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ORIGINAL RESEARCH

Prognostic Significance of Cervical Lymph Node Biopsy in Nasopharyngeal Carcinoma Patients: A Retrospective Analysis

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Background: The impact of cervical lymph node biopsy on survival, distant metastasis, and local recurrence in nasopharyngeal carcinoma (NPC) patients remains controversial. This study aims to compare the effects of cervical lymph node biopsy and nasopharyngeal biopsy on these outcomes.

Methods: This retrospective study enrolled NPC patients treated at the First Affiliated Hospital of Soochow University between January 2013 and December 2021. Kaplan-Meier method was used to evaluate the overall survival (OS), distant metastasis-free survival (DMFS), locoregional recurrence-free survival (LRFS), nodal recurrence-free survival (NRFS), and progression-free survival (PFS), with comparisons using the Log rank test. Univariate and multivariate Cox regression models were used to identify independent prognostic factors.

Results: A total of 721 NPC patients who underwent radiotherapy were retrospectively analyzed. Among them, 591 were diagnosed with nasopharyngeal biopsy, and 130 patients with cervical lymph node metastasis suspected to originate from NPC underwent confirmatory nasopharyngeal biopsy. In cervical lymph node biopsy, 36 had excisional biopsies, 85 had fine needle aspirations, and 9 cases were unspecified. Survival was not significantly different between patients with nasopharyngeal biopsy and cervical lymph node biopsy (5-year OS: 81.1% vs 85.0%; DMFS: 75.2% vs 80.6%; LRFS: 79.5% vs 78.7%; NRFS: 80.4% vs 80.4%; PFS: 74.3% vs 74.3%; all $p>0.05$). Results were similar for the propensity-matched cohort of 260 patients.Additionally, survival was not significantly different between the fine needle aspiration and excision biopsy groups (5-year OS: 85.1% vs 83.5%; DMFS: 79.7% vs 80.3%; LRFS: 85.2% vs 74.8%; NRFS: 85.1% vs 77.7%; PFS: 79.8% vs 71.7%; all $p>0.05$). Targeted therapy and >3 cycles of chemotherapy were prognostic factors in NPC patients ($p<0.05$).

Conclusion: Cervical lymph node biopsy did not increase the risk of locoregional recurrence, distant metastasis, or death in NPC patients.

Keywords: nasopharyngeal carcinoma, intensity-modulated radiotherapy, cervical lymph node biopsy, nasopharyngeal biopsy, overall survival, volumetric-modulated arc therapy

Introduction

Nasopharyngeal carcinoma (NPC), a malignant tumor originating from the nasopharyngeal epithelium, is one of the most common cancers in China, ranking first among head and neck tumors. With the high incidence, it is significantly distributed geographically and racially, with over 70% of cases occurring in East and Southeast Asia, displaying a north-to-south gradient within China.[1] The annual incidence is 20–50 cases per 100,000 people in southern China, compared to 0.5–1 cases per 100,000 people among Caucasians.[2] The incidence rate in men is higher than in women, with a male-to-female ratio of approximately 2.5:1 in China.[3,4]

The common clinical presentations of NPC are neck masses (76%), nasal symptoms (73%), auditory symptoms (62%), and cranial nerve affection (20%). Patients with neck masses are frequently asymptomatic at initial presentation. Rapidly enlarging unilateral or bilateral neck masses are located at the posterior cervical triangle or the area of cervical lymph node chains, with or without other clinical symptoms and signs.[5] Cervical lymph node metastasis can be seen

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upon MRI in 75–87% of patients at the time of diagnosis.[6,7] The diagnosis of NPC is made by histopathological examination of biopsied suspected nasopharyngeal tumor tissue. However, 1–2% of patients with cervical lymphadenopathy and elevated plasma EBV DNA or EBV antibody levels, have occult primary lesions undetected by nasopharyngoscopy, often indicating nasopharyngeal mucositis on the histopathological examination of biopsied nasopharyngeal tissue.[8,9] Due to the uncertainty of the cancerous lesion, repeated nasopharyngeal biopsies are sometimes necessary. Repeated nasopharyngeal biopsies before treatment may adversely affect NPC patients' survival, possibly increasing the risk of metastasis.[10] In some patients, cervical lymph node biopsy is performed for histopathological evaluation before identifying the primary lesion, and based on the result the primary lesion is determined.

Cervical lymph node resection or puncture biopsy in NPC may affect patient prognosis by shedding cancer cells, vascular damage, and compression of tumor tissue, promoting tumor cell dissemination and micrometastasis. Theoretical concerns exist that cervical lymph node biopsy could mechanically disseminate tumor cells, potentially increasing distant metastasis risk. Some studies from the last century also indicate that cervical lymph node puncture or excisional biopsy increased the rate of distant metastasis by over 20%.[11] However, in recent studies, cervical lymph node biopsy before treatment did not increase the risk of death in NPC patients.[12–14] The NCCN Guidelines for Head and Neck Cancers since 2016 have recommended "primary site biopsy or cervical lymph node fine needle aspiration biopsy (FNA)" for NPC patients.[15] The CSCO Guidelines also suggest cervical lymph node biopsy as a level II expert recommendation for patients who cannot have a nasopharyngeal biopsy.[16] However, the 2012 European Society for Medical Oncology (ESMO) - European Society for Radiotherapy and Oncology (ESTRO) Clinical Practice Guidelines for Nasopharyngeal Carcinoma do not recommend cervical lymph node biopsy. When the primary tumor is not identified, lymph node excision with the preservation of the capsule or percutaneous biopsy under ultrasound guidance is advised.[17]

Radiotherapy is the main treatment modality for NPC. Intensity-modulated radiation therapy (IMRT) has improved the local control and survival rate of NPC while reducing the toxic side effects of radiotherapy.[18] For locally advanced NPC, combined targeted therapy with chemoradiotherapy in addition to radiotherapy has shown positive survival benefits and tolerable toxicity.[19] Survival impact by cervical lymph node biopsy for histopathological evaluation in NPC is questionable. Although previous studies[12,13] compared the diagnostic benefits of different biopsy types, they did not provide information on chemotherapy regimens and sequences, radiotherapy technology and doses, or targeted therapy. Furthermore, they lacked data on local recurrence or distant metastasis and did not comprehensively assess their impact on all survival outcomes (overall survival, distant metastasis-free survival, local recurrence-free survival, and disease-free survival) while controlling for confounding factors through propensity score matching. Whether biopsy selection affects locoregional control or survival in advanced NPC (Stage III–IV) remains unresolved, particularly in cohorts receiving modern targeted therapy and IMRT regimens—a gap our study directly addresses.This study aimed to explore the effect of cervical lymph node biopsy on the prognosis of NPC compared to nasopharyngeal biopsy, and identify significant prognostic factors.

Methods

Study Design and Participants

This retrospective study enrolled NPC patients treated at the First Affiliated Hospital of Soochow University between January 2013 and December 2021. The inclusion criteria were: 1) Patients ultimately diagnosed with NPC via nasopharyngeal biopsy; 2) Patients without distant metastasis, confirmed through nasopharyngeal MRI, chest CT, abdominal CT or ultrasound, and bone scans; 3) Patients who received initial treatment at this hospital and completed curative radiotherapy. The exclusion criteria were: 1) Patients with only positive cervical lymph node biopsy without nasopharyngeal histopathological confirmation; 2) Patients diagnosed with distant metastasis before initial treatment; 3) Patients with a second primary tumor concurrent to NPC; 4) Patients who did not complete radiotherapy for various reasons; 5) Patients who developed distant metastasis during radiotherapy; 6) Patients who terminated radiotherapy due to severe complications, such as cardiac, pulmonary, hepatic, or renal insufficiency, severe infection, or severe bone marrow suppression. The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital

of Soochow University (approval number: NO.2024 (232)), and informed consent was waived due to the retrospective nature.

All cases were retrospectively restaged according to the 8th edition of the UICC/AJCC staging system. Patients were divided into two groups based on whether they had cervical lymph node biopsy: the nasopharyngeal biopsy group and the cervical lymph node biopsy group. The cervical lymph node biopsy group was further, subdivided into the cervical lymph node fine-needle aspiration (FNA) biopsy group and the cervical lymph node excisional biopsy group.

Data Collection and Definition

Treatment Regimen

All patients received individualized treatments based on the guidelines of the Chinese Society of Clinical Oncology (CSCO) and the National Comprehensive Cancer Network (NCCN) for head and neck tumors. Treatment modalities included radiotherapy, chemotherapy, targeted therapy, and general supportive care.

All patients underwent radical radiotherapy, either intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT). Patients were placed in a supine position with a thermoplastic mask for head, neck, and shoulder fixation, followed by enhanced CT scanning from the cranial vertex to the tracheal bifurcation. The prescribed radiation doses were as follows. GTVnx (primary nasopharyngeal tumor): 70–70.2 Gy/32-33 fractions; GTVnd (positive cervical lymph nodes): 68–70 Gy/32-33 fractions; CTV1 (high-risk subclinical region of the primary tumor): 66 Gy/32-33 fractions; CTV2 (upper cervical lymphatic drainage region): 64 Gy/32-33 fractions; andCTV3 (lower cervical and supraclavicular lymphatic drainage region): 54–60 Gy/28-33 fractions. All patients received radiation therapy once daily, five times a week.

Chemotherapy included induction chemotherapy before radiotherapy, concurrent chemotherapy during radiotherapy, and adjuvant chemotherapy after radiotherapy. Induction and adjuvant chemotherapy regimens included taxanes plus platinum (TP) or fluorouracil plus platinum (PF), specifically docetaxel/paclitaxel/fluorouracil plus cisplatin/nedaplatin with the administration of once every three weeks. Concurrent chemotherapy consisted of cisplatin at 80–100 mg/m^2 every three weeks. Chemotherapy dosage and cycles, not exceeding six, were calculated based on the patient's age, height, weight, cancer stage, overall health, and treatment tolerance.

Nimotuzumab was administered to patients meeting: (1) Stage III–IVb disease, (2) ECOG ≤2, (3) EGFR over-expression (IHC ≥2+), and (4) no prior anti-EGFR therapy, after obtaining informed consent from the patients, we used Nimotuzumab combined with radical radiotherapy. Nimotuzumab was administered at a dosage of 200 mg once a week for a total of 6 to 7 doses.

Definitions of Local Recurrence, Lymph Node Recurrence, and Distant Metastasis

Local recurrence was defined as the reappearance of the same pathological type of tumor in the nasopharynx, confirmed by histopathological examination of the biopsied specimen, at least six months after clinical tumor remission following radical radiotherapy. Lymph node recurrence was referred to the reappearance of tumor-positive cervical lymph nodes at least six months after clinical tumor remission following radical radiotherapy, confirmed by imaging or histopathological examination of the biopsied cervical lymph node. Distant metastasis refers to the occurrence of metastasis in distant organs after the completion of radiotherapy.[20]

Follow-up

Patients were followed up every 3–4 months during the first 2 years, every 6 months during years 3–5, and annually after 5 years. Follow-up evaluations were blood analysis, nasopharyngoscope examination, nasopharynx MRI, chest CT, abdominal CT or ultrasound, and bone scans. Medical records for the treatment and follow-up periods were reviewed, and data on gender, age, biopsy method, pathological type of tumor, TNM stage, treatment regimen, recurrence, and metastasis were retrieved. Information on survival was obtained through medical records or phone interviews. For deceased patients, survival endpoints were verified through hospital records or next-of-kin interviews.

The overall survival (OS) time, distant metastasis-free survival (DMFS) time, local recurrence-free survival (LRFS) time, lymph node recurrence-free survival (NRFS) time, and progression-free survival (PFS) time were calculated from

the date of initial pathological diagnosis to death or the last follow-up date of December 31, 2023. OS was defined as the interval between diagnosis and death from any cause. DMFS was defined as the interval between diagnosis and the first metastasis event. LRFS was defined as the interval between diagnosis and the first local recurrence event. NRFS was defined as the interval between diagnosis and the first cervical lymph node metastasis event. PFS was defined as the interval between diagnosis and disease progression (recurrence and/or metastasis) or death from any cause.[21]

Statistical Analysis

Statistical analyses were conducted using SPSS version 29.0. The chi-square (χ^2) test was employed to compare clinical characteristics between groups. Kaplan-Meier survival curves were constructed, and the Log rank test was used to evaluate the significance of differences between these curves.

PSM was used for randomization in this study to correct for selection bias and confounding bias. We employed a 1:1 propensity score matching method with 0.2 SD caliper to balance patient characteristics. The following variables were used for matching: age, gender, tumor stage (T stage), node stage (N stage), clinical stage, targeted therapy, number of chemotherapy cycles, and the time from diagnosis to treatment. Covariate balance was assessed via standardized mean differences (post-matching SMD<0.1 or P>0.5 for all variables). Outcomes were analyzed using multivariable Cox regression, adjusting for residual imbalances. Analyses were conducted in R with the "MatchIt" package (version 4.3.0).

Univariate and multivariate Cox regression models were used to identify independent prognostic factors, with hazard ratios (HR) and 95% confidence intervals (CI) calculated. Significant prognostic factors from the univariate analysis ($p<0.05$) were further incorporated into the multivariate analysis. A two-sided p-value of less than 0.05 was deemed statistically significant. Missing covariate data (<3% of cases) were handled using multiple imputation with fully conditional specification. Sensitivity analyses confirmed that results were robust to alternative approaches (eg, complete-case analysis).

Results

Demographic Characteristics

A total of 813 NPC patients were initially identified. Among them, 40 had a concurrent second primary tumor, 49 had distant metastasis at the initial diagnosis, 1 was diagnosed with NPC based only on imaging, and 2 did not complete curative radiotherapy. Ultimately, 721 patients were included in this study. There were 534 males and 187 females, with a male-to-female ratio of 2.86:1. The age ranged from 13 to 82 years, with a median age of 56 years and an average age of 54 ± 12 years. The median follow-up period was 77.8 months. All patients received radical radiotherapy, 675 patients with stage II–IVA received platinum-based chemotherapy.Among them, 337 patients received additional targeted therapy with nimotuzumab (200 mg/week for 6–7 weeks).During the follow-up period, 25 patients experienced local recurrence in the nasopharynx, 17 patients had cervical lymph node recurrence, and 103 patients developed distant metastases. Among all patients, 591 (81.97%) underwent a nasopharyngeal biopsy and 130 (18.03%) underwent both nasopharyngeal and cervical lymph node biopsies. Among them, 36 patients (4.99%) had lymph node excisional biopsy, 85 patients (11.79%) had fine needle aspiration biopsy (FNAB), and 9 patients (1.25%) had cervical lymph node biopsy but unclear whether it was a fine needle aspiration biopsy or an excisional biopsy. After conducting propensity score matching, a total of 260 patients were successfully matched, including 130 patients in the cervical lymph node biopsy group and 130 patients in the nasopharyngeal biopsy group, with no significant differences in baseline covariates (all p>0.05; Table 1).

Comparison of Survival Outcome Between Nasopharyngeal Biopsy Group and Cervical Lymph Node Biopsy Group

The median follow-up time for the 721 patients was 77.8 months (95% CI, 75.1 to 80.3 months). The median follow-up time for the nasopharyngeal biopsy group was 78.2 months (95% CI, 75.3 to 81.4 months), while for the cervical lymph node biopsy group, it was 75.7 months (95% CI, 66.9 to 80.3 months). The 5-year OS rate was 81.1% (95% CI, 77.9–84.5%) for the nasopharyngeal biopsy group and 85.0% (95% CI, 78.8–91.7%) for the cervical lymph node biopsy group (p=0.19). The 5-year DMFS rate was 75.2% (95% CI, 71.7–78.9%) for the nasopharyngeal biopsy group and

Table 1 Clinical Characteristics of 721 NPC Patients in Nasopharynx Biopsy Group and Cervical Lymph Node Biopsy Group Before Propensity Score Matching (PSM) and 260 Patients After PSM

Variables	Before PSM					After PSM				
	Total (N=721)	Nasopharynx biopsy group (N=591)	Cervical lymph node biopsy (N=130)	P value	SMD	Total (N=260)	Nasopharynx biopsy group (N=130)	Cervical lymph node biopsy (N=130)	P value	SMD
Age, year n%				0.3	0.11				1	0.018
≤45	161(22.3)	127(21.5)	34(26.2)			67(25.8)	33(25.4)	34(26.2)		
>45	560(77.7)	464(78.5)	96(73.8)			193(74.2)	97(74.6)	96(73.8)		
Gender, n%				0.8	0.037				1	0.018
Male	534(74.1)	436(73.8)	98(75.4)			197(75.8)	99(76.2)	98(75.4)		
Female	187(25.9)	155(26.2)	32(24.6)			63(24.2)	31(23.8)	32(24.6)		
Tumor stage, n%				<0.01	0.406				0.886	0.1
T1	192(26.6)	149(25.2)	43(33.1)			91(37.0)	48(36.9)	43(33.1)		
T2	277(38.4)	219(73.1)	58(44.6)			113(43.5)	55(42.3)	58(44.6)		
T3	167(23.2)	143(24.2)	24(18.4)			45(17.3)	21(16.2)	24(18.5)		
T4	85(11.8)	80(13.5)	5(3.9)			11(4.2)	6(4.6)	5(3.8)		
Node stage, n%				<0.01	0.516				0.149	0.276
N0	35(4.9)	35(5.9)	0(0.0)			1(0.4)	1(0.8)	0(0.0)		
N1	119(16.5)	96(16.2)	23(17.7)			41(15.8)	18(13.8)	23(17.7)		
N2	486(67.4)	408(69.0)	78(60.00)			170(65.4)	92(70.8)	78(60.0)		
N3	81(11.2)	52(8.8)	29 (22.3)			48(18.4)	19(14.6)	29(22.3)		
Clinical stage, n%				0.1	0.256				0.319	0.228
I	12(1.7)	12 (2.0)	0 (0.0)			1(0.4)	1(0.8)	0(0.0)		
II	82(11.4)	63 (10.7)	19 (14.6)			34(13.1)	15(11.5)	19(14.6)		
III	472(65.5)	393 (66.5)	79 (60.8)			169(65.0)	90(69.2)	79(60.8)		
IVA	155(21.5)	123 (20.8)	32 (24.6)			56(21.5)	24(18.5)	32(24.6)		
Targeted therapy, n%				0.2	0.136				0.804	0.046
Yes	337(46.7)	269 (45.5)	68 (52.3)			121(46.5)	59(45.4)	62(47.7)		
No	384(53.7)	322 (54.5)	62 (47.7)			139(53.5)	71(54.6)	68(52.3)		
Chemotherapy-cycles				0.09	0.182				1	0.019
≤3	206(28.6)	177 (29.9)	29 (22.3)			55(21.2)	27(20.8)	28(21.5)		
>3	515(71.4)	414 (70.1)	101 (77.7)			205(78.8)	103(79.2)	102(78.5)		
Interval time (days)				<0,01	0.567				1	0.018
≤15	340(47.2)	307 (51.5)	33 (25.4)			195(75.0)	98(75.4)	97(74.6)		
>15	381(52.8)	284 (48.5)	97 (74.6)			65(25.0)	32(24.6)	33(25.4)		
5-year OS	81.8%(78.9–84.8%)	81.1%(77.9–84.5%)	85.0%(78.8–91.7%)	0.19		83.3%(78.5–88.3%)	81.3%(74.2–89.1%)	85.0%(78.8–91.7%)	0.30	
5-year DMFS	76.2%(73.0–79.5%)	75.2%(717–78.9%).	80.6%(73.9–87.9%)	0.20		79.0%(73.9–84.4%)	77.3%(69.9–85.4%)	80.6%(73.9–87.9%)	0.41	
5-year LRFS	79.3%(76.3–82.5%)	79.5%(76.2–83.0%)	78.7%(71.7–86.4%)	0.95		79.6%(74.5–85.0%)	80.7%(73.5–88.5%)	78.7%(71.7–86.4%)	0.88	
5-year NRFS	80.4%(77.5–83.5%)	80.4%(77.2–83.9%)	80.4%(73.7–87.8%)	0.85		80.9%(76.0–86.2%)	81.3%(74.2–89.1%)	80.4%(73.7–87.8%)	0.96	
5-year PFS	74.3%(71.1–77.6%)	74.3%(70.7–78.0%)	74.3%(66.9–82.4%)	0.82		75.3%(70.0–81.0%)	76.6%(69.2–84.8%)	74.3%(66.9–82.4%)	0.92	

Notes: TNM staging followed the 8th edition of the AJCC/UICC staging system.

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80.6% (95% CI, 73.9–87.9%) for the cervical lymph node biopsy group (p=0.20). The 5-year LRFS rate was 79.5% (95% CI, 76.2–83.0%) for the nasopharyngeal biopsy group and 78.7% (95% CI, 71.7–86.4%) for the cervical lymph node biopsy group (p=0.95). The 5-year NRFS rate was 80.4% (95% CI, 77.2–83.9%) for the nasopharyngeal biopsy group and 80.4% (95% CI, 73.7–87.8%) for the cervical lymph node biopsy group (p=0.85). The 5-year PFS rate was 74.3% (95% CI, 70.7–78.0%) for the nasopharyngeal biopsy group and 74.3% (95% CI, 66.9–82.4%) for the cervical lymph node biopsy group (p=0.82).

Of the 260 patients after propensity score matching, The 5-year OS rate was 81.3% (95% CI, 74.2–89.1%) for the nasopharyngeal biopsy group and 85.0% (95% CI, 78.8–91.7%) for the cervical lymph node biopsy group (p=0.3). The 5-year DMFS rate was 77.3% (95% CI, 69.9–85.4%) for the nasopharyngeal biopsy group and 80.6% (95% CI, 73.9–87.9%) for the cervical lymph node biopsy group (p=0.41. The 5-year LRFS rate was 80.7% (95% CI, 73.5–88.5%) for the nasopharyngeal biopsy group and 78.7% (95% CI, 71.7–86.4%) for the cervical lymph node biopsy group (p=0.88). The 5-year NRFS rate was 81.3% (95% CI, 74.2–89.1%) for the nasopharyngeal biopsy group and80.4% (95% CI, 73.7–87.8%) for the cervical lymph node biopsy group (p=0.96). The 5-year PFS rate was 76.6% (95% CI, 69.2–84.8%) for the nasopharyngeal biopsy group and 74.3% (95% CI, 66.9–82.4%) for the cervical lymph node biopsy group (p=0.92).

There were no significant differences between the two groups in overall survival, distant metastasis-free survival, local recurrence-free survival, nodal recurrence-free survival, and progression-free survival before and after propensity score matching. (all p>0.05). (Table 1, Figures 1 and 2).

Comparison of Survival Outcome Between Fine Needle Aspiration Biopsy Group and Lymph Node Excisional Biopsy Group

The 5-year OS rate for the fine needle aspiration biopsy group compared to the lymph node excisional biopsy group was 85.1% (95% CI, 73.8–98.1%) vs 83.5% (95% CI, 75.5–92.2%) (p=0.49). The 5-year DMFS rate was 79.7% (95% CI, 67.3–94.4%) vs 80.3% (95% CI, 72.0–89.5%) (p=0.88). The 5-year LRFS rate was 85.2% (95% CI, 73.9–98.1%) vs 74.8% (95% CI, 65.7–85.1%) (p=0.18). The 5-year NRFS rate was 85.1% (95% CI, 73.8–98.1%) vs 77.7% (95% CI, 69.0–87.4%) (p=0.28). The 5-year PFS rates were 79.8% (95% CI, 67.4–94.4%) vs 71.7% (95% CI, 62.4–82.3%) (p=0.30). None of these differences were statistically significant (Figure 3). Propensity score matching could not be performed because of the small sample size in the cervical lymph node biopsy group.

Prognostic Factor Analysis for Patients in the Nasopharyngeal Biopsy Group

Univariate and multivariate Cox regression models found that in 591 nasopharynx biopsy patients, male gender (HR 2.10, 95% CI 1.31–3.36, p=0.002), age over 45 years (HR 1.71, 95% CI 1.02–2.84, p=0.040), tumor stage T4 vs T1 (HR 3.58, 95% CI 2.00–6.43, p<0.001), targeted therapy (HR 0.65, 95% CI 0.44–0.96, p=0.030), and chemotherapy cycles >3 (HR 0.58, 95% CI 0.40–0.83, p=0.002) as significant factors of OS; male gender (HR 1.70, 95% CI 1.14–2.55, p=0.009), tumor stage T2 vs T1 (HR 1.63, 95% CI 1.03–2.59, p=0.038), T3 vs T1 (HR 1.90, 95% CI 1.16–3.11, p=0.010), and T4 vs T1 (HR 3.45, 95% CI 2.08–5.72, p<0.001) as significant factors of DMFS; male gender (HR 1.84, 95% CI 1.19–2.84, p=0.006), age over 45 years (HR 1.66, 95% CI 1.02–2.69, p=0.040), tumor stage T2 vs T1 (HR 1.80, 95% CI 1.09–2.96, p=0.022), T3 vs T1 (HR 1.99, 95% CI 1.16–3.42, p=0.012), and T4 vs T1 (HR 3.48, 95% CI 1.99–6.10, p<0.001), targeted therapy (HR 0.68, 95% CI 0.47–0.99, p=0.042) and chemotherapy cycles >3 (HR 0.59, 95% CI 0.42–0.83, p=0.003) as significant factors of LRFS; male gender (HR 1.95, 95% CI 1.24–3.07, p=0.004), age over 45 years (HR 1.69, 95% CI 1.03–2.78, p=0.037), tumor stage T2 vs T1 (HR 1.85, 95% CI 1.11–3.08, p=0.018), T3 vs T1 (HR 2.03, 95% CI 1.17–3.51, p=0.012), and T4 vs T1 (HR 3.40, 95% CI 1.91–6.05, p<0.001), targeted therapy (HR 0.65, 95% CI 0.44–0.95, p=0.028) and chemotherapy cycles >3 (HR 0.59, 95% CI 0.42–0.84, p=0.003) as significant factors of NRFS; male gender (HR 1.60, 95% CI 1.09–2.35, p=0.017), tumor stage T3 vs T1 (HR 1.82, 95% CI 1.13–2.93, p=0.014), and T4 vs T1 (HR 3.45, 95% CI 2.12–5.63, p<0.001) as significant factors of PFS (Table 2).

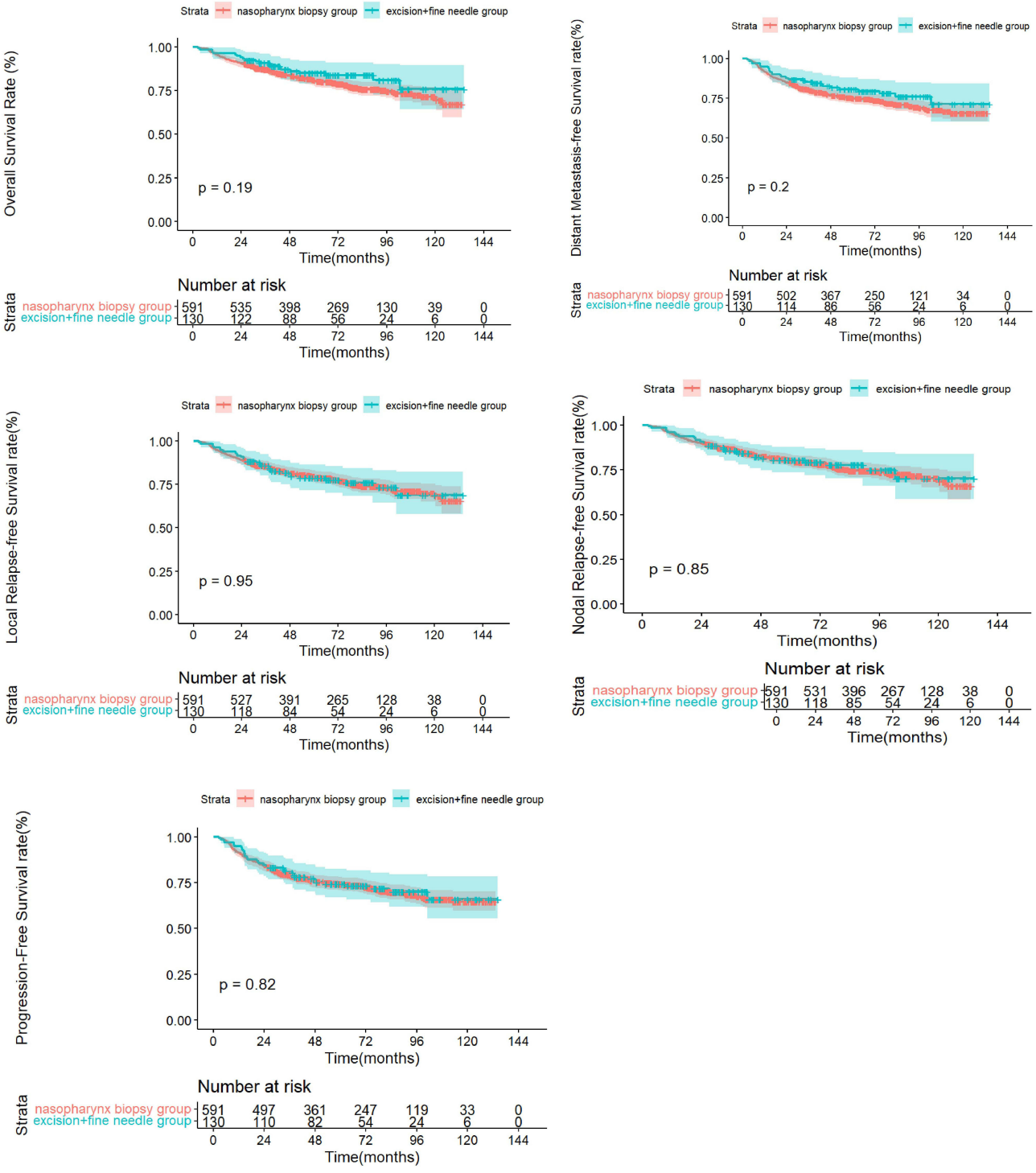

Figure 1 Comparisons of overall survival (OS), distant metastasis-free survival (DMFS), local relapse-free survival (LRFS), nodal relapse-free survival (NRFS) and progression-free survival (PFS) curves between nasopharyngeal biopsy patients (n=591) and cervical lymph node biopsy patients (n=130).

Prognostic Factor Analysis for Patients in the Cervical Lymph Node Biopsy Group

Univariate and multivariate Cox regression models found that in 130 cervical lymph node biopsy patients, age >45 years (HR 8.99, 95% CI 1.20–67.53, p=0.033) and targeted therapy (HR 0.34, 95% CI 0.12–0.93, p=0.036), chemotherapy cycles >3 (HR 0.35, 95% CI 0.14–0.88, p=0.026) as significant factors of OS; chemotherapy cycles >3 (HR 0.38, 95% CI

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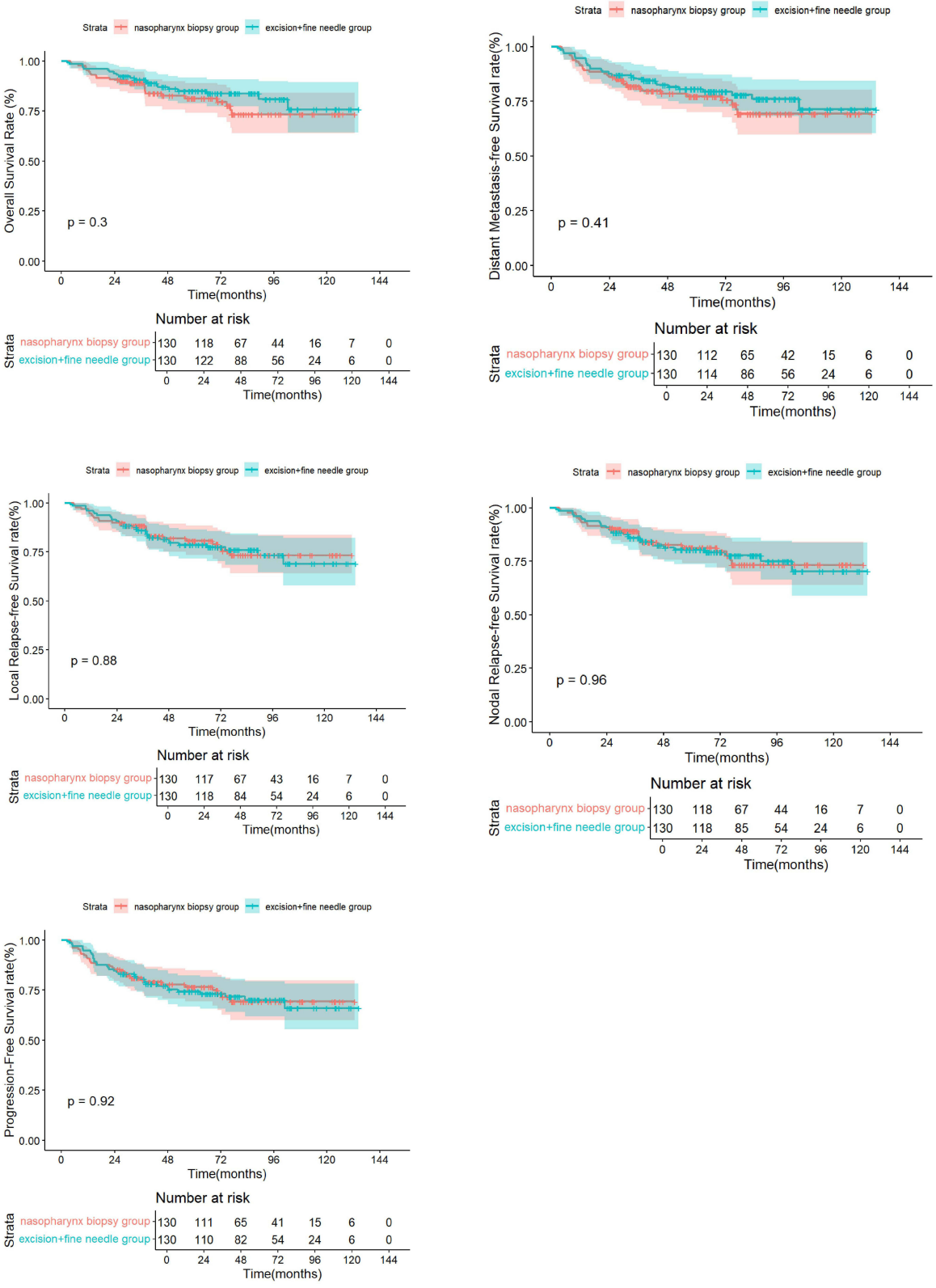

Figure 2 Comparisons of overall survival (OS), distant metastasis-free survival (DMFS), local relapse-free survival (LRFS), nodal relapse-free survival (NRFS) and progression-free survival (PFS) curves between nasopharyngeal biopsy patients (n=130) and cervical lymph node biopsy patients (n=130) after propensity score matching (PSM).

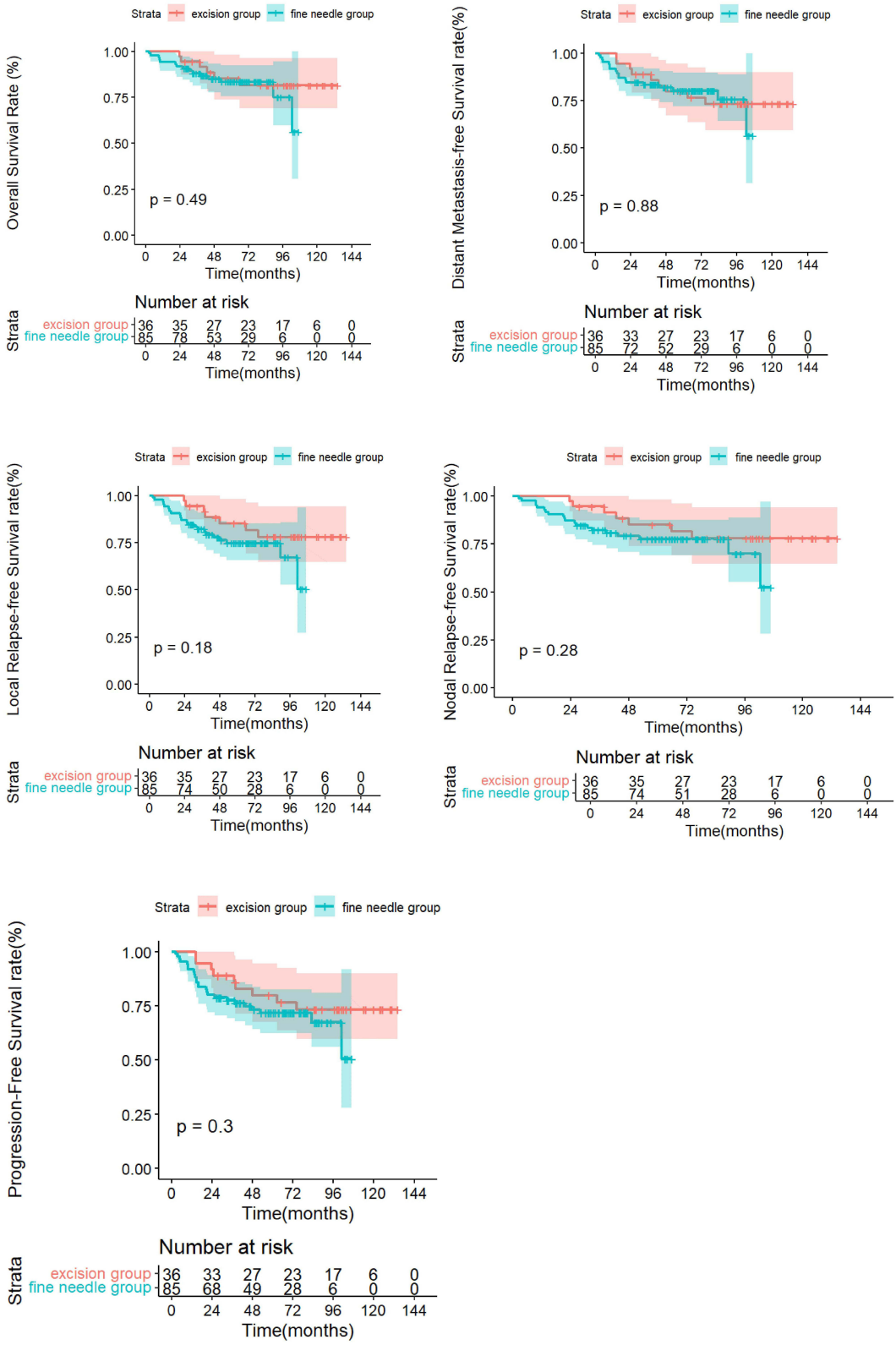

Figure 3 Comparisons of overall survival (OS), distant metastasis-free survival (DMFS), local relapse-free survival (LRFS), and progression-free survival (PFS) curves between cervical lymph node excisional biopsy patients (n=36) and cervical lymph node fine needle biopsy patients (n=85).

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Table 2 Univariate and Multivariate Cox Hazards Proportional Regression Analysis of Factors Associated with OS, DMFS, LRFS, NRFS, and PFS (N=591 Nasopharynx Biopsy Patients)

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
OS (Overall Survival)				
Gender (Male vs female)	2.07 (1.30, 3.30)	0.002	2.10 (1.31, 3.36)	0.002
Age (> 45 years vs ≤ 45 years)	1.97 (1.19, 3.24)	0.008	1.71 (1.02, 2.84)	0.040
Tumor stage (T2 vs T1)	1.84 (1.10, 3.10)	0.021	1.87 (1.11, 3.16)	0.018
Tumor stage (T3 vs T1)	2.00 (1.15, 3.49)	0.015	2.04 (1.16, 3.59)	0.012
Tumor stage (T4 vs T1)	3.31 (1.86, 5.91)	<0.001	3.58 (2.00, 6.43)	<0.001
Nodal stage (N1 vs N0)	1.04 (0.44, 2.47)	0.932		
Nodal stage (N2 vs N0)	1.18 (0.55, 2.54)	0.676		
Nodal stage (N3 vs N0)	1.60 (0.65, 3.98)	0.309		
Clinical stage (II vs I)	0.94 (0.21, 4.20)	0.935		
Clinical stage (III vs I)	2.00 (0.25, 4.07)	1.000		
Clinical stage (IV-A vs I)	2.01 (0.48, 8.31)	0.337		
Targeted therapy (Yes vs No)	0.60 (0.41, 0.88)	0.009	0.65 (0.44, 0.96)	0.030
Chemotherapy cycles (> 3 vs ≤ 3)	0.61 (0.43, 0.86)	0.005	0.58 (0.40, 0.83)	0.002
Time interval (> 15 vs ≤ 15)	1.32 (0.93, 1.86)	0.120		
DMFS (Distant Metastasis-free Survival)				
Gender (Male vs Female)	1.78 (1.19, 2.65)	0.005	1.70 (1.14, 2.55)	0.009
Age (> 45 years vs ≤ 45 years)	1.55 (1.02, 2.36)	0.041	1.44 (0.94, 2.19)	0.091
Tumor stage (T2 vs T1)	1.65 (1.04, 2.63)	0.033	1.63 (1.03, 2.59)	0.038
Tumor stage (T3 vs T1)	1.99 (1.22, 3.25)	0.006	1.90 (1.16, 3.11)	0.010
Tumor stage (T4 vs T1)	3.56 (2.15,5.91)	<0.001	3.45 (2.08, 5.72)	<0.001
Nodal stage (N1 vs N0)	1.39 (0.60, 3.21)	0.438		
Nodal stage (N2 vs N0)	1.46 (0.68, 3.12)	0.336		
Nodal stage (N3 vs N0)	1.93 (0.80, 4.65)	0.145		
Clinical stage (II vs I)	1.14 (0.26, 5.02)	0.861		
Clinical stage (III vs I)	1.33 (0.33, 5.38)	0.692		
Clinical stage (IV-A vs I)	2.77 (0.67, 11.38)	0.158		
Targeted therapy (Yes vs No)	0.74 (0.54, 1.03)	0.076		
Chemotherapy cycles (> 3 vs ≤ 3)	0.78 (0.57, 1.08)	0.139		
Time interval (> 15 vs ≤ 15)	1.17 (0.86, 1.59)	0.327		
LRFS (Local Relapse-free Survival)				
Gender (Male vs Female)	1.81 (1.17, 2.79)	0.007	1.84 (1.19, 2.84)	0.006
Age (> 45 years vs ≤ 45 years)	1.87 (1.17, 3.01)	0.009	1.66 (1.02, 2.69)	0.040
Tumor stage (T2 vs T1)	1.77 (1.08, 2.91)	0.024	1.80 (1.09, 2.96)	0.022
Tumor stage (T3 vs T1)	1.98 (1.17, 3.37)	0.011	1.99 (1.16, 3.42)	0.012
Tumor stage (T4 vs T1)	3.20 (1.84, 5.58)	< 0.001	3.48 (1.99, 6.10)	< 0.001
Nodal stage (N1 vs N0)	1.15 (0.49, 2.70)	0.753		
Nodal stage (N2 vs N0)	1.28 (0.60, 2.77)	0.524		
Nodal stage (N3 vs N0)	1.74 (0.71, 4.27)	0.228		
Clinical stage (II vs I)	0.94 (0.21, 4.21)	0.940		
Clinical stage (III vs I)	1.11 (0.27, 4.52)	0.882		
Clinical stage (IV-A vs I)	2.19 (0.53, 9.03)	0.280		
Targeted therapy (Yes vs No)	0.63 (0.44, 0.92)	0.015	0.68 (0.47, 0.99)	0.042
Chemotherapy cycles (>3 vs ≤3)	0.61 (0.43, 0.85)	0.004	0.59 (0.42, 0.83)	0.003
Time interval (>15 vs ≤15)	1.18 (0.84, 1.64)	0.341		

(*Continued*)

Table 2 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
NRFS (Nodal Relapse-free Survival)				
Gender (Male vs Female)	1.93 (1.23, 3.03)	0.004	1.95 (1.24, 3.07)	0.004
Age (> 45 years vs ≤ 45 years)	1.93 (1.19, 3.14)	0.008	1.69 (1.03, 2.78)	0.037
Tumor stage (T2 vs T1)	1.83 (1.10, 3.03)	0.020	1.85 (1.11, 3.08)	0.018
Tumor stage (T3 vs T1)	2.03 (1.18, 3.49)	0.011	2.03 (1.17, 3.51)	0.012
Tumor stage (T4 vs T1)	3.14 (1.77, 5.56)	< 0.001	3.40 (1.91, 6.05)	< 0.001
Nodal stage (N1 vs N0)	1.10 (0.46, 2.59)	0.834		
Nodal stage (N2 vs N0)	1.22 (0.57, 2.64)	0.609		
Nodal stage (N3 vs N0)	1.75 (0.71, 4.29)	0.224		
Clinical stage (II vs I)	0.94 (0.21, 4.20)	0.934		
Clinical stage (III vs I)	1.06 (0.26, 4.30)	0.938		
Clinical stage (IV-A vs I)	2.07 (0.50, 8.56)	0.315		
Targeted therapy (Yes vs No)	0.61 (0.42, 0.89)	0.011	0.65 (0.44, 0.95)	0.028
Chemotherapy cycles (> 3 vs ≤ 3)	0.61 (0.43, 0.86)	0.0045	0.59 (0.42, 0.84)	0.003
Time interval (> 15 vs ≤ 15)	1.24 (0.89, 1.74)	0.209		
PFS (Progression-Free Survival)				
Gender (Male vs Female)	1.65 (1.12, 2.43)	0.011	1.60 (1.09, 2.35)	0.017
Age (> 45 years vs ≤ 45 years)	1.48 (0.99, 2.22)	0.059		
Tumor stage (T2 vs T1)	1.59 (1.01, 2.48)	0.044	1.55 (0.98, 2.42)	0.058
Tumor stage (T3 vs T1)	1.89 (1.17, 3.04)	0.009	1.82 (1.13, 2.93)	0.014
Tumor stage (T4 vs T1)	3.49 (2.14, 5.69)	< 0.001	3.45 (2.12, 5.63)	< 0.001
Nodal stage (N1 vs N0)	1.45 (0.63, 3.32)	0.383		
Nodal stage (N2 vs N0)	1.55 (0.72, 3.32)	0.260		
Nodal stage (N3 vs N0)	1.94 (0.80, 4.68)	0.141		
Clinical stage (II vs I)	1.15 (0.26, 5.04)	0.858		
Clinical stage (III vs I)	1.42 (0.35, 5.74)	0.627		
Clinical stage (IV-A vs I)	2.91 (0.71, 11.95)	0.138		
Targeted therapy (Yes vs No)	0.75 (0.54, 1.03)	0.078		
Chemotherapy cycles (> 3 vs ≤ 3)	0.77 (0.57, 1.06)	0.112		
Time interval (> 15 vs ≤ 15)	1.09 (0.80, 1.47)	0.598		

Notes: Time interval: the time from biopsy to first treatment. TNM staging followed the 8th edition of the AJCC/UICC staging system.

0.17–0.84, p=0.016) as significant factors of DMFS; chemotherapy cycles > 3 (HR 0.35, 95% CI 0.16–0.75, p=0.007) as significant factors of LRFS; chemotherapy cycles > 3 (HR 0.28, 95% CI 0.14–0.58, p<0.001) as significant factors of NRFS; chemotherapy cycles >3 (HR 0.42, 95% CI 0.21–0.87, p=0.019) as significant factors of PFS (Table 3).

Table 3 Univariate and Multivariate Cox Hazards Proportional Regression Analysis of Factors Associated with OS, DMFS, LRFS, NRFS, and PFS (N=130 Cervical Lymph Node Biopsy Patients)

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
OS (Overall Survival)				
Gender (Male vs Female)	3.26 (0.76, 14.03)	0.112		
Age (> 45 years vs ≤ 45 years)	8.99 (1.20, 67.53)	0.033	5.77 (0.73, 45.68)	0.097

(*Continued*)

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Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
Tumor stage (T2 vs T1)	0.79 (0.29, 2.10)	0.633		
Tumor stage (T3 vs T1)	0.90 (0.27, 2.98)	0.859		
Tumor stage (T4 vs T1)	1.12 (0.14, 8.98)	0.914		
Nodal stage (N2 vs N1)	0.82 (0.26, 2.59)	0.741		
Nodal stage (N3 vs N1)	1.22 (0.34, 4.31)	0.763		
Clinical stage (III vs II)	1.64 (0.37, 7.26)	0.517		
Clinical stage (IV-A vs II)	1.64 (0.37, 7.26)	0.517		
Targeted therapy (Yes vs No)	0.34 (0.12, 0.93)	0.036	0.44 (0.15, 1.27)	0.131
Chemotherapy cycles (> 3 vs ≤ 3)	0.20 (0.08, 0.47)	<0.001	0.35 (0.14, 0.88)	0.026
Time interval (> 15 vs ≤ 15)	0.72 (0.29, 1.77)	0.470		
DMFS (Distant Metastasis-free Survival)				
Gender (Male vs Female)	4.62 (1.10, 19.49)	0.037	3.65 (0.85, 15.70)	0.082
Age (> 45 years vs ≤ 45 years)	3.57 (1.07, 11.89)	0.039	2.42 (0.68, 8.61)	0.173
Tumor stage (T2 vs T1)	0.95 (0.39, 2.28)	0.900		
Tumor stage (T3 vs T1)	1.44 (0.53, 3.87)	0.472		
Tumor stage (T4 vs T1)	0.97 (0.12, 7,68)	0.979		
Nodal stage (N2 vs N1)	0.99 (0.32, 3.03)	0.981		
Nodal stage (N3 vs N1)	2.39 (0.76, 7.51)	0.136		
Clinical stage (III vs II)	1.90 (0.43, 8.30)	0.395		
Clinical stage (IV-A vs II)	3.66 (0.81, 16.54)	0.091		
Targeted therapy (Yes vs No)	0.61 (0.28, 1.33)	0.211		
Chemotherapy cycles (> 3 vs ≤ 3)	0.25 (0.12, 0.52)	<0.001	0.38 (0.17, 0.84)	0.016
Time interval (> 15 vs ≤ 15)	0.65 (0.30, 1.40)	0.271		
LRFS (Local Relapse-free Survival)				
Gender (Male vs Female)	3.12 (0.95, 10.31)	0.061		
Age (> 45 years vs ≤ 45 years)	2.78 (0.96, 8.00)	0.058		
Tumor stage (T2 vs T1)	1.05 (0.46, 2.39)	0.914		
Tumor stage (T3 vs T1)	0.89 (0.30, 2.60)	0.829		
Tumor stage (T4 vs T1)	1.91 (0.42, 8.73)	0.405		
Nodal stage (N2 vs N1)	1.04 (0.38, 2.81)	0.942		
Nodal stage (N3 vs N1)	1.35 (0.44, 4.14)	0.597		
Clinical stage (III vs II)	1.53 (0.45, 5.19)	0.496		
Clinical stage (IV-A vs II)	1.97 (0.53, 7.30)	0.308		
Targeted therapy (Yes vs No)	0.54 (0.25, 1.16)	0.111		
Chemotherapy cycles (> 3 vs ≤ 3)	0.28 (0.14, 0.58)	<0.001	xx	xx
Time interval (> 15 vs ≤ 15)	0.59 (0.28, 1.23)	0.159		
NRFS (Nodal Relapse-free Survival)				
Gender (Male vs Female)	2.90 (0.87, 9.60)	0.082		
Age (> 45 years vs ≤ 45 years)	2.58 (0.89, 7.48)	0.082		
Tumor stage (T2 vs T1)	1.16 (0.50, 2.72)	0.732		
Tumor stage (T3 vs T1)	0.98 (0.33, 2.94)	0.978		
Tumor stage (T4 vs T1)	0.98 (0.12, 7.72)	0.983		
Nodal stage (N2 vs N1)	0.90 (0.33, 2.48)	0.836		
Nodal stage (N3 vs N1)	1.34 (0.44, 4.09)	0.611		
Clinical stage (III vs II)	1.42 (0.42, 4.84)	0.577		

(*Continued*)

Table 3 (Continued).

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p	HR (95% CI)	p
Clinical stage (IV-A vs II)	1.71 (0.45, 6.47)	0.427		
Targeted therapy (Yes vs No)	0.42 (0.18, 0.97)	0.042	0.53 (0.23, 1.25)	0.148
Chemotherapy cycles (> 3 vs ≤ 3)	0.30 (0.14, 0.63)	0.001	0.35 (0.16, 0.75)	0.007
Time interval (> 15 vs ≤ 15)	0.62 (0.29, 1.34)	0.226		
PFS (Progression-Free Survival)				
Gender (Male vs Female)	3.97 (1.22, 12.96)	0.022	3.27 (0.99, 10.86)	0.053
Age (>45 years vs ≤45 years)	2.62 (1.01, 6.75)	0.047	1.90 (0.69, 5.20)	0.211
Tumor stage (T2 vs T1)	1.09 (0.50, 2.37)	0.837		
Tumor stage (T3 vs T1)	1.36 (0.55, 3.38)	0.511		
Tumor stage (T4 vs T1)	1.66 (0.37, 7.51)	0.509		
Nodal stage (N2 vs N1)	1.12 (0.42, 3.02)	0.822		
Nodal stage (N3 vs N1)	2.39 (0.85, 6.71)	0.098		
Clinical stage (III vs II)	1.64 (0.48, 5.53)	0.428		
Clinical stage (IV-A vs II)	3.29 (0.94, 11.43)	0.062		
Targeted therapy (Yes vs No)	0.76 (0.39, 1.49)	0.427		
Chemotherapy cycles (>3 vs ≤3)	0.30 (0.15, 0.58)	< 0.001	0.42 (0.21, 0.87)	0.019
Time interval (>15 vs ≤15)	0.53 (0.27, 1.05)	0.067		

Notes: Time interval: the time from biopsy to first treatment. TNM staging followed the 8th edition of the AJCC/UICC staging system.

Discussion

In this study, the proportion of demographic characteristics did not differ between the nasopharyngeal biopsy group and the cervical lymph node biopsy group after propensity score matching. No significant differences were found between the two groups in OS, DMFS, LRFS, NRFS, and PFS before and after propensity score matching. These endpoints did not differ between the fine needle aspiration group and the excisional biopsy group within the cervical lymph node biopsy group. In the nasopharyngeal biopsy group, male patients and patients older than 45 years had poorer prognoses specific to OS, local recurrence, cervical lymph node recurrence, and distant metastasis, compared to female patients and patients aged 45 years or younger. T-stage, concurrent targeted therapy, and more than three cycles of chemotherapy were independent prognostic factors for OS, LRFS, and NRFS. T stage was an independent prognostic factor for DMFS and PFS. In the cervical lymph node biopsy group, "more than three cycles of chemotherapy" was the only independent prognostic factor for OS, DMFS, NRFS, and PFS.

Cervical lymph node biopsy affecting the survival, distant metastasis, and local recurrence risk in nasopharyngeal carcinoma (NPC) patients has been a contentious issue. The NCCN Head and Neck Cancer Guidelines, the Chinese CSCO Nasopharyngeal Cancer Diagnosis and Treatment Guidelines, and the ESMO-ESTRO Nasopharyngeal Carcinoma Clinical Practice Guidelines differ regarding cervical lymph node biopsy. In a study conducted in Taiwan[22] that included 2761 NPC patients treated from 1969 to 1983, cervical lymph node biopsy before definitive initial treatment reduced the survival rate of NPC patients (5-year survival rate: 41% vs 59%, p=0.0104), emphasizing not to perform unless necessary. However, in that study, the majority of patients received only radiotherapy. Cai et al[23] found that the 5-year survival rate of NPC patients was not affected by cervical lymph node biopsy (35% vs 35%, p>0.05). However, with movable cervical lymph nodes, the 5-year survival rate was higher in patients with complete excision, compared to patients with partial excision (50% vs 22%). Yet, the radiotherapy methods among enrolled patients varied, and no other treatments were combined. These studies were conducted when combined chemotherapy was not frequently used, and targeted therapy did not exist. Therefore, these findings may not apply to NPC patients now with the adoption of precision treatment.

Nasopharyngeal carcinoma (NPC) is highly sensitive to ionizing radiation, and therefore, radiotherapy remains the primary treatment for non-metastatic NPC. Intensity-modulated radiotherapy (IMRT) is the most widely used technique and significantly improves 5-year local-regional control rate and overall survival.[24] For locally advanced NPC, chemoradiotherapy is often required in addition to radiotherapy. In numerous previous studies, concurrent chemoradiotherapy, with or without adjuvant chemotherapy, provided survival benefits compared to radiotherapy alone.[1] The NCCN guidelines recommend concurrent chemoradiotherapy with adjuvant chemotherapy or induction chemotherapy followed by concurrent chemoradiotherapy as category 2A evidence for stage II–IVA NPC, while concurrent chemoradiotherapy alone is considered category 2B evidence.[25] Epidermal growth factor receptor (EGFR) is highly expressed in most NPC cases and is associated with poor prognosis (27). The efficacy of EGFR-targeted therapies in NPC, including EGFR monoclonal antibodies and tyrosine kinase inhibitors was evaluated in multiple studies (28, 29, 30). Nimotuzumab, approved in China in 2008, was the first targeted drug for NPC, suitable for use in combination with radiotherapy for EGFR-positive stage III/IV NPC. In clinical trials, nimotuzumab combined with chemotherapy, radiotherapy, or concurrent chemoradiotherapy provided encouraging advantages for patients with locally advanced NPC as well as recurrent or metastatic NPC.[26]

A study conducted by Sun Yat-sen University Cancer Center[12] included 1492 patients with newly diagnosed non-metastatic NPC from January 2010 to September 2013. Cervical lymph node biopsy did not increase the risk of death, distant metastasis, or lymph node recurrence in that study. However, that study did not discuss the impact of chemotherapy and targeted therapy on patient survival. Two other studies based on the data from the SEER database[13,14] found no association between cervical lymph node biopsy and a higher risk of death in NPC patients. These results were consistent across different diagnostic years, races/ethnicities, and histological subtypes. However, the SEER database does not provide information on chemotherapy, radiotherapy, EBV status, or complications. It also lacks data on post-treatment local recurrence and distant metastasis. Moreover, the SEER database includes only data from cancer patients in the United States, making the findings difficult to apply to populations in endemic regions.

In this retrospective analysis of the survival and recurrence patterns in patients who underwent cervical lymph node biopsy versus nasopharyngeal biopsy, cervical lymph node biopsy did not increase the mortality risk (5-year OS: 85.0% vs 81.1%, p=0.19). Additionally, distant metastasis, local recurrence, and cervical lymph node recurrence were not affected by cervical lymph node biopsy (5-year DMFS: 80.6% vs 75.2%, p=0.2; 5-year LRFS: 78.7% vs 79.5%, p=0.95; 5-year NRFS: 80.4% vs 80.4%, p=0.85). Results were similar after propensity score matching.These findings were consistent with previous research.[12] Upon univariate and multivariate analyses, male patients had a worse prognosis than female patients (OS: HR=2.1, p=0.002), and patients older than 45 years had worse outcomes compared to those 45 years or younger (OS: HR=1.71, p=0.040) in the nasopharyngeal biopsy group. Although the hazard ratio (HR) has increased with higher T-stage, N-stage, and overall clinical stage only the T-stage showed statistical significance, consistent with the findings from the Taiwanese study.[21] In the current study, concurrent radiotherapy with targeted therapy and an increased number of chemotherapy cycles (>3) significantly benefited survival and reduced nasopharyngeal and cervical lymph node recurrences. In the cervical lymph node biopsy group, gender, age, or stage did not affect the prognosis, possibly due to the smaller sample size and relatively advanced stages of cases. Chemotherapy cycles of >3 was the sole independent prognostic factor for survival and reduced recurrence and metastasis (OS: HR=0.35, p=0.026; DMFS: HR=0.38, p=0.016; LRFS: HR=0.28, p<0.001; NRFS: HR=0.35, p=0.007). Given that over 95% of nasopharyngeal carcinoma cases in China are non-keratinizing squamous cell carcinoma,[1] the impact of pathological type on prognosis was not analyzed. With the increasing adoption of precision medicine, the widespread use of IMRT, along with chemotherapy and targeted therapy, may have mitigated the risks associated with cervical lymph node biopsy.

Due to the difficulty of early diagnosis of nasopharyngeal carcinoma and its risk for cervical lymph node metastasis, patients presenting with neck masses require further investigation to identify the primary tumor to prevent delay in diagnosis and treatment. The delayed treatment might increase the risk of distant metastasis. Cai et al[23] found a significant difference in 5-year survival rates between patients who received treatment within 14 days of biopsy and patients who started treatment after 15 days (55% vs 33%, p<0.05) in cancer stages III and IV with the difference in metastasis (14% vs 25%, respectively). Conversely, a study from Zhejiang Cancer Hospital[10] found that a treatment delay of more than two weeks was not associated with worse survival outcomes (5-year OS: 87.7% vs 84.6%, p=0.786) or

higher metastasis risk (5-year DMFS: 89.2% vs 89.2%, p=0.724). In the current study, the cervical lymph node biopsy group had a longer interval from biopsy to treatment initiation, compared to the nasopharyngeal biopsy group, with the proportion of patients starting treatment after more than 15 days being 74.63% vs 48.05% (p<0.01). Nonetheless, treatment delays did not result in poorer survival or higher recurrence and metastasis risks in either group. This may have resulted from effective radiotherapy, chemotherapy, and targeted therapies.

This study also had some limitations. First, it was a retrospective study, not a prospective randomized control study. Although the proportions of demographic variables did not differ between the two test groups, other unexplored events might have influenced this study outcome. Second, the results may have been subject to selection bias because this was a single-center retrospective study. Third, a smaller sample size in the cervical lymph node biopsy group may have influenced the study outcome. Finally, this analysis was based on data from a single center in a region with a high prevalence of nasopharyngeal carcinoma, which may have limited the generalizability of the findings to other regions, particularly non-endemic areas. Therefore, large-scale prospective studies are needed to validate our conclusions.

Conclusion

Carrying out cervical lymph node excisional biopsy and fine-needle aspiration biopsy did not increase the risk of local recurrence, distant metastasis, or death compared to performing nasopharyngeal biopsy in nasopharyngeal carcinoma patients. Therefore, cervical lymph node biopsy can be used as a routine diagnostic procedure to detect nasopharyngeal carcinoma. Survival, metastasis, and recurrence in nasopharyngeal carcinomas primarily depend on the tumor stage at diagnosis and adoption of treatment, not on the diagnostic biopsy types.

Ethics Approval and Consent to Participate

This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital of Soochow University (approval number: NO.2024 (232)), and informed consent was waived due to the retrospective nature. Data were anonymized and stored securely to protect patient privacy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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