Am J Cancer Res 2024;14(6):3142-3152
www.ajcr.us /ISSN:2156-6976/ajcr0155377

Original Article

The use of adjuvant chemotherapy combined with concurrent chemoradiotherapy enhances survival rates in cases of locally advanced nasopharyngeal carcinoma

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Received January 10, 2024; Accepted May 3, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: This study aimed to evaluate the impact of adjuvant chemotherapy on survival rates, adverse events, and quality of life (QOL) in patients with locally advanced nasopharyngeal carcinoma (NPC). A retrospective cohort study was conducted, including patients with firstly histologically confirmed non-metastatic stage III-IVB NPC between February 2018 and February 2020, and with continuous follow-up data available, were chosen from the medical records of the affiliated hospital of Qingdao University and Zibo Central Hospital. There were 395 patients receiving concurrent chemoradiotherapy (CCRT) with adjuvant chemotherapy (adjuvant chemotherapy group) and 428 patients receiving CCRT alone (control group). The two groups were compared for treatment response, adverse events, and QOL scores. Besides, Kaplan-Meier plots, and multivariate COX analysis were conducted. The adjuvant chemotherapy group demonstrated a significantly higher overall survival and disease-free survival compared to the control group. The use of adjuvant chemotherapy was significantly correlated with improved overall survival and disease-free survival. Adjuvant chemotherapy was associated with reduced local recurrence and distant metastasis rates. However, higher rates of adverse events were observed in the adjuvant chemotherapy group. QOL scores for physical functioning, emotional functioning, and overall quality of life were higher in the adjuvant chemotherapy group. The findings of this study indicate that adjuvant chemotherapy in locally advanced NPC is associated with improved treatment response, extended overall and disease-free survivals, and better QOL, despite higher rates of adverse events.

Keywords: Locally advanced nasopharyngeal carcinoma, adjuvant chemotherapy, treatment response, survival outcomes, quality of life

Introduction

Nasopharyngeal carcinoma (NPC) represents a distinct and geographically specific head and neck malignancy, with a notably higher incidence in certain ethnic populations, particularly in Southern China, Southeast Asia, and North Africa [1-3]. Evidently, NPC poses a significant health burden in these regions, accounting for approximately 30% of all head and neck cancers in endemic areas [3-5].

While advancements in treatment modalities, such as radiotherapy, have led to improved outcomes for patients with early-stage NPC, those with locally advanced disease continue to face considerable challenges [6, 7]. Historically, the treatment of locally advanced NPC has posed considerable challenges due to its anatomical location and high likelihood for locoregional spread [8]. Recently, the contribution of adjuvant chemotherapy to improving outcomes has emerged as a focus of evolving research interest [9, 10]. Given the intricate interaction of various treatment approaches and the necessity to identify strategies that offer superior disease control and survival benefits, the investigation of adjuvant chemotherapy in the

https://doi.org/10.62347/WMLA4979

management of locally advanced NPC demands comprehensive exploration [7, 10].

Adjuvant chemotherapy, which involves administering systemic cytotoxic agents following locoregional treatment, has been the subject of growing interest for its potential to target micrometastases and residual disease, thereby potentially enhancing overall survival rates [11-14]. Despite advancements in the treatment of locally advanced NPC, the specific impact of adjuvant chemotherapy on patient prognosis remains a subject of ongoing debate and investigation within the medical community [15]. The debate encompasses various aspects, including the selection of chemotherapy drugs, their efficacy in targeting micrometastases and residual disease, as well as concerns about safety and treatment-related adverse events. The current study is necessitated by the need to thoroughly assess adjuvant chemotherapy's role within the multimodal treatment framework for locally advanced NPC. By addressing the ongoing debate and filling existing knowledge, this study contributes to elucidating the potential benefits and drawbacks of adjuvant chemotherapy, thereby enhancing the understanding of its impact on patient outcomes and the overall management of locally advanced NPC. This study evaluates the utilization of adjuvant chemotherapy in the management of locally advanced NPC and its impact on survival rates, aiming to assess the rationality and efficacy of incorporating adjuvant chemotherapy in the multimodal treatment paradigm for this challenging malignancy.

Materials and methods

Sample size calculation

The sample size for this retrospective cohort study was determined using the power calculation method for a two-sample t-test. This calculation aimed to identify a predefined effect size (Cohen's d) of 0.2, with a significance level set at 0.05 and a statistical power of 0.8. A statistical power of 0.8 was selected to ensure sufficient sensitivity in detecting the anticipated difference in survival outcomes between the two treatment groups. Based on these parameters, the calculated sample size (n) required for each group was approximately 393.4057. To accommodate the practical challenges often encountered in observational studies, the minimum sample size was rounded up to 394.

Patient selection

Patients with firstly histologically confirmed non-metastatic stage III-IVB NPC between February 2018 and February 2020, and who had continuous follow-up data, were chosen from the medical records of the affiliated hospital of Qingdao University and Zibo Central Hospital. There were 395 patients receiving concurrent chemoradiotherapy (CCRT) with adjuvant chemotherapy (adjuvant chemotherapy group) and 428 patients receiving CCRT alone (control group). This study was approved by the Zibo Central Hospital Institutional Review Board and Ethics Committee (Ethics number: 20221101D). Informed consent was waived for this retrospective study because it solely utilized de-identified patient data, eliminating any potential harm or impact on patient care.

Inclusion criteria: (1) Patients with confirmed NPC through biopsy; (2) Comprehensive metastasis screening for patients with metastasis using PET/CT, head and neck MR, chest X-ray, abdominal B-ultrasound, and bone scan; (3) Extensive pre-treatment clinical examination data, such as complete blood count, full biochemical testing, quantitative EBV DNA testing, and Epstein-Barr virus antibody titer testing; (4) Systematic follow-up schedule: every 1-3 months for the first 3 years, then semi-annually for the 4th to 5th years, utilizing phone calls, text messages, and outpatient visits; (5) No prior history of other malignant tumors.

Exclusion criteria: (1) Patients with NPC presenting with distant metastasis at diagnosis; (2) Insufficient diagnostic basis for distant metastasis, such as incomplete imaging examinations or lack of biopsy; (3) Incomplete clinical data or lacking data on relevant outcomes.

The criteria to determine distant metastasis required that any indicative imaging be followed by additional investigations like CT, MRI, or biopsy to confirm suspected sites and to rule out metastasis from other organs. If a lesion couldn't be conclusively diagnosed in the follow-up, it was monitored every three months for at least a year. Lesions unchanged after one year could be considered local, leading to ex-

clusion if no further development was noted. Conversely, progression during follow-up indicated distant metastasis. The study's endpoint was either reported death or the last follow-up.

Concurrent chemoradiotherapy

In the initial evaluation of patients diagnosed with locally advanced NPC, the decision regarding the administration of adjuvant chemotherapy in conjunction with concurrent chemoradiotherapy or opting for concurrent chemoradiotherapy alone was influenced by a variety of critical factors. These factors, while emphasizing tumor stage, also considered patient preferences, and physician judgment. The tumor stage, detailing the extent of the primary tumor, was pivotal in shaping the treatment strategy. Additionally, patient-centered factors such as individual preferences and tolerability, along with thorough clinical assessments made by physicians, also contributed to the decision-making process. The allocation of patients to the adjuvant chemotherapy group or the control group entailed a comprehensive evaluation of these factors to ensure the individualized and tailored approach to treatment.

In the Concurrent chemoradiotherapy (CCRT) regimen, cisplatin was administered at a dose of 40 mg/m^2 as a 2-hour intravenous infusion weekly for up to seven cycles, commencing on the first day of radiotherapy. No dosage adjustments were allowed during CCRT. The radiotherapy regimen involved delivering 2.0-2.27 Gy per fraction, with five daily fractions per week for a duration of 6-7 weeks, utilizing megavoltage photon 3D conformal radiotherapy. The total radiation doses reached 66 Gy or more for the primary tumor and 60-66 Gy for the affected neck area, nsuring that all areas of potential local spread and bilateral cervical lymph nodes received at least 50 Gy.

Adjuvant chemotherapy

For adjuvant chemotherapy, patients were treated with cisplatin at a dose of 80 mg/m^2 administered intravenously over 4 hours on day 1, and fluorouracil at a dose of 4 g/m^2 given via a continuous intravenous infusion over 96 hours, with cycles repeated every 4 weeks for up to three cycles. These cycles commenced on days 28, 56, and 84 following the completion of radiotherapy.

Data collection

Data on patient characteristics, including age, gender, and relevant clinical factors, were collected from the medical records. Additionally, information on adjuvant chemotherapy status, detailed treatment regimens, and records of adverse events was obtained. The follow-up period for assessing the outcomes ranged from 1 year to 5 years, tailored to the specific outcome under assessment. Quality of life (QOL) scores were assessed using the EORTC QLQ-HN35, administered both during and after the completion of treatment.

Outcome measures

The primary outcome measures in this study were overall survival, disease-free survival, local control rate, and distant metastasis rate. Overall survival was defined as the duration from the point of diagnosis until death from any cause. Disease-free survival represented the time from diagnosis to disease recurrence or death from any cause. Local control rate referred to the percentage of patients without local disease progression during the follow-up period. Distant metastasis rate indicated the percentage of patients with the appearance of distant metastasis during the follow-up period. Additionally, the incidence of adverse events was assessed as a secondary outcome.

Statistical analysis

Descriptive statistics, including mean and standard deviation were utilized to summarize patient characteristics and outcomes. Continuous variables were compared between the two groups using the t-test or Wilcoxon test. Additionally, the association between categorical variables was assessed using the chi-square test or Fisher's exact test. Sperman correlation analysis was applied to identify correlations among various variables. Kaplan-Meier Plots were used to illustrate overall and disease-free survival rates. The COX proportional hazards model was utilized to assess the relationship between various parameters and the prognosis of patients with locally advanced NPC. These parameters included in the analysis were age, gender, hypertension, diabetes, tumor stage, tumor size, and the application of adjuvant chemotherapy. The model aimed to ascertain the influence of these parameters

Table 1. Demographic characteristics of study participants

Parameter	CCRT + Adjuvant Chemotherapy (n = 395)	CCRT (n = 428)	t/χ^2	P
Age (years)	50.51 ± 5.85	51.15 ± 6.82	1.451	0.147
Gender (Male/Female)	228	219	3.296	0.069
Hypertension	48	55	0.039	0.844
Diabetes	68	71	0.021	0.884
Tumor Stage (stage III/IVA)	247	274	0.137	0.712
Tumor Size (cm)	4.39 ± 0.95	4.51 ± 0.98	1.859	0.063
Histology			8.652	0.651
Differentiated keratinising	0	0		
Differentiated non-keratinising	36	34		
Undifferentiated non-keratinising	359	394		

Note: CCRT, concurrent chemoradiotherapy.

Table 2. Treatment response for the two types of strategy

Parameter	CCRT + Adjuvant Chemotherapy (n = 395)	CCRT (n = 428)
Complete Response	273	170
Partial Response	79	126
No Response	43	132
χ^2	78.79	
P	< 0.001	

Note: CCRT, concurrent chemoradiotherapy.

on overall survival. The Wald statistic was employed to assess the significance of each parameter, and the results were reported as coefficients (Coef), standard errors (S.E.), Wald statistics (Wald Z), and *p*-values (Pr(>|Z|)). The significance level was set at $P < 0.05$ to determine the statistical significance of the findings.

Results

Comparison of patient characteristics

The demographic characteristics of the study participants revealed comparable distributions across key parameters between the adjuvant chemotherapy and control groups. There were no significant differences in age (50.51 ± 5.85 vs. 51.15 ± 6.82, P = 0.147), gender distribution (P = 0.069), prevalence of hypertension (P = 0.844), diabetes incidence (P = 0.884), tumor stage (P = 0.712), tumor size (4.39 ± 0.95 vs. 4.51 ± 0.98, P = 0.063) and histological types were comparably distributed between the two groups (**Table 1**). These findings suggest that the baseline characteristics of the participants were evenly matched, effectively minimizing the risk of confounding factors and supporting the validity of subsequent comparative analyses assessing the effects of adjuvant chemotherapy on clinical outcomes.

Comparison of treatment response

The comparison of treatment response between the adjuvant chemotherapy and control groups revealed a significantly higher rate of complete response in the adjuvant chemotherapy cohort compared to the control group. Conversely, the control group demonstrated a higher incidence of no response compared to the adjuvant chemotherapy group (**Table 2**).

Comparison of overall survival

The analysis of overall survival demonstrated a significantly extended survival time in the adjuvant chemotherapy group in comparison to the control group (55.34 ± 4.43 vs. 47.49 ± 7.06 months, P < 0.001) (**Figure 1**). These findings emphasize the substantial survival advantage linked to the incorporation of adjuvant chemotherapy, highlighting its critical role in improving overall survival outcomes for patients with the locally advanced NPC.

Comparison of disease-free survival

The examination of disease-free survival between the adjuvant chemotherapy and control

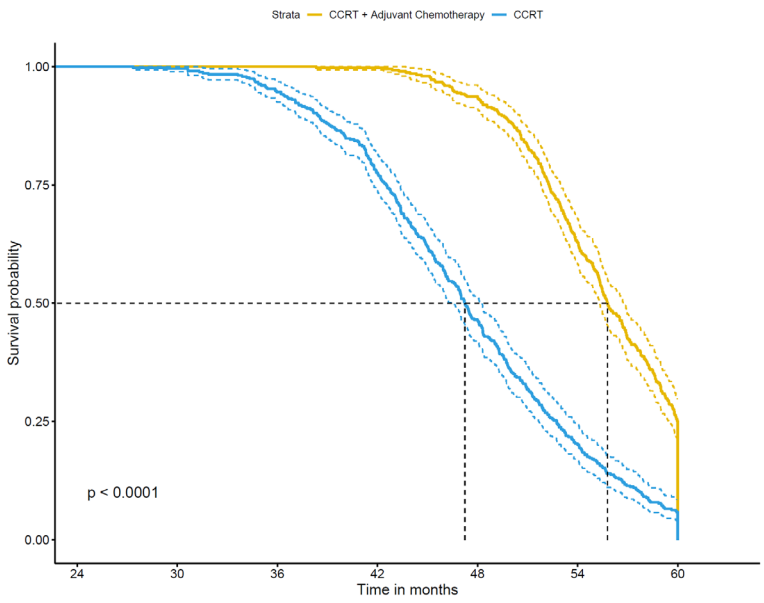

Figure 1. Overall survival analysis for the two types of strategy.

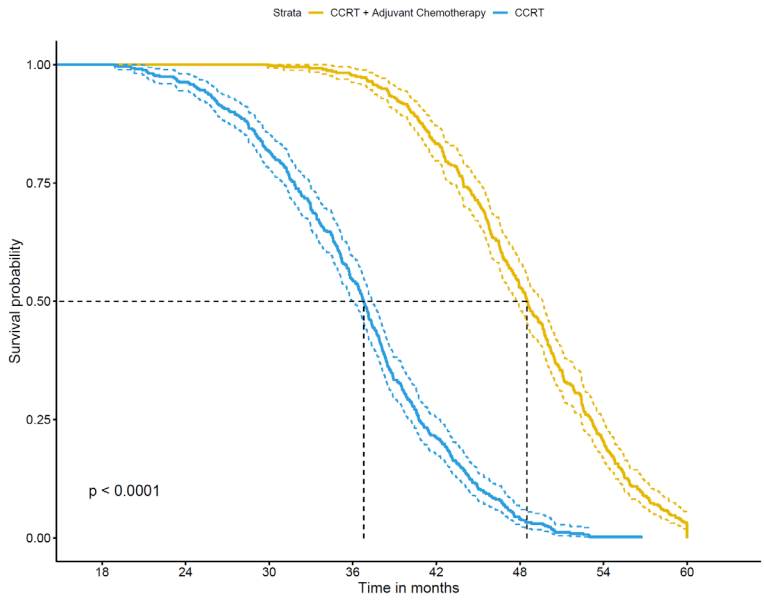

Figure 2. Disease-free survival analysis for the two types of strategy.

groups demonstrated a significantly extended disease-free interval in the adjuvant chemotherapy cohort compared to the control group (48.41 ± 6.21 vs. 36.45 ± 6.85 months, P < 0.001) (**Figure 2**). These findings underscore the substantial impact of adjuvant chemotherapy in conferring a pronounced benefit in terms of disease control, implicating its pivotal role in augmenting disease-free survival rates in the specified patient population.

Comparison of local recurrence rate

The analysis of local recurrence rates between the adjuvant chemotherapy and control groups revealed a lower incidence of local recurrence in the adjuvant chemotherapy group compared to the control group (χ^2 = 12.094, P < 0.001) (**Table 3**). While the difference did not reach statistical significance, a trend towards reduced local recurrence was observed in the adjuvant chemotherapy group.

Comparison of distant metastasis

The comparison of distant metastasis rates between the adjuvant chemotherapy and control groups indicated a relative lower occurrence of distant metastasis in the adjuvant chemotherapy cohort compared to the control group (χ^2 = 6.806, P = 0.009) (**Table 4**). While the noted variance did not achieve statistical significance, a trend towards decreased distant metastasis was apparent in the adjuvant chemotherapy group.

Comparison of adverse events

The comparison of treatment-related adverse events between the adjuvant chemotherapy and control groups revealed substantially higher rates of nausea (χ^2 = 151.005, P < 0.001), fatigue (χ^2 = 146.591, P < 0.001), hair loss (χ^2 = 61.072, P = 0.002) and hematological toxicity (χ^2 = 5.007, P = 0.025) in the adjuvant chemotherapy cohort (**Table 5**). These findings highlight the markedly elevated occurrence of specific adverse events in patients receiving adjuvant chemotherapy and underscore the importance of diligently considering and mitigating chemotherapy-related side effects in the clinical management of the specified patient population.

Table 3. Local recurrence rate for the two types of strategy

Group	Value	χ^2	*p*-value
CCRT + Adjuvant Chemotherapy (n = 395)	57	12.094	< 0.001
CCRT (n = 428)	104		

Note: CCRT, concurrent chemoradiotherapy.

Table 4. Distant metastasis rate for the two types of strategy

Group	Value	χ^2	*p*-value
CCRT + Adjuvant Chemotherapy (n = 395)	79		
CCRT (n = 428)	120	6.806	0.009

Note: CCRT, concurrent chemoradiotherapy.

Comparison of QoL

The comparison of QOL scores between the adjuvant chemotherapy and control groups demonstrated significantly higher scores in physical functioning (76.71 ± 10.95 vs. 75.1 ± 10.69, W = 91609.5, P = 0.038), emotional functioning (71.91 ± 12.06 vs. 70.21 ± 11.74, t = 2.05, P = 0.041), and overall QOL assessment (71.74 ± 10.32 vs. 70.13 ± 9.08, t = 2.376, P = 0.018) in the adjuvant chemotherapy cohort (**Figure 3**). These findings underscore the positive impact of adjuvant chemotherapy in promoting superior physical and emotional functioning, as well as overall QOL, signifying its potential role in enhancing the holistic well-being of patients undergoing treatment for the specified condition.

Multivariate COX analysis between the adjuvant chemotherapy and prognosis

The correlation analysis of overall survival in locally advanced NPC patients revealed the following associations (**Table 6**). Age showed a minimal positive correlation with survival (r = 0.05, R2 = 0.003, P = 0.536). Gender exhibited a weak positive correlation (r = 0.088, P = 0.281), while hypertension demonstrated a weak negative correlation with survival and diabetes showed minimal impact (r = -0.045, P = 0.578 and r = 0.026, P = 0.748, respectively). Tumor stage and size displayed negligible correlations with survival (r = 0.015, P = 0.855 and r = -0.088, R2 = 0.008, P = 0.282, respectively). Importantly, adjuvant chemotherapy indicated a minimal inverse relationship with survival outcomes (r = -0.028, R2 = 0.001, P < 0.001), suggesting its potential positive impact on overall survival.

The multivariate analysis using COX proportional hazards model revealed several key findings regarding the impact of adjuvant chemotherapy on the prognosis of patients with locally advanced NPC (**Table 7**). The analysis demonstrated that the use of adjuvant chemotherapy was significantly correlated with improved overall survival, as evidenced by a negative coefficient of -0.9529 (P < 0.001). Other factors such as age, gender, hypertension, diabetes, tumor stage, tumor size, and nodal involvement did not show statistically significant correlations with overall survival. Besides, the multivariate COX analysis also revealed that adjuvant chemotherapy had a significant impact on disease-free survival in patients with locally advanced NPC (Coef = -1.6997, Wald Z = -20.33, P < 0.0001) (**Table 8**), emphasizing the substantial contribution of adjuvant chemotherapy to prolonging the disease-free interval in this patient population. These results underscore the pivotal role of adjuvant chemotherapy in positively influencing the prognosis of patients with locally advanced NPC, thereby underlyinging its potential as a valuable treatment modality in improving clinical outcomes.

Discussion

Adjuvant chemotherapy, as a systemic treatment, has the ability to target micrometastases and residual disease beyond the confines of the primary tumor and the irradiated area [16, 17]. Its role in addressing potential micro-metastatic disease is critical in lowering the risk of distant metastases, significant contributing to improved survival outcomes and disease-free survival [18, 19]. The integration of adjuvant chemotherapy into a multimodal treatment paradigm, alongside CCRT, achieves a synergistic effect in overcoming the complex challenges posed by locally advanced NPC [20]. This comprehensive approach may effectively target both primary and micrometastatic disease, leading to improved treatment response and outcomes [20]. Particularly noticeable in this study was the significant enhancement in treatment response with adjuvant chemotherapy, evidenced by an increase in complete response and a considerable reduction in cases with no response when compared to the control group.

Table 5. Treatment-related adverse events for the two types of strategy

Parameter	CCRT + Adjuvant Chemotherapy (n = 395)	CCRT (n = 428)	X^2	P
Nausea (%)	194	43	151.005	< 0.001
Fatigue (%)	158	21	146.591	< 0.001
Hair Loss (%)	78	11	61.072	< 0.001
Hematological Toxicity (%)	36	21	5.007	0.025

Note: CCRT, concurrent chemoradiotherapy.

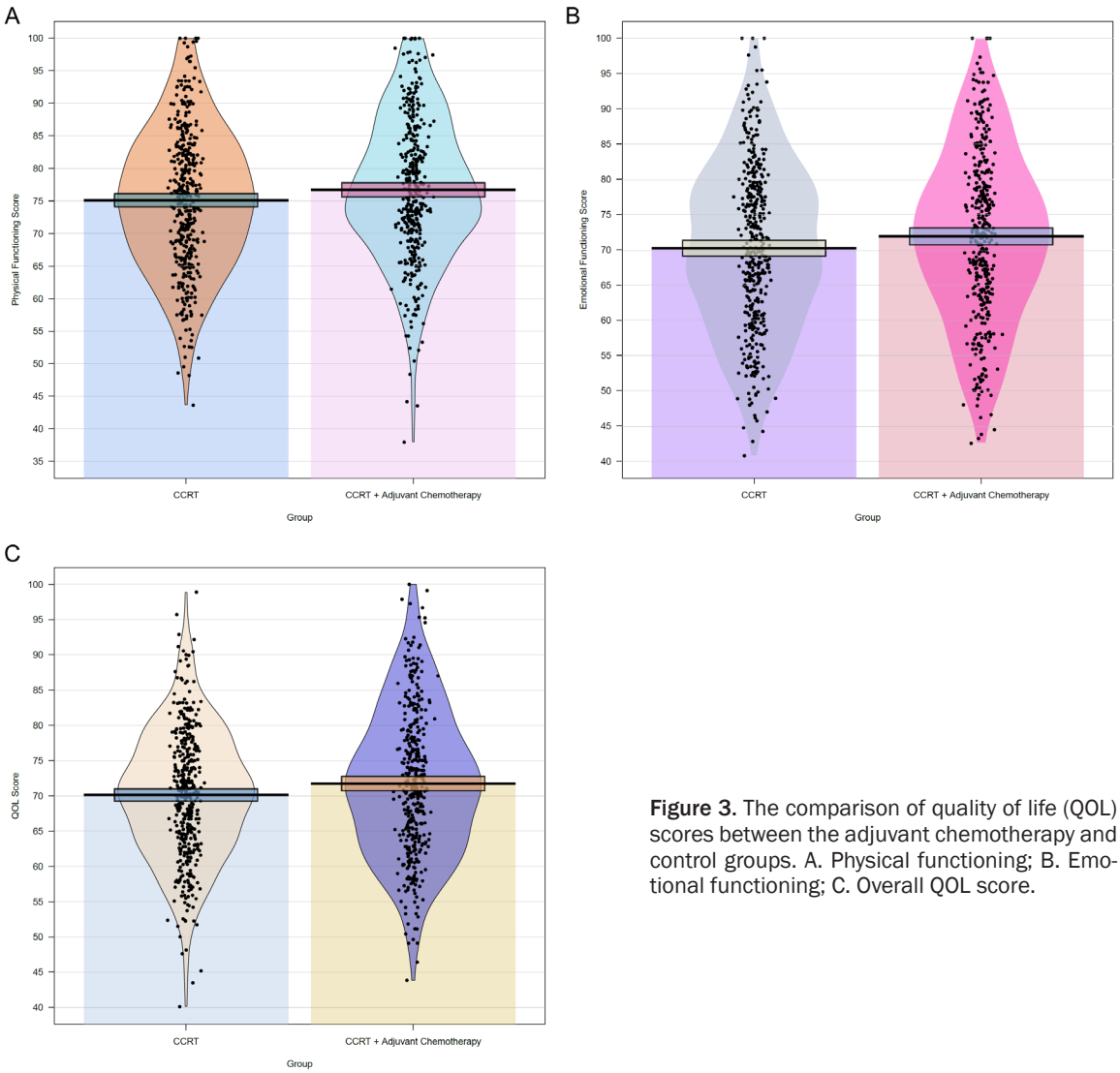

Figure 3. The comparison of quality of life (QOL) scores between the adjuvant chemotherapy and control groups. A. Physical functioning; B. Emotional functioning; C. Overall QOL score.

This aligns with previous research indicating that adjuvant chemotherapy increases the probability of tumor eradication and decreases the likelihood of treatment failure [21, 22]. Furthermore, the overarching implication is the substantial positive effect of adjuvant chemotherapy on prognosis, enhancing patient response rates while mitigating the incidence of non-responsive cases.

This study highlighted the crucial advantages of adjuvant chemotherapy in terms of overall survival and disease-free survival durations. Patients in both experienced a notable improvement in survivorship, underscoring the role of adjuvant chemotherapy in extending survival times and periods without disease. This finding is consistent with numerous other studies that have reinforced the positive corre-

Table 6. The correlation analysis of overall survival

Parameters	r	R2	*p* value
Age	0.05	0.003	0.536
Gender	0.088	-	0.281
Hypertension	-0.045	-	0.578
Diabetes	0.026	-	0.748
Tumor Stage	0.015	0	0.855
Tumor Size	-0.088	0.008	0.282
Adjuvant Chemotherapy	-0.028	0.001	< 0.001

Table 7. COX analysis between the adjuvant chemotherapy and overall survival

Parameters	Coef	S.E.	Wald Z	Pr(>|Z|)
Age	0.0045	0.0056	0.8	0.424
Gender	0.1043	0.0705	1.48	0.1389
Hypertension	-0.0651	0.1058	-0.62	0.5385
Diabetes	-0.0325	0.0936	-0.35	0.7284
Tumor Stage	0.0219	0.0728	0.3	0.7636
Tumor Size	0.0059	0.0373	0.16	0.8749
Adjuvant Chemotherapy	-0.9529	0.0723	-13.18	< 0.0001

Table 8. COX analysis between the adjuvant chemotherapy and disease free survival

Parameters	Coef	S.E.	Wald Z	Pr(>|Z|)
Age	0.0078	0.0057	1.37	0.1695
Gender	0.0709	0.0705	1.01	0.3141
Hypertension	-0.0219	0.1061	-0.21	0.8362
Diabetes	0.0318	0.0937	0.34	0.734
Tumor Stage	0.023	0.073	0.32	0.7521
Tumor Size	-0.0274	0.0368	-0.74	0.4565
Adjuvant Chemotherapy	-1.6997	0.0836	-20.33	< 0.0001

lation between utilization of adjuvant chemotherapy and improved survivorship outcomes in locally advanced NPC [23, 24].

When it comes to local recurrence and distant metastasis, our study delivered a latent trend towards reduced incidences in the adjuvant chemotherapy group. Although these findings did not reach statistical significance, they support the concept that the systemic reach of chemotherapy acts as a protective measure against both local and distant disease recurrence [25, 26]. The capacity of systemic chemotherapy to target micro-metastases and limit the spread of local disease highlights its critical role in comprehensive disease management [2, 27]. Our results suggest that adjuvant chemotherapy may offer a more robust and prolonged control over local disease, potentially preventing or delaying local recurrences - a key factor in long-term disease management and patient survival.

Treatment-related adverse events were distinctly more prevalent in the adjuvant chemotherapy group, aligning with well-documented side effects associated with chemotherapy, such as nausea, fatigue, and hair loss [26, 28]. Despite these challenges, such side effects are generally predictable and can be effectively managed with modern supportive care strategies. This underscores the necessity of carefully weighing the adverse events against the potential survival advantages, highlighting the critical role of personalized care in treatment decisions [29-31]. Intriguingly, despite the higher rates of adverse events associated with adjuvant chemotherapy, the study demonstrated that patients receiving adjuvant chemotherapy reported higher quality of life scores in physical and emotional functioning domains. This suggests that the potential benefits of adjuvant chemotherapy in terms of improved disease control and survival may outweigh its adverse effects, contributing to a more favorable overall QoL for treated patients.

Though chemotherapy is often associated with deterioration in QoL [32, 33], particularly in terms of physical and emotional well-being, the incorporation of adjuvant chemotherapy in this study led to higher QOL scores in these areas. This compelling evidence suggests that adjuvant chemotherapy may not only extend survival but also maintain or even improve health-related quality of life [34, 35]. It is worth discussing with patients these compelling findings during consultation, as QoL remains a critical aspect of cancer care [36].

The essence of this study lies in the robust positive correlations observed between the use of adjuvant chemotherapy and prognosis in terms of overall survival, disease-free sur-

vival, and QoL. These correlations highlight adjuvant chemotherapy's favorable prognostic implications to patients and healthcare stakeholders, emphasizing its role in the systemic control of micrometastases, potential for tumor eradication, enhancement of multimodal treatment approaches, reduction in local recurrence rates, and its capacity to preserve or improve patients' QoL. Collectively, these aspects reaffirm adjuvant chemotherapy's critical contribution to enhancing treatment responses and long-term outcomes for patients facing this complex cancer.

These factors collectively underscore the integral role of adjuvant chemotherapy in improving treatment response and long-term outcomes for patients with this challenging malignancy.

However, the study has limitations, including the lack of randomization and a relatively small sample size, which may diminish the statistical robustness of the findings. The retrospective design may also introduce selection bias. Future research should examine the long-term impacts of adjuvant chemotherapy more comprehensively. A well-structured, randomized controlled trial would provide stronger evidence to definitively address these limitations. Nonetheless, pending the outcomes of such trials, our study presents persuasive arguments for incorporating adjuvant chemotherapy into the treatment regimen for locally advanced nasopharyngeal carcinoma, always with a view towards customizing treatment based on individual patient profiles, prognostic factors, and preferences.

In summary, presents a compelling case for the incorporation of adjuvant chemotherapy in treating locally advanced NPC. Demonstrating enhanced survival rates, effective containment of local recurrence and distant metastases, and positive impacts on quality of life, the findings significantly advance our understanding of the benefits associated with adjuvant chemotherapy.

Acknowledgements

This study was supported by China Postdoctoral Science Foundation (2023M741859), Key Research and Development project of Shandong Province (2019GSF108269); the Natural Science Foundation of Shandong Province (ZR2020MC062); Key Research and Development project of Zibo City (2019gy010003).

Disclosure of conflict of interest

None.

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