopharyngeal carcinoma. Patients with nodal tumor volume > 45 cc have worse metastasis-free survival than patients with nodal tumor volume ≤ 45 cc. Consideration of nodal tumor volume may increase the accuracy of patient selection to escalate systemic therapy.

Keywords: Nasopharyngeal carcinoma, intensity modulated radiotherapy , nodal tumor volume, induction chemotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma of the nasopharynx, which is particularly common in Southeast Asia.[1] It differs from other head and neck cancers in terms of etiology, lymphatic involvement, prognosis, and treatment. Radiotherapy (RT) is the curative choice of the disease due to its high radiosensitivity and localization. While RT is applied alone in early stages, concurrent ± neoadjuvant/adjuvant chemotherapy (AC) is added in advanced stages.

In last decades, with the advances in radiation technology and integration of chemotherapy, locoregional control rates have exceeded 90% for most patients. In consequence, overall survival (OS) rates have now increased from 50%-60% to 80%-90%. However, distant metastasis remains the main failure pattern of NPC up to 30%.[2] Recently, the common issue in NPC treatment is to estimate the risk of distant metastasis and to intensify the systemic therapy in high-risk patients. The addition of concomitant and AC to RT has shown to improve locoregional and distant disease control rates in the landmark Intergroup-0099 Study.[3] However, the timing and type of chemotherapy have been questioned. The evaluation of chemotherapy from adjuvant to more tolerant neoadjuvant, and the combination of more potent agents were investigated. In recent years, induction chemotherapy (IC) has gained popularity with encouraging results reported in phase 3 randomized trials.[4-6] Induction chemotherapy is considered to be more advantageous due to earlier elimination of microscopic metastasis and allowing better RT dose coverage near critical neural tissues by shrinkage of the tumor. However, it is obvious that additional chemotherapy will bring more toxicity, and appropriate patient selection is of the utmost importance to intensify treatments.

Nasopharynx has a broad submucosal lymphatic chain. At presentation, ipsilateral neck nodes are involved in 85% to 90% of patients and bilateral neck nodes are involved in approximately 50% of patients.[7] Studies have shown that advanced N stage is a predictor of distant metastasis.[8] Recent Tumor-node-metastasis (TNM) classification uses a combination of size, laterality, and location to assess nodal tumor staging. Nevertheless, it does not account for clustered/multiple lymph nodes, which is not rare in NPC. The contribution of nodal tumor burden to N staging may have an additional value on prognosis.

The aim of this study is to explore the role of the nodal tumor volume (NTV) in predicting distant metastasis in NPC and to investigate the feasibility of NTV-guided patient selection for IC.

Methods

Patient Characteristics

We retrospectively reviewed the medical records of patients treated with intensity-modulated radiotherapy

Received: May 4, 2022 **Accepted:** November 16, 2022
Publication Date: August 22, 2023
Corresponding author: Halil Cumhur Yıldırım, Department of Radiation Oncology, İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, İstanbul, Turkey
e-mail: halilcumhur.yildirim@iuc.edu.tr
DOI: 10.5152/cjm.2023.22030

(IMRT) ± chemotherapy for NPC between 2010 and 2016. There were 88 patients available for analyses. The patients' characteristics are given in Table 1. The study was approved by the local ethics committee of the İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Date: March 4, 2020, Number: 37452).

Staging

All patients were evaluated with physical and endoscopic examination. Biochemical and hematological blood tests, magnetic resonance imaging (MRI), and 18F-fluorodeoxyglucose positron emission tomography and computed tomography (PET-CT) were performed before treatment. The patients were restaged according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.

Table 1. Clinical Characteristics of Patients

Characteristics	Number of Patients (%)
Age, median 48 (range15-79)	
<50	47 (53.4)
≥50	41 (46.6)
Gender	
Male	67 (76.1)
Female	21 (23.9)
Histology	
WHO 1	1 (1.1)
WHO 2	87 (98.9)
T stage	
1	29 (33.0)
2	30 (34.1)
3	8 (9.1)
4	21 (23.9)
N stage	
0	19 (21.6)
1	17 (19.3)
2	31 (35.2)
3	21 (23.9)
Clinical stage	
1-2	21 (23.9)
3-4	67 (76.1)
Treatment type	
RT	14 (15.9)
CCRT	49 (55.7)
IC+RT	3 (3.4)
IC+CCRT	22 (25.0)

CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; RT, radiotherapy; WHO, World Health Organization.

Treatment

Patients were treated according to stage, patient performance status, and physician preference. In general, early-stage patients received RT only and advance-stage patients received concurrent chemoradiotherapy (CCRT). Induction chemotherapy was added in bulky tumors.

Radiotherapy

All patients were immobilized using a thermoplastic head and shoulder mask in a supine position. Computed tomography simulation was performed for all patients with a 2.5 mm slice thickness from top of the head to bifurcation of carina. Both PET-CT and MRI were co-registered and fused with RT planning CT. Gross tumor volume of the primary tumor and involved lymph nodes (GTVp and GTVnd) were delineated according to clinical and radiological (mainly MRI) findings. Clinical tumor volume of the primary tumor and involved lymph nodes (CTVp and CTVnd) were defined as added 5-10 mm to GTVp and GTVnd. High-risk regions were generated with a 5-10 mm margin to CTVp and CTVnd and encompass the entire nasopharyngeal mucosa and whole involved nodal levels. Intermediate-risk regions included parapharyngeal space, pterygoid fossae, retrostyloid space, skull base, posterior third of nasal cavity and maxillary sinuses, anterior half of clivus (entire clivus, if involved), and inferior sphenoid sinus (entire sphenoid sinus and cavernous sinus for advanced T stages). The CTV (lymphatic) includes the retropharyngeal nodal regions, levels 2, 3, 4, 5 and 1B (if level 2 is involved) in bilateral nevk sites for NPC. The prescribed doses for CTVp and CTVnd were 66-70 Gy (2-2.12 Gy/fraction), for high-risk regions the doses were 60 Gy (1.81-2 Gy/fraction), and for intermediate-risk regions and elective lymph nodes, the doses were 54 Gy (1.63-2 Gy/fraction). Radiotherapy plans were made with IMRT in 40 patients (45.5%) and with volumetric modulated arc therapy (VMAT) in 48 (54.5%) patients. Intensity-modulated radiotherapy plans and VMAT plans were optimized on the Eclipse treatment planning system using 6MV from a RapidArc linear accelerator (Varian Medical Systems, Palo Alto, Calif, USA).

Chemotherapy

Induction chemotherapy consisting of platin (75 mg/m^2), docetaxel (75 mg/m^2), and fluorouracil (750 mg/m^2/day/1-5 days) was delivered every 3 weeks for 3 cycles for 23 patients and 2 cycles for 2 patients. For the patients treated with CCRT, 33 had 3 cycles, 25 had 2 cycles, and 1 had 1 cycle of cisplatin 100 mg/m^2. One patient had 1 cycle and 7 patients had 2 cycles of cisplatin 75 mg/m^2. Two patients had low-dose weekly cisplatin (40 mg/m^2).

Follow-Up

All patients were reevaluated with MRI at 1.5-2 months and with PET-CT at 3-4 months after completion of RT. Eighty-three (94.3%) of them had complete responses and 5 (5.7%) had partial responses. For the first 2 years, the patients were followed up every 3 months and every 6 months thereafter. Follow-up visits include complete physical and fiber-optic head and neck examination and biochemical and hematological blood tests. Nasopharyngeal/neck MRI was performed every 6 months. Chest x-ray was performed in every year.

Nodal Tumor Volume Measurement

Nodal tumor volume was calculated retrospectively with initial MRI and PET-CT guidance in the RT planning CT. Two radiation

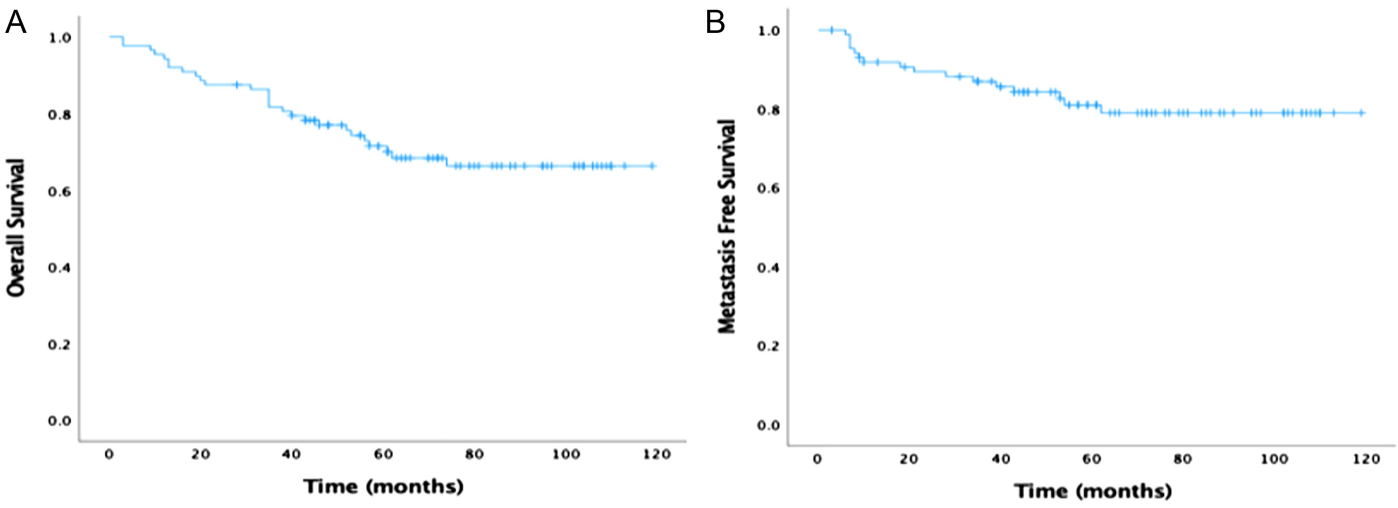

Figure 1. (A) Overall survival curve. (B) Metastasis-free survival curve.

oncologists reviewed the delineation of GTVnd and calculated the total nodal tumor burden. Retropharyngeal nodes were also included in the NTV. Median and mean NTV were 16 (0-243) cc and 32.57 ± 4.67 cc. The percentage of patients with high nodal volume (>45cc) was 38.5% in stage N2-3 and 13.8% in stage T3-4.

Statistical Analysis

All analyses were performed with Statistical Package for Social Sciences version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Receiver operating characteristic analysis was used to define the optimum cutoff value of NTV. The OS, disease-free survival (DFS), metastasis-free survival (MFS), and locoregional recurrence-free survival (LRFS) were defined from the start of first treatment (RT or chemotherapy) to the last follow-up or death, to the last follow-up or to any event, to the last follow-up or distant metastasis, and to the last follow-up or to locoregional recurrence, respectively. Survival analysis was made by the Kaplan–Meier method. Comparisons between groups were made with the log-rank test. Cox-proportional hazard models were developed to find independent prognostic factors. *P*-values <.05 were considered statistically significant.

Results

The median follow-up for living patients was 76 (40-113) months. At the time of review, 27 (30.7%) patients died. Two- and 5-year OS was 87.5% and 71.5%, respectively (Figure 1A). Thirteen (14.8%) patients died because of disease progression. Causes of the death for others were 4 secondary malignancies (lung, gastric, brain, and lymphoma), 1 trauma, 1 pneumonia, 4 cardiac/cerebral vascular disease, 2 treatment related (RT necrosis at 35th month, infection at third month), and 2 unknown reasons. Nine (10.2%) patients developed locoregional recurrence. Four patients had local, 3 had regional, and 2 had both local and regional recurrences. Locoregional recurrences appeared in a median of 28 (8-53) months. Two- and 5-year LRFS was 95.2% and 87.7%, respectively. Sixteen (18.2%) patients developed distant metastasis. Metastases were seen in bone (5), lung (2), liver (2), pelvic lymph node (2), brain (1), and multiple sites (4). Distant metastases occurred in a median of 20 (6-62) months. Two- and 5-year MFS was 89.4% and 79.4%, respectively (Figure 1B). Four patients had locoregional and distant metastases. Two- and 5-year DFS was 84.7% and 75.0%.

Univariate Analyses

Age (≥50 years old) and absence of IC were found to be negative prognostic factors of OS. Patients with NTV > 45 cc had worse DFS and MFS than others. Advanced T stage was associated with lower rates of MFS. No factors were found to affect locoregional tumor control such as age, gender, stage, chemotheraphy and nordal tumor volume (Table 2).

Multivariate Analyses

Age (≥50) is the only independent factor of OS ($P < .020$). Nodal tumor volume was found to be the most predictive factor for MFS ($P < .001$). Although T stage was not a significant prognostic factor for OS and LRFS, advanced T stages were associated with lower rates of MFS ($P = .018$, Table 3).

Distant metastases occurred in 7/67 patients with NTV ≤ 45 cc and in 9/21 patients with NTV > 45 cc. Patients with NTV > 45 cc had lower 5-year MFS rates than patients with NTV ≤ 45cc (50.6% vs. 87.9%, $P < .001$, Figure 2). In patients with NTV > 45 cc, 3 of 13 patients who received IC had metastasis within 3 years, while 6 of 8 patients who did not receive IC had metastasis within 3 years.

Discussion

In the present study, distant metastasis (18.2%) was found to be the common failure pattern of patients treated with IMRT ± chemotherapy for NPC. At present, distant metastasis is the common issue to be solved in locally advanced NPC. In addition to RT, chemotherapy has become the standard in the advanced stages of NPC after the intergroup trial which resulted in higher rates of OS with additional chemotherapy (47% vs. 78% at 3 years, $P = .005$).[3] In that study, 3 cycles of cisplatin during RT and 3 cycles of cisplatin/fluorouracil (PF) after RT were planned. However, compliance to CCRT and AC was 63% and 55%, respectively. Adjuvant chemotherapy has limitations in daily practice due to decreased patient tolerance following CCRT. Furthermore, a randomized study from endemic region reported that the 2-year failure-free survival rate was similar with CCRT and CCRT + AC (86% vs. 84%, $P = 0.13$), and an individual patient meta-analysis showed that the survival gain of chemotherapy mostly came from the concurrent phase.[9,10] In NPC 9901 Trial, better locoregional control rates with CCRT + adjuvant PF were shown. On the other hand, the rate of distant metastasis was the same as for RT alone and CCRT + AC, and it was concluded that better distant control was needed, especially for 4a-b stages.[11] Distant failure may be attributed to decreased

Table 2. Univariate Analysis

Factors	Number of patients	OS 5-Year Control	OS *P*	DFS 5-Year Control	DFS *P*	MFS 5-Year Control	MFS *P*	LRFS 5-Year Control	LRFS *P*
Age									
<50	47	84.3	.001	74.2	.981	78.0	.909	87.5	.958
≥50	41	57.9		75.3		80.9		87.4	
Gender									
Male	67	69.1	.180	72.6	.227	76.8	.191	89.9	.653
Female	21	79.2		82.5		87.8		82.5	
T stage									
1-2	59	73.4	.341	79.9	.163	85.0	.095	89.8	.360
3-4	29	67.4		64.2		67.3		82.9	
N stage									
0-1	36	63.5	.157	79.5	.753	88.6	.251	90.7	.752
2-3	52	76.8		72.4		74.1		86.1	
Stage									
1-2	23	66.3	.755	80.4	.694	90.5	.277	89.3	.928
3-4	65	73.1		73.2		75.9		87.2	
Induction chemotherapy									
Absent	63	63.8	.023	74.4	.519	81.0	.984	89.0	.890
Present	25	92.0		75.0		75.0		84.2	
Nodal tumor volume									
≤45 cc	67	72.3	.232	81.9	.004	87.9	<.001	90.0	.318
>45 cc	21	70.8		51.4		50.6		75.9	

DFS, disease-free survival; LRFS, locoregional recurrence-free survival; MFS, metastasis-free survival; OS, overall survival.

patient tolerance and the inability to complete full course of AC. Second, PF may not be an ideal chemotherapy regimen for NPC. Hypothetically, IC is more tolerable and can eradicate distant metastasis sooner. In last years, the usefulness of IC with various chemotheraupetic combinations has been demonstrated in phase 3 randomized trials. Disease-free survival rates increased from 72%-76% to 80%-85% at 3 years with PF, docetaxel/cisplatin/fluorouracil (TPF), and gemcitabine/cisplatin, respectively.[4-6] A recent meta-analysis also revealed a significant advantage in progression-free survival (PFS) [hazard ratio (HR): 0.657; 95% CI: 0.568-0.760; $P < .001$) and OS (HR: 0.680; 95% CI: 0.511-0.905; $P = .001$) with IC in locoregionally advanced NPC.[12] Lastly, 5-year results of NPC 0501 Trial showed improvement in PFS and OS rates by modification of chemotherapy pattern from CCRT + AC to IC + CCRT and by changing the chemotherapy regimen from PF to cisplatin/capecitabine.[13] It should be noted that the benefit comes mostly from distant control in this study. With the growing literature, IC + CCRT is becoming standard in locally advanced NPC. However, concerning about the toxicities, the selection of the appropriate patient and chemotherapy regimen is crucial.

Table 3. Multivariate Analysis

	Factors	HR	95% CI	*P*
OS	Age	2.939	1.182-7.308	.020
	Induction chemotherapy	2.240	0.630-7.971	.213
MFS	T stage	3.419	1.238-9.442	.018
	Nodal tumor volume	7.160	2.560-20.024	<.001

HR, hazard ratio; MFS, metastasis-free survival; OS, overall survival.

Intermediate-risk patients (T3-4 N0 and T3N1) were excluded in IC trials. The benefit of additional chemotherapy for the backbone CCRT has not been shown in this patient group.[14,15] A recent study exploring the benefits of IC in T3N0–T4N0–T3N1 subgroups reported the advantage of IC in high-risk patients [male and Epstein Barr Virus (EBV) - DNA >2000 copies/mL] and showed that node-positive group provided more benefit than node-negative group, mostly with the TPF regimen.[16] A recent nomogram, which tested a prognostic index with the factors including gender, T stage, N stage, Lactate dehydrogenase (LDH) level, and EBV-DNA level, revealed the importance of high EBV-DNA levels and N3 stage.[17] The number of positive lymph nodes (>9) and the number of regions (according to the updated 2013 consensus guidelines for head and neck tumors) of positive lymph nodes were also proposed as prognostic factors.[18,19] Lymph node tumor burden appears to be a key component of microscopic distant metastasis and has been evaluated for possible prognostic effects in addition to N staging. In the present study, the rate of distant metastasis increased in patients with NTV > 45 cc. In former studies, different

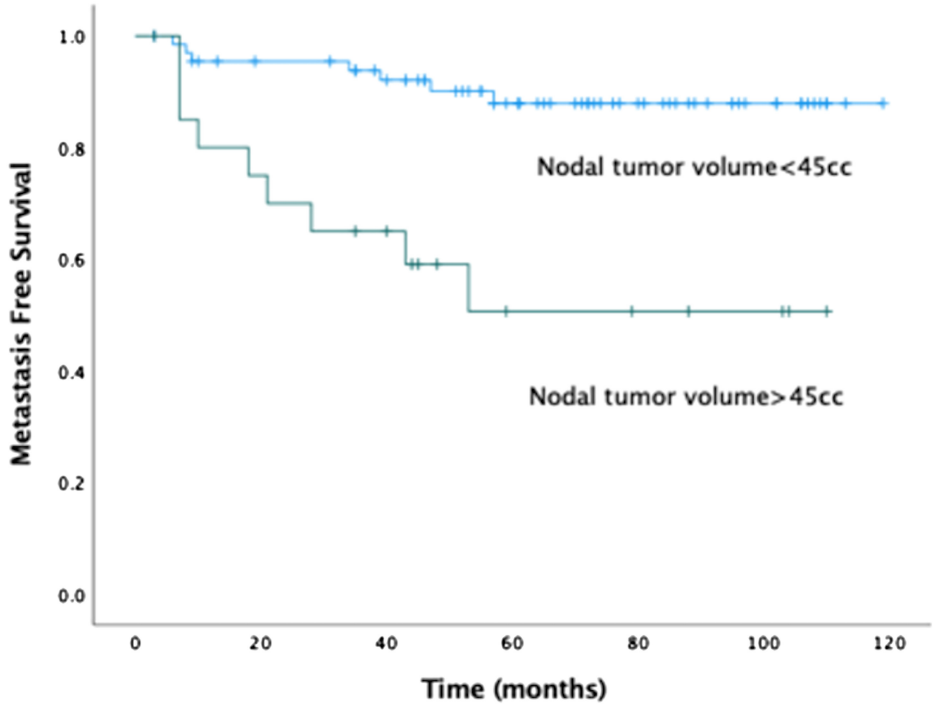

Figure 2. Metastasis-free survival curves according to nodal tumor volume.

cutoff values of NTV have been reported for prognostication of survival outcomes. A worse regional control was found with NTV > 10 cc and NTV > 35.7 cc, respectively.[20,21] Higher distant failure rates were associated with NTV > 30 cc.[22] A recent report found that NTV ≥32.8 cc improved positive predictive value for distant metastasis at N1-N2 stages, but not in N3.[8] In another study, lower rates of MFS were reported among patients with N1 stage with a smaller NTV threshold (18.9 cc). In addition, EBV-DNA copy number was found to be associated with NTV.[23] The prognostic value of plasma EBV-DNA level has been shown, and it was integrated into the last staging system. Nodal tumor volume may have a correlation with EBV-DNA and can be further evaluated as a surrogate if EBV-DNA is not available.

In this study, locoregional recurrences were half of the distant metastases. With the advances in radiation technology, the importance of T and N staging in early stages has diluted. A simplified T and N staging was proposed by combining T2 and T1 and defining all cervical nodes <6 cm above the supraclavicular fossa as N1.[24] A huge data from Hong Kong also revealed 8-year local control rates of >87% in T1-2-3 stage, 71.6% in T4 stage and >90% in N0-1-2 stage, and 76.4 in N3a and 81.8% in N3b stage.[25] Moreover, 2 main types of disease patterns have been identified: ascending (advanced local, T3-4 N0-1) and descending (advanced regional, T1-2 N2-3). Descending type is associated with more aggressive clinical features and an increased risk of distant failure.[26] In a recent study, no significant correlation was found between nodal metastasis and T stage. Therefore, it is recommended that treatment decisions be considered separately at both T and N stages rather than the total clinical stage.[27] In the light of these studies, it is rational to consider more intensive treatments to locally advanced stages, particularly to N3 and/or T4 stage. Novel systemic agents and combinations are of common interest for this patient group.

Limitation of the study: Although the study has significance outside of NPC's endemic regions, it is a single-center retrospective study involving a small number of patients, limiting the findings. Second, EBV-DNA values are not valid for all patients, and the combination of EBV-DNA with other factors can increase the accuracy of predicting distant metastasis. Finally, a clear assessment of the OS comparison could not be made, as half of the deaths were not related to the disease.

Conclusion

Nodal tumor burden has a significant prognostic value in predicting distant metastasis in NPC. Patients with NTV > 45 cc have worse MFS than patients with NTV ≤ 45 cc. It may be useful to consider NTV in patient selection for IC.

Ethics Committee Approval: Ethical committee approval was received from the İstanbul University-Cerrahpaşa, Cerrahpaşa School of Medicine (Date: March 4, 2020, Number: 37452).

Informed Consent: Informed consents were not required for retrospective review of the medical and radiological data of the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.C.Y.; Design – Ö.U.; Supervision – M.D.; Resources – S.K.; Materials – E.S.A., S.Ç.K.; Data Collection and/or Processing – S.K.; Analysis and/or Interpretation – H.C. Literature Search – M.D.; Writing Manuscript – H.C.Y.; Critical Review – Ö.U., S.Ç.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

References

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115-132. [CrossRef]

2. Sun XS, Liu SL, Luo MJ, et al. The association between the development of radiation therapy, image technology, and chemotherapy, and the survival of patients with nasopharyngeal carcinoma: a cohort study from 1990 to 2012. *Int J Radiat Oncol Biol Phys*. 2019;105(3):581-590. [CrossRef]
3. Al-Sarraf M, LeBlanc M, Giri PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol*. 1998;16(4):1310-1317. [CrossRef]
4. Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. *Lancet Oncol*. 2016;17(11):1509-1520. [CrossRef]
5. Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and cisplatin induction chemotherapy in nasopharyngeal carcinoma. *N Engl J Med*. 2019;381(12):1124-1135. [CrossRef]
6. Cao SM, Yang Q, Guo L, et al. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase III multicentre randomised controlled trial. *Eur J Cancer*. 2017;75:14-23. [CrossRef]
7. Lok BH, Leeman JE, Lee NY. Nasopharynx. In: Halperin EC, Wazer DE, Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*. 7th ed. Philadelphia : Wolters Kluwer; 2018.
8. Ai QY, King AD, Mo FKF, et al. Prediction of distant metastases from nasopharyngeal carcinoma: improved diagnostic performance of MRI using nodal volume in N1 and N2 stage disease. *Oral Oncol*. 2017;69:74-79. [CrossRef]
9. Chen L, Hu CS, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol*. 2012;13(2):163-171. [CrossRef]
10. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys*. 2006;64(1):47-56. [CrossRef]
11. Lee AWM, Tung SY, Ng WT, et al. A multicenter, phase 3, randomized trial of concurrent chemoradiotherapy plus adjuvant chemotherapy versus radiotherapy alone in patients with regionally advanced nasopharyngeal carcinoma: 10-year outcomes for efficacy and toxicity. *Cancer*. 2017;123(21):4147-4157. [CrossRef]
12. Mané M, Benkhaled S, Dragan T, et al. Meta-analysis on induction chemotherapy in locally advanced nasopharyngeal carcinoma. *Oncologist*. 2021;26(1):e130-e141. [CrossRef]
13. Lee AWM, Ngan RKC, Ng WT, et al. NPC-0501 trial on the value of changing chemoradiotherapy sequence, replacing 5-fluorouracil with capecitabine, and altering fractionation for patients with advanced nasopharyngeal carcinoma. *Cancer*. 2020;126(16):3674-3688. [CrossRef]
14. Wu LR, Yu HL, Jiang N, et al. Prognostic value of chemotherapy in addition to concurrent chemoradiotherapy in T3-4N0-1 nasopharyngeal carcinoma: a propensity score matching study. *Oncotarget*. 2017;8(44):76807-76815. [CrossRef]
15. Lan XW, Xiao Y, Zou XB, Zhang XM, OuYang PY, Xie FY. Outcomes of adding induction chemotherapy to concurrent chemoradiotherapy for stage T3N0-1 nasopharyngeal carcinoma: a propensity-matched study. *Onco Targets Ther*. 2017;10:3853-3860. [CrossRef]
16. Xu C, Zhang S, Li WF, et al. Selection and validation of induction chemotherapy beneficiaries among patients with T3N0, T3N1, T4N0 nasopharyngeal carcinoma using Epstein-Barr virus DNA: a joint analysis of Real-World and clinical trial data. *Front Oncol*. 2019;9:1343. [CrossRef]
17. Sun XS, Xiao BB, Lu ZJ, et al. Stratification of candidates for induction chemotherapy in Stage III-IV nasopharyngeal carcinoma: a large cohort study based on a comprehensive prognostic model. *Front Oncol*. 2020;10:255. [CrossRef]
18. Ma H, Liang S, Cui C, et al. Prognostic significance of quantitative metastatic lymph node burden on magnetic resonance imaging in nasopharyngeal carcinoma: a retrospective study of 1224 patients from two centers. *Radiother Oncol*. 2020;151:40-46. [CrossRef]
19. Zhou X, Ou X, Yang Y, et al. Quantitative metastatic lymph node regions on magnetic resonance imaging are superior to AJCC N classification for the prognosis of nasopharyngeal carcinoma. *J Oncol*. 2018;2018:9172585. [CrossRef]
20. Chen FP, Zhou GQ, Qi ZY, et al. Prognostic value of cervical nodal tumor volume in nasopharyngeal carcinoma: analysis of 1230 patients with positive cervical nodal metastasis. *PLoS One*. 2017;12(5):e0176995. [CrossRef]
21. Wang W, Feng M, Fan Z, Li J, Lang J. Clinical outcomes and prognostic factors of 695 nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. *BioMed Res Int*. 2014;2014:814948. [CrossRef]
22. Chua DT, Sham JS, Kwong DL, et al. Volumetric analysis of tumor extent in nasopharyngeal carcinoma and correlation with treatment outcome. *Int J Radiat Oncol Biol Phys*. 1997;39(3):711-719. [CrossRef]
23. Yao JJ, Zhou GQ, Wang YQ, et al. Prognostic values of the integrated model incorporating the volume of metastatic regional cervical lymph node and pretreatment serum Epstein-Barr virus DNA copy number in predicting distant metastasis in patients with N1 nasopharyngeal carcinoma. *Chin J Cancer*. 2017;36(1):98. [CrossRef]
24. Lee AWM, Ng WT, Chan LK, et al. The strength/weakness of the AJCC/UICC staging system (7th edition) for nasopharyngeal cancer and suggestions for future improvement. *Oral Oncol*. 7th ed. 2012;48(10):1007-1013. [CrossRef]
25. Au KH, Ngan RKC, Ng AWY, et al. Treatment outcomes of nasopharyngeal carcinoma in modern era after intensity modulated radiotherapy (IMRT) in Hong Kong: a report of 3328 patients (HKNPCSG 1301 study). *Oral Oncol*. 2018;77:16-21. [CrossRef]
26. Yao JJ, Qi ZY, Liu ZG, et al. Clinical features and survival outcomes between ascending and descending types of nasopharyngeal carcinoma in the intensity-modulated radiotherapy era: a big-data intelligence platform-based analysis. *Radiother Oncol*. 2019;137:137-144. [CrossRef]
27. Xu Y, Huang T, Fan L, Jin W, Chen X, Chen J. Patterns and prognostic value of lymph node metastasis on distant metastasis and survival in nasopharyngeal carcinoma: a surveillance, epidemiology, and end results study, 2006-2015. *J Oncol*. 2019;2019:4094395. [CrossRef]