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Authors

Goshtasbi, Khodayar
Abiri, Arash
Lehrich, Brandon M
et al.

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The Influence of Facility Volume on Patient Treatments and Survival Outcomes in Nasopharyngeal Carcinoma

Khodayar Goshtasbi, MS[#1], **Arash Abiri, BS**[#1], **Brandon M. Lehrich, BS**[2], **Yarah M. Haidar, MD**[1], **Tjoson Tjoa, MD**[1], **Edward C. Kuan, MD MBA**[1]

[1]Department of Otolaryngology–Head and Neck Surgery, University of California, Irvine, Orange, CA, USA

[2]Medical Scientist Training Program, University of Pittsburgh and Carnegie Mellon University, Pittsburgh, PA, USA

[#] These authors contributed equally to this work.

Abstract

Background: This study evaluates the influence of facility case-volume on nasopharyngeal carcinoma (NPC) treatments and overall survival (OS).

Methods: The 2004-2015 National Cancer Database was queried for NPC patients receiving definitive treatment.

Results: A total of 8,260 patients (5-year OS: 63.4%) were included. The 1,114 unique facilities were categorized into 854 low-volume (treating 1-8 patients), 200 intermediate-volume (treating 9-23 patients), and 60 high-volume (treating 24-187 patients) facilities. Kaplan-Meier log-rank analysis demonstrated significantly improved OS with high-volume facilities (p<0.001). On cox proportional-hazard multivariate regression after adjusting for age, gender, income, insurance, comorbidity index, histology, AJCC clinical stage, and treatment type, high-volume facilities were associated with lower mortality risk than low-volume (HR=0.865, p=0.019) and intermediate-volume facilities (HR=0.916, p=0.004). Propensity score matching analysis confirmed this association (p<0.001).

Conclusion: Higher facility volume was an independent predictor of improved OS in NPC, suggesting a possible survival benefit of referrals to high-volume medical centers.

Keywords

Nasopharyngeal carcinoma; hospital volume; facility volume; outcomes; overall survival

Corresponding author: Edward C. Kuan, MD, MBA, Department of Otolaryngology–Head and Neck Surgery, University of California, Irvine Medical Center, 200 S. Manchester Ave, Ste 400, Orange, CA 92868, Phone: (714) 456-5753, Fax: (714) 456-5747, eckuan@uci.edu.

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Level of Evidence: N/A

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Introduction

With approximate annual worldwide and U.S. incidences of 80,000 and 3,000 patients, respectively, nasopharyngeal carcinoma (NPC) is the most common primary malignancy of the nasopharynx.[1] The current standard-of-care treatments according to Physician Data Query (U.S. National Cancer Institute's comprehensive cancer information)[2] and National Comprehensive Cancer Network (alliance of top 30 cancer centers in the U.S.)[3] guidelines include radiotherapy for stage I, radiotherapy or chemoradiotherapy with adjuvant chemotherapy for stage II, chemoradiotherapy with adjuvant chemotherapy for stage III, and chemoradiotherapy with adjuvant chemotherapy for stage IVA NPC.[4] Since NPC is often diagnosed late into its disease course, patients commonly present with large primary tumors, locoregional advanced stages, and nodal involvement.[5, 6] Therefore, recent large-population studies have estimated modest 5-year and 10-year overall survival (OS) rates of 59-63% and 48-50%, respectively.[7-9] A variety of clinical and socioeconomic factors have been noted to significantly influence OS in NPC, including age, race, histology, American Joint Committee on Cancer (AJCC) stage, and treatment type.[7, 10-12] A Taiwan-based study based on NPC patients treated between 1998-2000 suggested that hospitals' caseload correlated positively with survival rates,[13] warranting further investigation of this relationship among U.S.-based patients in recent years.

Elucidating the influence of facility volume on short- or long-term patient outcomes (i.e., volume-outcomes relationship) is an important endeavor that can lead to better delivery of quality care and more centralized cancer treatment in the future.[14, 15] Although recent studies have demonstrated improved survival with increasing hospital volume in a variety of cancers including lung cancer,[16] Hodgkin lymphoma,[17] Merkel cell carcinoma,[18] meningioma,[19] and malignant bone tumors,[20] a thorough investigation regarding NPC is needed. Herein, this study investigates a large U.S.-based patient population from the National Cancer Database (NCDB) to elucidate the facility volume-outcomes relationships in patients with NPC.

Methods

This study did not require approval from the Institutional Review Board because of the de-identified and publicly available nature of NCDB. The 2004-2015 NCDB was queried for all patients diagnosed with NPC using *International Classification of Disease for Oncology, 3rd Edition* (ICD-O-3) topography codes for the nasopharynx primary site (C11.0-C11.9) and NPC histology/behavior codes (8070/3, 8071/3, 8072/3, 8073/3, 8020/3, 8021/3, 8082/3, 8010/3). Inclusion and exclusion criteria were in-line with a previous NPC study by this group.[7] Specifically, exclusion criteria for this study included patients with multiple primary malignancies, those receiving treatment outside the reporting facility, subjects receiving palliative care, hormone therapy, or immunotherapy, and patients with unspecified treatments, <3 months of follow-up, or unknown follow-up time or outcomes. Charlson/Deyo (C/D) comorbidity indices reported by NCDB to indicate patient health status due to existing comorbidities were binarized as 0 and ≥1. Histology was categorized as World Health Organization (WHO) Type I, WHO Type II, WHO Type III, and carcinoma not otherwise specified (NOS). Biologically effective dose (BED_{10}) was calculated using the

linear quadratic model,[21] with α/β ratio defined to be 10 Gy in the context of rapidly dividing head and neck tumor cells.[22] BED_{10} was evaluated categorically with a cutoff value (83 Gy) selected based on the median of the analyzed population.

Each patient's treatment facility was designated by NCDB with an anonymous but unique code (variable PUF_FACILITY_ID) which was used to calculate how many NPC patients were treated at each given facility. Of note, this facility volume number was for the acquired timeline of the database (NCDB 2004-2015). The facilities were divided into three approximately equal tertiles (via 33 and 66 percentile thresholds of total number of patients) for categorizing low-, intermediate-, and high-volume facilities.[23] This corresponded to defining low-volume facilities as those diagnosing/treating 1-8 NPC patients, intermediate-volume facilities as those diagnosing/treating 9-23 NPC patients, and high-volume facilities as those diagnosing/treating 24-187 NPC patients.

Statistical analyses were performed via R (version 3.6.1; The R Foundation for Statistical Computing) in RStudio (version 1.2.1335). A *p*-value of <0.05 was considered statistically significant. Survival analyses were performed using Kaplan-Meier log-rank tests, and the associations between various clinical factors (including facility volume) and OS were analyzed via multivariate Cox proportional-hazards models to account for confounders. To further address confounding factors, propensity score matching was performed to create propensity-matched cohorts that were statistically similar in clinical/demographic variables that were previously found to be significantly different on univariate analysis. Propensity scores were calculated using logistical regression, and 1-to-1 propensity matching without replacement was performed utilizing the nearest neighbor method. Survival outcomes in propensity-matched cohorts were assessed using log-rank tests and multivariate Cox regression analyses.

Results

A total of 8,260 patients with NPC met the inclusion criteria (Figure 1). With a mean age of 52.1±15.1 years, the cohort consisted of 28.7% females, 58.7% Caucasians, and 68.8% with AJCC clinical stage III-IV. The overall cohort's 2-year, 5-year, and 10-year estimated overall survival (OS) were 77.2% (95% confidence interval [CI]: 76.3-78.2%), 61.5% (95% CI: 60.3-62.7%), and 48.1% (95% CI: 46.6-49.7%), respectively. The diagnosis/treatment of this cohort involved 1,114 unique treatment facilities, categorized into 854 low-volume (1-8 patients treated per facility, total n=2,909 patients), 200 intermediate-volume (9-23 patients treated per facility, total n=2,647 patients), and 60 high-volume (24-187 patients treated per center, total n=2,704 patients) facilities. Compared to low-volume facilities, intermediate-volume and high-volume facilities were more likely to treat AJCC clinical stage III-IV patients (odds ratio [OR]=1.302, 95% CI: 1.125-1.509, $p<0.001$ and OR=1.514, 95% CI: 1.307-1.757, $p<0.001$, respectively). Moreover, high-volume facilities provided more chemoradiation treatment than low-volume facilities (OR=1.258, 95% CI: 1.108-1.463, $p=0.003$).

Table 1 compares several clinical/sociodemographic information and treatment modalities among low-, intermediate-, and high-volume facilities. This highlighted that higher facility

volume was associated with younger age at presentation, lower rates of C/D ≥1, higher income, higher means of travelling to the treatment site, higher rates of TNM stage III-IV, and lower rates of WHO Type 1 tumors (all $p<0.001$). Following the diagnosis of NPC, higher facility volume was also associated with increased time from diagnosis to radiotherapy or chemotherapy, lower rates of ≥35 radiotherapy fractions with higher rates of ≥60 Gy radiotherapy dosage, higher rates of ≥ 83 Gy BED_{10}, and higher rates of chemoradiation treatment (all $p<0.001$). Kaplan-Meier log-rank test demonstrated significantly improved OS associated with increased facility volume (Figure 2, $p<0.001$), which remained statistically significant when comparing low- to intermediate volume ($p=0.028$) and intermediate to high volume facilities ($p<0.001$) individually. On univariate Cox proportional-hazards analysis, compared to high-volume facilities, NPC patients at intermediate-volume (hazard ratio [HR]=1.192, 95% confidence interval [CI] 1.088-1.306, $p<0.001$) and low-volume facilities (HR=1.311, 95% CI 1.201-1.431, $p<0.001$) had higher risk of mortality. Furthermore, there was a higher risk of NPC mortality in low-volume compared to intermediate-volume facilities (HR=1.101, 95% CI 1.010-1.198, $p=0.027$).

Table 2 demonstrates that, on multivariate Cox proportional-hazards analysis, after adjusting for age, gender, insurance, income, C/D comorbidity score, AJCC clinical stage, histology, and treatment type as important clinical confounders, high-volume facilities were associated with lower risk of mortality compared to low-volume (HR=0.865, 95% CI 0.766-0.970, $p=0.019$) and intermediate-volume facilities (HR=0.916, 95% CI 0.863-0.972, $p=0.004$).

To further verify the facility volume-outcomes relationship, propensity score matching was performed to create volume-stratified NPC cohorts that had no statistical differences in age, gender, insurance, income, C/D comorbidity index, AJCC stage, tumor histology, BED_{10}, or treatment type (all $p>0.05$). Kaplan-Meier log-rank test did not demonstrate a significant difference in OS between low- and intermediate volume facilities ($p=0.216$, Figure 3A). However, there were significantly improved OS rates among propensity-matched NPC patients at high-volume versus intermediate-volume facilities ($p<0.001$, Figure 3B), and high-volume vs. low-volume facilities ($p<0.001$, Figure 3C). Univariate Cox proportional-hazards analysis of the propensity-matched cohorts further demonstrated that patients at high-volume facilities had lower mortality risks than those at low-volume (HR=0.711, 95% CI 0.629-0.803, $p<0.001$) and intermediate-volume facilities (HR=0.748, 95% CI 0.658-0.849, $p<0.001$).

Of note, there were 3,360 M0 NPC subjects that received curative radiation dosage (~70 Gy). This corresponded to 1080 (37.1%) of low-volume facility patients, 1112 (42.0%) of intermediate-volume facility patients, and 1168 (43.2%) of high-volume facility patients that received curative radiation dosage. Kaplan-Meier analysis demonstrated that high-volume facility patients still had significantly superior OS (estimated 114.9 ± 2.4 months) compared to low- (102.6 ± 2.4 months) and intermediate-volume (109 ± 2.6 months) facilities ($p=0.001$).

Discussion

This population-based study of patients with NPC demonstrated facility volume to be an independent predictor of overall survival. After adjusting for several demographic, socioeconomic, and clinical factors, our multivariate regression model continued to demonstrate a significantly lower (by as much as ~37%) mortality risk among high-volume facilities. Similarly, propensity score matching of NPC patients demonstrated significantly increased OS rates among individuals who were treated at high-volume facilities. It is plausible to hypothesize that favorable outcomes at high-volume centers may also be attributed to other underlying clinical processes, such as greater access to subspecialized treating radiation and medical oncologists with extensive training, more advanced equipment and technologies, or better compliance with the latest clinical guidelines and evidence-based practices.[24-28] Moreover, differences in the expertise of dosimetrists and medical physicists may have contributed to survival disparities due to variations in radiation quality, which have been shown to be particularly influential in treatment outcomes for NPC.[7] In our NCDB patient population, we found lower radiotherapy doses and higher treatment fractions to be more common among low- and intermediate-volume facilities. According to a multi-institutional study of head and neck cancers, such a radiation schedule may likely result in suboptimal patient outcomes, as higher radiotherapy doses can generally yield greater survival rates, while hyperfractionation can lead to increased radiation-associated complications.[29]

Some studies have also suggested that enhanced survival rates among high-volume facilities may be a result of their greater tendency to treat patients more aggressively, such as enrolling patients for adjuvant treatments or clinical trials or offering salvage nasopharyngectomy when appropriate.[25, 30, 31] This was likely consistent with our findings, which demonstrated a significantly higher rate of chemoradiotherapy among higher-volume centers. Interestingly, not only is radiation with concomitant chemotherapy the standard of care for treating locally advanced NPC, but studies have also recommended administering adjuvant or induction chemotherapy. However, chemoradiation trials have shown that a large number of NPC patients fail to complete concurrent or adjuvant chemotherapy due to the intensity of the regimen.[32-34] Incorporating a multidisciplinary approach to patient care with readily accessible ancillary services such as nutrition, palliative care, and oncologic psychiatry has been shown to promote treatment compliance even in patients with advanced cancer requiring aggressive therapy.[35, 36] Greater availability of resources to implement such an approach may explain why, despite treating more late-stage cancers, high-volume facilities had better survival outcomes for patients. Furthermore, greater radiation doses and lower radiation fractions among high-volume centers might have been facilitated by a similar process. Specifically, increased access to supportive services may have better equipped high-volume facilities to care for patients with radiotherapy-related toxicities, thereby reducing interruptions to planned radiation treatment regimens.[37] Recent studies have also suggested that lower radiation dose/volume, when delivered in a more targeted setting, may also improve outcomes and survival due to lower toxicity and side effects,[38, 39] which may be another contributing factor for improved outcomes at high-volume facilities.

In our analyses, we also recognized differences in key demographic and socioeconomic factors among patients treated in the three facility volume cohorts. Many high-volume facilities were distantly located from patients' residences, suggesting the presence of a regionalized pattern of care (i.e., centralized cancer care). While regionalization of health services has been shown to confer mortality benefits, this concept introduces significant socioeconomic and psychosocial barriers.[40-42] Treating NPC oftentimes requires several weeks of radiotherapy and chemotherapy, and extensive travel for treatment, especially if beyond their means, can incur significant scheduling and financial strains on patients and their families. Additionally, treatment at distant facilities can be more psychologically exhausting, as patients have to endure physically demanding therapies without assistance from their personal support systems. These considerations oftentimes lead patients to prefer local care facilities, despite the prospect of lower mortality and better treatment outcomes at regional specialized centers.[41, 43, 44] Furthermore, some studies have found certain populations to more frequently tend towards localized care.[44-46] Symer *et al.* demonstrated that a reduced willingness to seek regionalized care was more prevalent among older patients and those from low socioeconomic backgrounds.[44] It is also possible that the healthiest patients are the ones that are able to travel to dedicated high-volume centers, which may translate into improved survival outcomes [47, 48] We observed a significantly higher occurrence of young and high-income patients among high-volume facilities. Thus, barriers such as life disruption from travel, lack of socioeconomic resources, and inadequate social support are all important considerations when formulating regionalization policy initiatives.

Despite our efforts to carefully analyze and interpret data, this study contains several limitations that are important to mention. First, patients were extracted from a de-identified national database which makes the data susceptible to inaccurate or missing information, inclusion bias, and limited number of variables. Second, we were only able to analyze the influence of facility volume and not individual physicians' patient volumes, which has also been shown to impact patient outcomes.[49] However, studies suggest that facility volume may be a stronger predictor of survival.[31, 50, 51] Third, we utilized overall survival as our main outcome variable, and could not elucidate the influence of facility volume on recurrence free or disease-free survival due to limitations of the database. Lastly, although we controlled for a wide variety of clinical and sociodemographic variables via multivariate regression and propensity score matching, there were additional variables (e.g., family support/marital status, adequate follow-up, chemotherapy regimen, etc.) that were not captured by NCDB and could not be accounted for in our analyses. Despite these limitations, this populated-based study nonetheless demonstrates a strong and independent relationship between facility volume and OS in NPC, which is an essential consideration in treating this important patient population.

Conclusion

Our analysis of 8,260 patients with NPC demonstrated that high facility volume was independently associated with increased OS. After adjusting for important clinical and sociodemographic variables via multivariate logistic regression and propensity score matching, high-volume facilities demonstrated superior OS outcomes to low- and

intermediate-volume facilities. Thus, patients with NPC may benefit from referrals to high-volume medical centers where they can access a large network of specialized and experienced physicians and ancillary supportive services.

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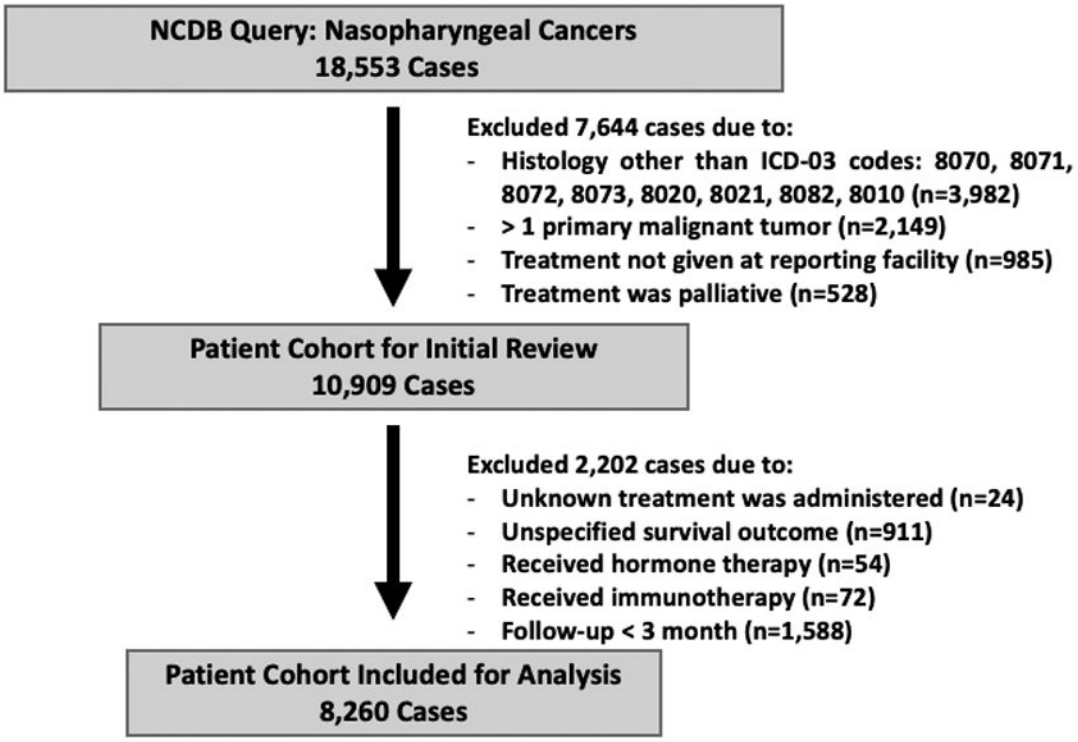

Figure 1.
Flowchart of patient selection process.

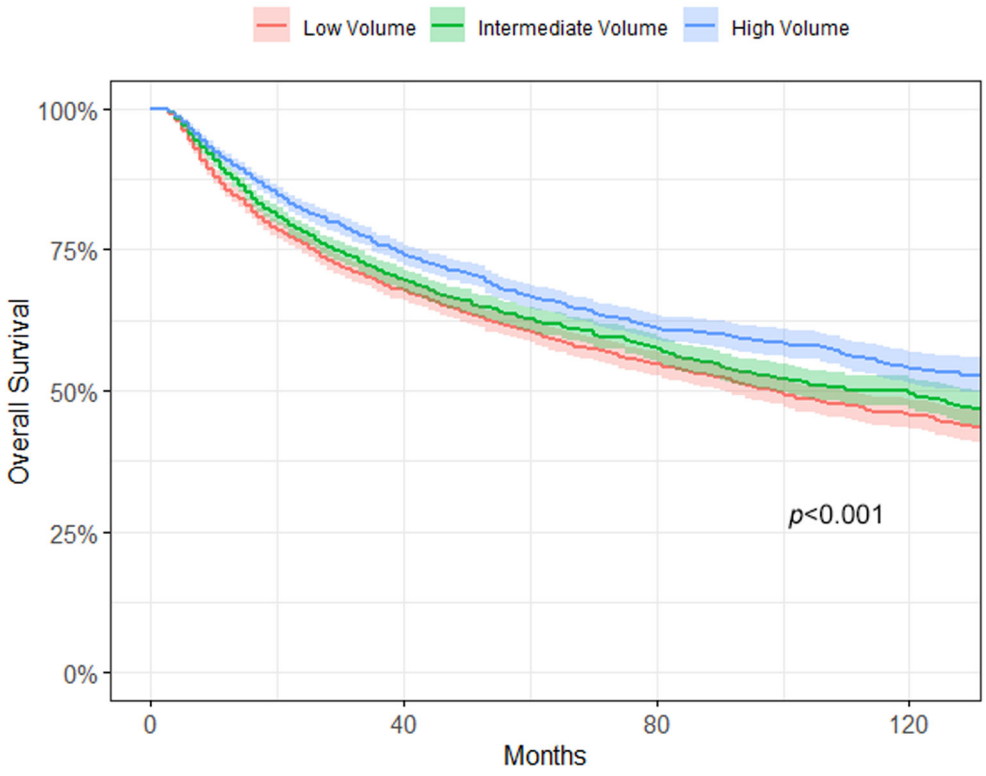

Figure 2.

Kaplan-Meier curves of overall survival in patients with nasopharyngeal carcinoma stratified by low-volume (1-8 patients treated per center, total n=2,909 patients), intermediate-volume (9-23 patients treated per center, total n=2,647 patients), and high-volume facility (24-187 patients treated per center, total n=2,704 patients) patients. The analysis demonstrated a statistically significant positive association between facility volume and OS (p<0.001). Shaded areas indicate 95% confidence intervals.

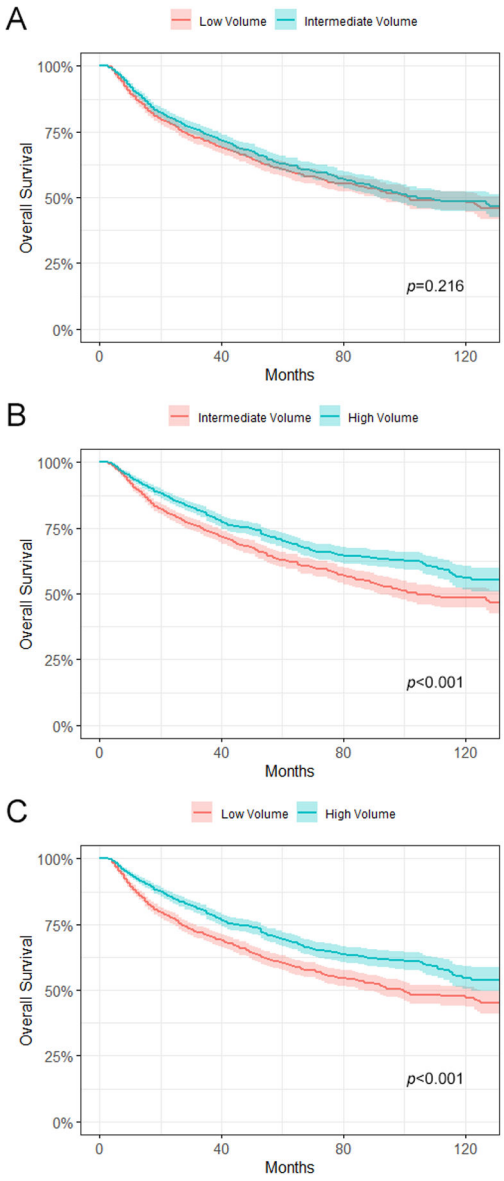

Figure 3.

Kaplan-Meier (KM) curves of overall survival (OS) in patients with nasopharyngeal carcinoma (NPC) matched by their demographic and clinical factors, demonstrating significant improvement of OS with high facility volume. Figure (A) compares matched patients treated at low (n=1,550) and intermediate (n=1,550) volume facilities. Figure (B) compares matched patients treated at intermediate (n=1,550) and high (n=1,550) volume facilities. Figure (C) compares matched patients treated at low (n=1,601) and high (n=1,601) volume facilities. Shaded areas indicate 95% confidence intervals.

Table 1.

Patient demographics, treatments, and overall survival rates stratified by facility volume.

Variable	Low volume (No. of patients=2909)	Intermediate volume (No. of patients=2647)	High volume (No. of patients=2704)	*p*-value[a]
Age at diagnosis	54.7 ± 14.1	52.1 ± 15.4	49.3 ± 15.4	**<0.001**
Gender: female	849 (29.2)	759 (28.7)	752 (27.8)	0.517
Insurance: Private[b]	1526 (52.5)	1413 (53.4)	1415 (52.3)	0.267
Income ≥$63,000	773 (26.6)	774 (29.2)	945 (34.9)	**<0.001**
C/D ≥1	435 (15.0)	365 (13.8)	300 (11.1)	**<0.001**
AJCC Stage: III-IV[b]	1842 (63.3)	1832 (69.2)	2011 (74.4)	**<0.001**
Histology: WHO Type 1	1485 (51.0)	1160 (43.8)	866 (32.0)	**<0.001**
Distance to facility, miles	20.7 ± 94.8	27.2 ± 123.8	38.9 ± 163.8	**<0.001**
Days from Dx to Radiotherapy	54.2 ± 41.5	56.1 ± 42.8	62.2 ± 43.2	**<0.001**
Radiotherapy Modality: IMRT[b]	1515 (58.0)	1446 (60.0)	1385 (56.2)	0.204
Radiotherapy fractions ≥35[b]	1586 (64.3)	1314 (57.7)	1054 (47.5)	**<0.001**
Radiotherapy ≥60 Gy[b]	1631 (64.5)	1617 (68.7)	1707 (72.1)	**<0.001**
BED_{10} ≥83 Gy[b]	1575 (54.1)	1534 (58.0)	1715 (63.4)	**<0.001**
Days from Dx to Chemotherapy	41.9 ± 30.1	43.9 ± 33.0	47.0 ± 34.9	**<0.001**
Treatment: Chemoradiation	2416 (83.1)	2229 (84.2)	2336 (86.4)	**0.011**
% 5-Year OS (95% CI)	60.7 (58.7-62.7)	62.8 (60.8-64.9)	66.9 (64.9-69.0)	**<0.001**
% 10-Year OS (95% CI)	45.9 (43.4-48.5)	49.9 (47.3-52.6)	54.2 (51.5-57.1)	**<0.001**

C/D: Charlson/Deyo; WHO: World Health Organization; AJCC: American Joint Committee on Cancer; Dx: Diagnosis; OS: Overall Survival; CI: Confidence Interval; IMRT: Intensity-Modulated Radiation Therapy; BED: Biologically Effective Radiation Dose.

[a]Categorical and continuous variables were analyzed using chi-squared and one-way ANOVA, respectively. Overall survival rates were compared using log-rank tests.

[b]Not all patients had information for these variables, thus the percentages reflect the number of patients with available data.

Table 2.

Multivariate cox proportional-hazards regression analysis of overall survival in patients with nasopharyngeal carcinoma.

	Multivariate Analysis	
Variable	**Hazard Ratio (95% Confidence Intervals)**	***P*-value**
Age, y		
<65	1 [reference]	
≥65	1.756 (1.560-1.976)	<0.001*
Sex		
Male	1 [reference]	
Female	0.857 (0.771-0.954)	0.005*
Insurance		
Government	1 [reference]	
Private	0.647 (0.580-0.722)	<0.001*
Income		
<$63,000	1 [reference]	
≥$63,000	0.898 (0.805-1.002)	0.0550
Charlson/Deyo Score		
0	1 [reference]	
≥1	1.326 (1.172-1.500)	<0.001*
AJCC Clinical Stage		
I-II	1 [reference]	
III-IV	2.532 (2.131-3.007)	<0.001*
Histology		
WHO Type 1	1 [reference]	
WHO Type 2	0.657 (0.576-0.750)	<0.001*
WHO Type 3	0.470 (0.401-0.551)	<0.001*
Carcinoma NOS	0.655 (0.574-0.748)	<0.001*
Radiotherapy Modality		
External Beam	1 [reference]	
IMRT	0.914 (0.829-1.007)	0.069
Biologically Effective Radiation Dose		
<83 Gy	1 [reference]	
≥83 Gy	0.825 (0.749-0.909)	0.003*
Chemoradiation		
No	1 [reference]	
Yes	0.754 (0.627-0.907)	<0.001*

	Multivariate Analysis	
Variable	**Hazard Ratio (95% Confidence Intervals)**	***P*-value**
Facility Volume		
Low	**1 [reference]**	
Intermediate	**0.974 (0.871-1.091)**	**0.655**
High	**0.865 (0.766-0.970)**	**0.019** *

AJCC: American Joint Committee on Cancer; WHO: World Health Organization; NOS: Not Otherwise Specified; Dx: Diagnosis.

* statistically significant, $p<0.05$