TURKISH JOURNAL of ONCOLOGY

Turk J Oncol 2025;40(2):112–119
doi: 10.5505/tjo.2025.4513

ORIGINAL ARTICLE

Does Adding Chemotherapy to Radiotherapy Improve Outcomes in Stage II Nasopharyngeal Carcinoma?

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OBJECTIVE

The benefit of adding chemotherapy (CHT) to radiotherapy (RT) in stage II nasopharyngeal carcinoma (NPC) remains uncertain. This study evaluates the impact of CHT on survival outcomes in these patients.

METHODS

A retrospective analysis was conducted on 107 AJCC 8th edition stage II NPC patients treated with RT alone or combined RT and CHT between 1994 and 2021.

RESULTS

Of the cohort, 31% received RT alone, while 69% underwent combined RT and CHT. After a median follow-up of 98 months, locoregional recurrence and distant metastasis rates were similar between groups. The addition of CHT did not significantly improve 10-year overall, locoregional recurrence-free, or distant metastasis-free survival. Subgroup analyses revealed no survival benefit of CHT, even in patients with lymph node metastasis or those treated using two-dimensional RT techniques.

CONCLUSION

For AJCC 8th edition stage II NPC patients, RT alone is an effective treatment, with no additional survival benefit from the inclusion of CHT. Further research is warranted to identify specific subgroups of patients who may derive benefit from the incorporation of CHT.

Keywords: Chemoradiotherapy; chemotherapy; induction chemotherapy; nasopharyngeal cancer; radiotherapy.

INTRODUCTION

Definitive radiotherapy (RT) is the cornerstone of treatment for early-stage nasopharyngeal carcinoma (NPC), offering excellent local control and favorable survival rates, with current guidelines specifically recommending RT alone for stage I disease.[1] By contrast, the survival benefit of adding induction and concurrent chemotherapy (CHT) to RT for patients with stage III-IV NPC has been well-documented for over two decades.[2,3] Yet, in stage II NPC, the role of CHT remains uncertain and a topic of ongoing research, even in the cur-

Preliminary findings of this study was presented as a poster at the 2024 European Society for Radiotherapy and Oncology (ESTRO) meeting (https://doi.org/10.1016/S0167-8140(24)02311-9).

Received: January 10, 2025
Revised: February 17, 2025
Accepted: March 10, 2025
Online: June 02, 2025

Accessible online at:
www.onkder.org

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rent era of advanced cancer care. Limited evidence in the literature supports a distinct clinical benefit of adding CHT to RT in stage II NPC, prompting concerns about the potential for overtreatment and added toxicity.[4] To address these gaps in knowledge, the present study investigates clinical outcomes in patients with stage II NPC treated with either RT alone or combined RT and CHT in a comprehensive cancer center.

MATERIALS AND METHODS

Study Population

A retrospective cohort analysis was conducted on patients diagnosed with NPC who underwent definitive RT ± CHT at our institution from 1994 to 2021. Clinical and pathological data, including demographic and tumor characteristics, staging, treatment modality, and follow-up outcomes, were systematically extracted from individual patient records and the institution's electronic medical records system. Staging was uniformly assigned according to the 8th edition of the American Joint Committee on Cancer (AJCC) classification system. The study cohort was limited to patients classified as AJCC 8th stage II disease (T1N1M0, T2N0M0, T2N1M0). Exclusion criteria included patients with incomplete follow-up data after definitive treatment. This study was conducted in accordance with the declaration of Helsinki and was approved by the by the Ethics Committee of Hacettepe University Health Sciences (No: SBA 24/118, Date 23/01/2024).

Treatment

RT was administered using one of two techniques, depending on the available technology at the time of treatment: two-dimensional radiotherapy (2DRT) or intensity-modulated radiotherapy (IMRT). None of the patients included in the study were treated with three-dimensional conformal radiotherapy (3DCRT). Early in the treatment period, 2DRT was commonly employed; however, IMRT gradually became the preferred method in recent years. The choice of CHT administration was determined at the discretion of the treating physician and both induction and concurrent CHT regimens also evolved over time, reflecting advancements in treatment protocols and improved understanding of optimal dosing strategies. In more recent cases, cisplatin became the standard concurrent CHT regimen, administered either as a weekly dose of 40 mg/m^2 or a higher dose of 100 mg/m^2 every three weeks. Induction CHT typically consisted of three cycles, including docetaxel (75 mg/m^2), cisplatin (75 mg/m^2), and fluorouracil (750–1000 mg/m^2).

Toxicity and Follow-up

Toxicity was evaluated in patients with available data using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Post-treatment follow-up was scheduled at 3-month intervals for the first 2 years, followed by 6-month intervals for the next 3 years, and annually thereafter. At each follow-up visit, patients underwent routine physical examinations and magnetic resonance imaging of the nasopharynx and neck to monitor for recurrence and assess late treatment-related toxicities.

Statistical Analysis

All statistical analysis, including descriptive statistics, overall survival (OS), locoregional recurrence-free survival (LRRFS), and distant metastasis-free survival (DMFS), were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM, Armonk, NY, USA). The follow-up period was measured from the initiation of RT. OS was defined as the time from RT initiation to death from any cause, while LRRFS and DMFS were defined as the time from RT initiation to either locoregional recurrence (LRR) or distant metastasis (DM), respectively, or death. The variables between the RT alone and combined RT and CHT groups were analyzed using independent samples t-test, Mann-Whitney U test, or Chi-square test, depending on whether they were numerical or categorical, and based on their distribution characteristics, including normality. Survival outcomes were analyzed using the Kaplan-Meier method, with comparisons made via the log-rank test. Univariate analysis (UVA) was employed to assess potential prognostic factors, with a significance threshold of $p<0.05$. Variables with a potential significance level ($p<0.1$) in UVA were included in the multivariate Cox proportional hazards model (MVA), with hazard ratios (HR) and 95% confidence intervals (CI) reported.

RESULTS

Patient, Tumor and Treatment Characteristics

Baseline patient, tumor, and treatment characteristics are summarized in Table 1. The median age of the patients was 50 years (Range: 17–74), with a cohort consisting of 71 males (66%) and 36 females (34%). TNM classifications, as per the AJCC 8th staging system, are shown in Figure 1. The most common tumor histology was non-keratinizing undifferentiated carcinoma (WHO type III, n=58, 54%), followed by non-keratinizing differentiated carcinoma (WHO type II,

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Table 1 Patient, tumor and treatment characteristics

	RT (n=33)		RT+CHT (n=74)		p
	n	%	n	%	
Age (median)	50 years (range: 17–74 years)		47 years (range: 21–74 years)		0.78
Gender					0.82
Male	21	64	50	68	
Female	12	36	24	32	
WHO tumor type					0.49
Type 1	3	9	3	4	
Type 2	9	27	34	46	
Type 3	21	64	37	50	
AJCC 8th stage group					0.74
T1N1M0	18	55	45	61	
T2N0M0	10	30	9	12	
T2N1M0	5	15	20	27	
LN metastasis					0.03
No	10	30	9	12	
Yes	23	70	65	88	
RT technique					0.01
2DRT	31	94	40	54	
IMRT	2	6	34	46	
Induction CHT					N/A
Yes	None		22	30	
No	None		52	70	

RT: Radiotherapy; CHT: Chemotherapy; WHO: World Health Organization; AJCC: American Joint Committee on Cancer; LN: Lymph node; 2DRT: Two-dimensional radiotherapy; IMRT: Intensity-modulated radiotherapy; N/A: Not available

n=43, 40%) and keratinizing squamous cell carcinoma (WHO type I, n=6, 7%). In terms of treatment, 74 patients (69%) received a combination of RT and CHT, while 33 patients (31%) were treated with RT alone. Among those receiving concurrent CHT with RT, cisplatin alone was administered in 81% of cases. For patients receiving induction CHT before RT or concurrent chemoradiotherapy, the median number of cycles was three (Range: 1–3 cycles). Baseline characteristics were generally similar between the RT alone and RT + CHT groups, with two notable differences: the RT + CHT group had a significantly higher proportion of patients with lymph node (LN) metastasis (88% vs. 70%, p=0.03) and a greater use of the IMRT technique (46% vs. 6%, p=0.01) compared to the RT alone group (Fig. 2).

Recurrence Patterns and Survival Outcomes

The median follow-up duration for this cohort was 98 months (Range: 11–381 months), with 69 out of 107 patients (64%) having a follow-up period exceeding five years. The overall LRR rate was 15%, with 9 cases (8%) of isolated LR, 2 cases (2%) of isolated LN recurrence, and 5 cases (5%) of both local and LN recurrence. DM were observed in 14 patients (13%), with the most frequent metastatic sites being bone (n=9), lungs (n=9), liver (n=5), and brain (n=2). The 10-year OS, LRRFS and DMFS rates were 69%, 68%, and 67%, respectively.

Prognostic Factors

Figure 3 illustrates the incidence rates of LRR and DM in patients treated with RT alone compared to those receiving combined RT and CHT. The rates of LRR (18% vs. 18%, p=0.564) and DM (14% vs. 11%, p=0.355) did not show a statistically significant difference between the RT alone and combined RT and CHT groups. The UVA of survival outcomes, summarized in Table 2, identified age as a significant factor for OS, with younger patients (≤50 years) achieving a higher 10-year OS rate (76% vs. 59%, p=0.04) compared to those over 50. Gender also had a notable impact, female patients demonstrated improved 10-year OS (78% vs. 64%, p=0.04), LRRFS (78% vs. 63%, p=0.009), and DMFS (78% vs. 61%, p=0.01)

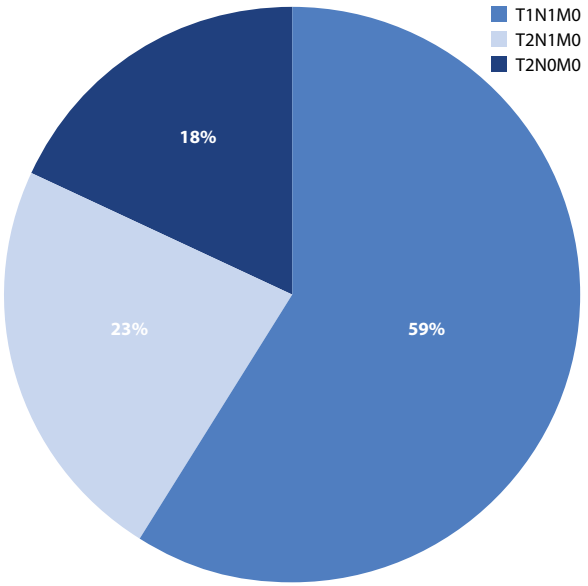

Fig. 1. American Joint Committee on Cancer 8th edition TNM classifications of the patients.
TNM: Tumor, node, metastasis.

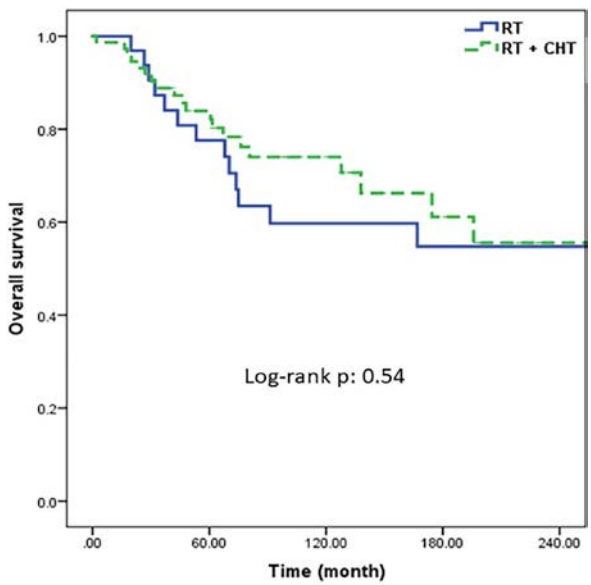

Fig. 2. Kaplan-Meier survival curve illustrating overall survival stratified by treatment.
RT: Radiotherapy; CHT: Chemotherapy.

compared to male patients. The 10-year OS, LRRFS and DMFS rates were 73%, 71% and 71% for patients who received induction CHT, 74%, 73% and 70% for those who received only concurrent CHT, and 61%, 57% and 57% for those treated with RT alone (p=0.72, p=0.51 and p=0.54, respectively). The combination of RT and CHT provided no additional oncological benefit across subgroups, including those treated with 2DRT technique (Fig. 4a) or patients with LN metastasis (Fig. 4b), compared to RT alone. In MVA, age emerged as the sole independent predictor of OS (HR: 1.4, 95% CI: 1.2–5.8, p=0.04), while female gender was the only independent predictor for both LRRFS (HR: 1.3, 95% CI: 1.1–2.8, p=0.02) and DMFS (HR: 1.3, 95% CI: 0.5–3.8, p=0.01).

Toxicity

Data on acute toxicity were incomplete for most patients due to the retrospective design of the study and thus were excluded from the analysis. Among late toxicities of grade 3 or higher, xerostomia was the most prevalent, affecting 21 patients (20%), followed by hearing loss in six patients (6%), trismus in two patients (2%), osteoradionecrosis in two patients (2%), brain necrosis in one patient (1%), and optic neuropathy in one patient (1%). No statistically significant difference was observed in the incidence of severe late toxicities between the RT alone and combined RT + CHT groups (33% vs. 29%, p=0.75).

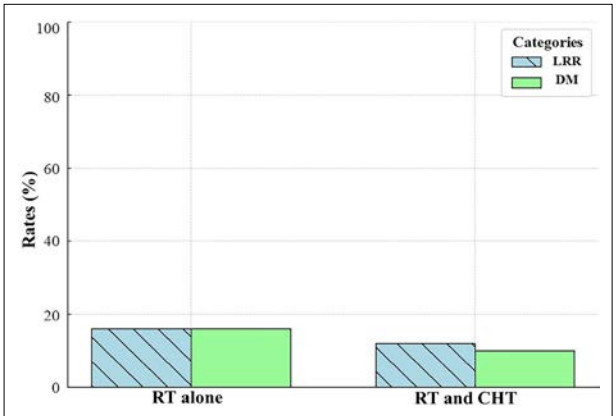

Fig. 3. The rates of locoregional recurrence and distant metastasis stratified by treatment.
LRR: Locoregional recurrence; DM: Distant metastasis.

DISCUSSION

In this 27-year, single-center retrospective study, the incorporation of either induction or concurrent CHT alongside definitive RT demonstrated no significant effect on preventing recurrence or improving survival rates in patients with stage II NPC as classified by the AJCC 8th edition.

While definitive RT alone provides excellent local control for early stage NPC, the addition of induction and concurrent CHT significantly improves oncological

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doi: 10.5505/tjo.2025.4513

Table 2 Univariate analysis for overall, locoregional recurrence-free and distant metastasis-free survival rates

	10y-OS (%)	p	10y-LRRFS (%)	p	10y-DMFS (%)	p
Age						
≤50 years	76	0.04	74	0.09	72	0.18
>50 years	59		58		58	
Gender						
Male	64	0.04	63	0.009	61	0.01
Female	78		78		78	
WHO tumor type						
Type 1	38	0.82	38	0.95	38	0.96
Type 2	67		66		65	
Type 3	72		71		69	
Treatment						
RT	60	0.54	57	0.34	57	0.45
RT+CHT	74		74		72	
AJCC T Stage						
T1	81	0.55	66	0.79	66	0.62
T2	74		71		73	
AJCC N stage						
N0	88	0.09	88	0.12	88	0.05
N1	65		64		62	
RT technique						
2DRT	73	0.31	72	0.13	72	0.19
IMRT	67		64		63	
Treatment period						
≤2010	67	0.31	64	0.15	63	0.11
>2010	72		71		71	

OS: Overall survival; LRRFS: Local regional recurrence-free survival; DMFS: Distant metastasis-free survival; WHO: World Health Organization; RT: Radiotherapy; CHT: Chemotherapy; AJCC: American Joint Committee on Cancer; 2DRT: Two-dimensional radiotherapy; IMRT: Intensity-modulated radiotherapy

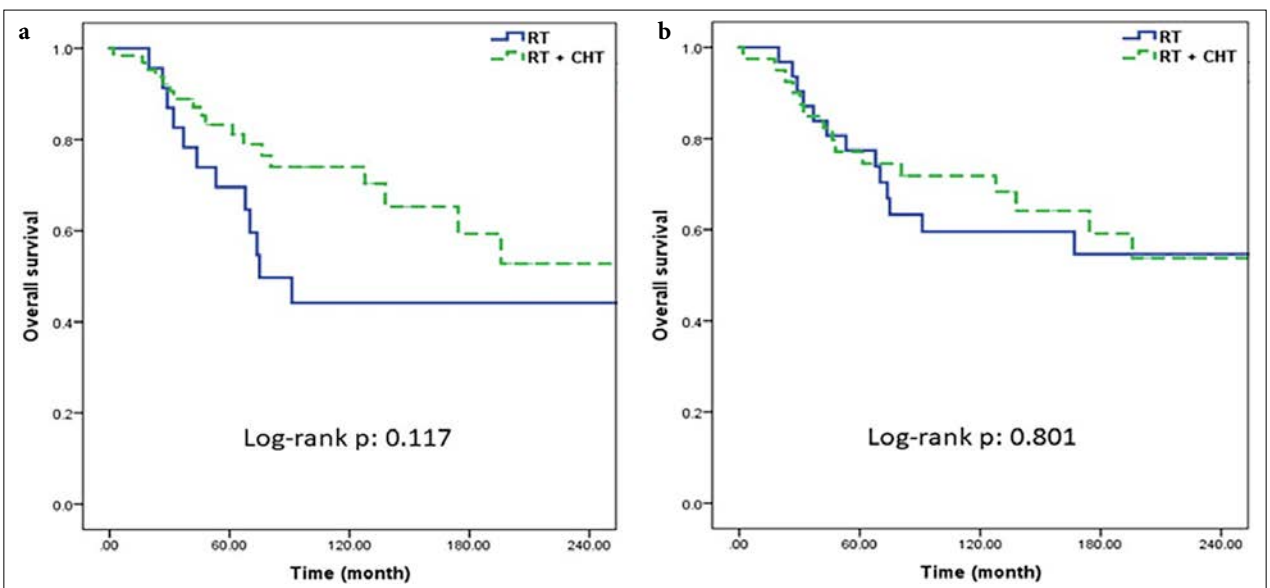

Fig. 4. Kaplan-Meier survival curves illustrating overall survival stratified by treatment for patients who received two-dimensional radiotherapy (a) and those with lymph node metastasis (b).
RT: Radiotherapy; CHT: Chemotherapy.

outcomes in more advanced stages.[2,5] However, for stage II disease, the optimal treatment strategy is still a topic of debate. When examining the historical progression of this debate, several small retrospective studies from past decades, utilizing older RT techniques, suggested that the addition of concurrent CHT to RT in stage II NPC improved oncological outcomes.[6,7] In the only prospective randomized phase III trial available on this subject, Chen et al.[8] evaluated 230 patients with stage II NPC. Their findings demonstrated that a notable improvement in 5-year OS, showing an 8.7% increase in patients who received concurrent CHT compared to those treated with RT alone. Although concurrent CHT significantly increased the rates of acute toxicity, late toxicity rates remained comparable between groups. Moreover, the 10-year results of the study confirmed that the OS benefit from concurrent CHT persisted, compared to RT alone.[9] However, it is important to critically assess the study's methodology, as it utilized the 2DRT technique for all patients and relied on the outdated 1992 Chinese staging system, potentially limiting the generalizability of its findings in the modern era. In contrast, our study demonstrated that even when the 71 patients treated with 2DRT technique were analyzed separately, the combination of RT and CHT did not yield a statistically significant improvement in survival outcomes for stage II NPC patients classified according to the AJCC 8th edition, compared to RT alone.

Advances in RT technologies have led to improved outcomes for patients with NPC and studies have shown that patients treated with IMRT experience significantly better local control and progression-free survival (PFS) compared to those treated with older techniques, highlighting the superiority of modern techniques of RT in enhancing both disease control and survival.[10–13] Thus, with advancements in technology and a more interconnected world, the critical question now becomes whether concurrent CHT will continue to offer benefits for stage II NPC patients who are treated with IMRT technique. A 2018 systematic review and meta-analysis, incorporating six retrospective and one prospective randomized study, revealed that the addition of concurrent CHT to treatment in stage II NPC patients during the IMRT era did not enhance LRRFS, DMFS, PFS or OS.[14] Furthermore, it significantly increased the rates of severe acute hematologic toxicities, highlighting the potential risks without clear survival benefits in this context. In another meta-analysis, also published in 2018, incorporating 16 studies with a total of 3,038 stage II NPC patients, it was found that concurrent CHT improved OS in the entire cohort. [15] However, when focusing solely on patients treated with IMRT, the analysis revealed that adding CHT did not result in better oncological outcomes compared to RT alone, suggesting that the benefit of CHT may not extend to those receiving modern RT techniques. In a randomized phase II trial published in 2020, 84 patients with stage II NPC treated with IMRT were analyzed. [16] The study concluded that adding concurrent CHT did not improve survival outcomes but was associated with an increase in hematologic toxicity. Beyond concurrent CHT, the role of induction CHT has also been examined in numerous retrospective studies for stage II NPC.[17] For instance, in a retrospective study by Fangzheng et al.,[4] no significant differences in survival parameters were observed among 37 patients treated with IMRT alone, 25 patients treated with concurrent CHT and IMRT, and 180 patients who received induction CHT followed by either IMRT alone or concurrent CHT and IMRT. Furthermore, in a subgroup analysis of 137 patients with T2N1M0 disease, they found that IMRT alone yielded similar oncological outcomes compared to IMRT combined with either concurrent and/or induction CHT. Similarly, in our study, induction CHT did not show any oncological benefit for stage II NPC patients, as classified by the AJCC 8th staging system, in any subgroup, including those with node-positive disease or those treated with the 2DRT technique.

Although current literature suggests that combining CHT with IMRT may lead to overtreatment in stage II NPC, the heterogeneity within this patient population underscores the importance of individualized treatment approaches. Certain patients may still derive significant benefit from concurrent CHT, particularly those with high-risk features. Tang et al.[18] conducted a randomized study targeting a lower-risk subgroup of NPC patients, specifically those with stage II/T3N0M0 disease and favorable clinical characteristics, defined as LNs smaller than 3 cm, no involvement of level IV/Vb nodes, absence of extranodal extension, and Epstein-Barr virus DNA levels below 4000 copies/mL.[19–23] By excluding higher-risk patients, the study aimed to evaluate treatment outcomes within a more homogeneous, lower-risk cohort and demonstrated that IMRT alone yields survival rates comparable to those achieved with concurrent IMRT and CHT. However, while no studies have specifically addressed patients with unfavorable clinical features, combining RT with CHT may still provide therapeutic benefits in high-risk populations, highlighting the need for focused research targeting these subgroups. Although LN metastasis is a key high-risk feature, a 2023 meta-analysis found that

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adding concurrent CHT to IMRT in stage II NPC did not significantly improve survival outcomes, even in patients with LN involvement.[24] Similarly, in our study, a subgroup analysis of patients with LN metastasis showed no additional survival benefit from the inclusion of induction or concurrent CHT. However, the 10-year survival rates were marginally lower in patients with LN metastasis, indicating that node-positive patients may be appropriate candidates for future studies exploring intensified treatment approaches.

In the era of advanced medical technology, integrating sophisticated tools with clinicopathological features offers significant potential for refining risk stratification in stage II NPC. Liang et al.[25] conducted a retrospective analysis of 999 stage II NPC patients and developed a prognostic model that combines deep learning-derived MRI features with clinical data to stratify patients into distinct risk categories. Their findings revealed that low-risk patients achieved satisfactory PFS rates with IMRT alone, while high-risk patients experienced substantial therapeutic benefits from the addition of concurrent CHT. Despite these promising advancements, the identification of factors to better determine which patients may benefit from combining CHT with RT remains an area requiring further exploration. Additionally, high-quality evidence supporting reliable and practical approaches for guiding treatment decisions in this heterogeneous population is still lacking, underscoring the need for continued research.

Limitations of the Study

Although our study included a homogeneous patient population uniformly diagnosed with stage II NPC according to the AJCC 8th staging system, it has several limitations. The retrospective design of the study introduces selection bias, and the small sample size may have reduced the statistical power needed to detect subtle differences between treatment groups. For instance, the higher rate of LN metastasis in the combined RT and CHT group may have masked potential benefits of CHT. On the other hand, as 94% of patients in the RT alone group were treated with 2DRT technique, this may have negatively impacted survival rates in the RT alone group. The absence of Epstein-Barr virus DNA data, a now-recognized key prognostic marker, further restricted our ability to conduct subgroup analyses that could identify patients most likely to benefit from concurrent CHT. Furthermore, 19% of patients received non-standard concurrent CHT regimens, and the cumulative dose data for those treated with cisplatin were incomplete.

CONCLUSION

In conclusion, our findings suggest that adding CHT to RT does not significantly improve survival outcomes in patients with AJCC 8th edition stage II NPC compared to RT alone, even among those with LN involvement or those treated with 2DRT. Avoiding unnecessary CHT in this population may reduce treatment-related toxicity and improve overall quality of life. However, stage II NPC, as classified by the AJCC 8th edition, is a heterogeneous disease, and certain patients—such as those with node-positive disease and elevated Epstein-Barr virus DNA levels—may still benefit from more intensive treatment. Future research should focus on identifying these specific subgroups through tumor biology, molecular profiling, and other key prognostic factors to enable more personalized and effective treatment strategies.

Ethics Committee Approval: The study was approved by the Hacettepe University Faculty of Medicine Ethics Committee (no: SBA 24/118, date: 23/01/2024).

Conflict of Interest: All authors declared no conflict of interest.

Financial Support: None declared.

Use of AI for Writing Assistance: No AI technologies utilized.

Authorship Contributions: Concept – A.K., M.T.Y., S.M., S.Y.S., M.C., İ.G., S.A., G.Ö., G.Y.; Design – A.K., M.T.Y., S.M., S.Y.S., M.C., G.Ö., G.Y.; Supervision – S.Y.S., M.C., G.Ö., G.Y.; Funding – S.Y.S., M.C., G.Ö., G.Y.; Materials – A.K., M.T.Y., S.M.; Data collection and/or processing – A.K., M.T.Y., S.M.; Data analysis and/or interpretation – A.K., M.T.Y.; Literature search – A.K., M.T.Y.; Writing – A.K.; Critical review – A.K., M.T.Y., S.M., S.Y.S., M.C., İ.G., S.A., G.Ö., G.Y.

Peer-review: Externally peer-reviewed.

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