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Effect of radiotherapy and chemotherapy on the survival rate of Asian Americans with nasopharyngeal carcinoma

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Abstract

Objective: To evaluate how the addition of concurrent chemotherapy to radiation therapy (RT) affects outcomes for Asian American patients with nasopharyngeal carcinoma.

Methods: Using the California Cancer Registry – a population-based, state-sponsored database – Asian American patients with newly-diagnosed, locally advanced nasopharyngeal carcinoma diagnosed between 1998 and 2010 were identified. The Kaplan–Meier method was used to analyze overall survival and cancer-specific survival. Cox proportional hazards models were constructed to investigate the association with chemotherapy. Propensity score methods were used to control for measure confounders.

Results: A total of 812 Asian Americans were included; 91 (11.2%) underwent RT alone, and 721 (88.8%) underwent RT with chemotherapy. The overall survival at 5 years was 65% with RT alone versus 72% with RT plus chemotherapy ($p = 0.31$). The corresponding rates of cancer-specific survival were 70% and 78% ($p = 0.35$). Cox regression analysis confirmed a trend toward reduced mortality (HR 0.88, 95% CI 0.62–1.25, $p = 0.37$) in patients receiving RT and chemotherapy.

Conclusion: Consistent with other studies that have been published, the addition of chemotherapy to RT was associated with improved clinical outcomes. Although this improvement did not reach statistical significance, the use of concurrent chemoradiation seems reasonable for Asian Americans with nasopharyngeal carcinoma.

KEYWORDS
Asian American, chemotherapy, nasopharyngeal cancer, radiation, survival rate

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy of the head-and-neck noted for its unique epidemiology and histological characteristics. The age-standardized incidence rate per 100,000 persons is as low as 0.5 in white people, but is greater than 20-fold higher among endemic populations residing in southern China and Southeast Asia, and is intermediate among Chinese descendants living in the USA.[1,2] In endemic areas, NPC is strongly associated with World Health Organization (WHO) type III histology, Epstein–Barr virus (EBV), and more advanced disease at presentation, whereas among white people in the USA and Western Europe, NPC is typically associated with tobacco use. These distinctions might be of importance, as questions regarding the optimal treatment for NPC persist, particularly with respect to the value of adding concurrent chemotherapy to radiation therapy (RT).[3–12]

In the USA, concurrent chemoradiation (CRT) has been widely accepted as the standard since 1998, with the publication of the North American Intergroup study showing a significant survival benefit with the addition of chemotherapy to RT.[4] As that study included a relatively large proportion of patients with WHO type I histology, a question that emerged was whether Asian Americans derived the same degree of benefit as white people with the addition of chemotherapy to RT for NPC. This is particularly relevant given that Asian Americans represent a rapidly expanding ethnic group that currently comprise greater than 5% of the population in the USA, and has the highest incidence of NPC. The present study utilized patients from a large state-sponsored, population-based cancer registry from California, home to one-third of Asian Americans living in the USA, to evaluate the role of CRT for locally advanced NPC.

2 | METHODS

2.1 | Study design and database

The California Cancer Registry (CCR) – a population-based, state-sponsored cancer reporting database – was surveyed for the retrospective collection of information used in the analysis. The state of California is home to approximately 12% of the USA population, including 36% of all Asian Americans. The CCR has prospectively collected data from all California residents diagnosed with cancer since 1988. This registry relies on medical records to organize information on demographics, cancer type, extent of disease, treatment, and survival. Area-based socioeconomic status (SES) data was also ascertained when CCR data was linked to census data by geographical residency status at the time of diagnosis. Stage at diagnosis was classified based on guidelines espoused by the Surveillance, Epidemiology, and End Results program. The Surveillance, Epidemiology, and End Results summary stage, supplemented with information on lymph node status, as well as the American Joint Committee on Cancer TNM classification stage was recorded for patients. Information regarding the first course of treatment (given within 4 months after diagnosis) included the use of surgery, RT, and chemotherapy.

Race-ethnicity information was collected from medical records, which was enhanced by the use of the North American Association of Central Cancer Registries Asian/Pacific Islander Identification Algorithm relying on birthplace and surname to characterize patients into more specific Asian American subgroups. For the purposes of this analysis, patients were then classified into the following: Chinese, Northeast Asian (Japanese and Korean), Southeast Asian (Vietnamese, Laotian, Hmong, Cambodian, Thai), Filipino, and others (including Indian and Pakistani). As all queried data were analyzed and reported in aggregate without the use of personal identifying information, the present study was granted an exemption from the institutional review board at the University of California, Davis.

2.2 | Chemotherapy treatment

We considered two treatment groups in the analysis, RT alone and CRT. Chemotherapy was classified by the CCR as: (1) none; (2) chemotherapy, not otherwise specified; (3) single or multi-agent; (4) contraindicated; (5) patient dies before admission; or (6) recommended but not administered and unknown. For the purposes of the current study, we considered the coding of (2) and (3) as indicative of receipt of chemotherapy. Logistical details of chemotherapy were not collected, including specific agents, dosages, cycles, or information regarding the actual timing, duration, and/or completion of chemotherapy.

2.3 | Case inclusions and exclusions

The analysis was limited to the cohort of Asian American patients diagnosed with biopsy proven NPC [ICD-O-3 codes] between 1998 and 2010 who received RT alone or CRT. We selected 1998 as the earliest year of diagnosis to be included in the study, because CRT had been widely accepted as standard since 1998 after the publication of the landmark Intergroup study by Al-Saraff et al.[4] Patients with ICD code 8070 (squamous cell carcinoma, not otherwise specified) and 8071 (squamous cell carcinoma, keratinizing, not otherwise specified) were considered WHO type I; whereas those with 8072 (squamous cell carcinoma, large cell, non-keratinizing), 8010 (carcinoma, not otherwise specified), 8020 (carcinoma, undifferentiated type), and 8082 (carcinoma, lymphoepithelial) were grouped as WHO type II/III. Other malignant histologies of the nasopharynx were excluded. Only cases with positive lymph nodes and/or direct extension beyond the primary site with negative lymph nodes were included. Patients with localized primary tumor and negative lymph nodes were intentionally excluded given that the role of chemotherapy for these patients has historically been questionable. Cases with remote disease (distant metastasis) and cases that did not actually receive RT or did not receive any type of treatment were also excluded. As a result of these specific inclusion criteria, only patients with American Joint Committee on Cancer combined stage II or higher, non-M1 disease were included in this analysis.

2.4 | Statistical analysis

We considered both overall survival (OS) and cancer-specific survival (CSS) as outcome variables in this analysis. OS was defined as the duration from the date of diagnosis to the date of death. CSS was defined as the duration from the date of diagnosis to the date of death from NPC. Cause of death was identified using ICD codes to distinguish cancer-specific death from other causes of death. Patient follow-up was reported to the last date in which records were available or to the date of expiration. All events were measured from the first day of RT.

Patient demographics and tumor characteristics between the two treatment groups (RT alone or CRT) were compared using χ^2-tests for categorical variables and two sample Student's *t*-tests for continuous variables. The Kaplan–Meier method was used to estimate the survival rates among patients in the two treatment groups, and log-rank tests were conducted to examine whether the differences in OSS and CSS between groups was statistically significant. To investigate the potential association between treatment (RT or CRT) and survival outcomes, we used Cox proportional hazard regression models, adjusting for other factors, including year of diagnosis, age, sex, SES, WHO histology, and stage. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for OS and CSS, using both unadjusted and adjusted Cox proportional hazards models. We also examined the interactions between treatment and year of diagnosis, age, WHO histology, and stage, respectively.

To account for covariates that may influence the receipt of a given treatment, propensity score analysis was used to balance measurable confounders between the RT alone and CRT groups. The probability that each patient received CRT was estimated using logistic regression models, which included year of diagnosis, age, sex, SES, WHO histology, and stage. The resultant propensity scores were adjusted for in the Cox proportional hazards regression models to compare survival of patients treated with RT alone and with CRT. The Cox proportional hazards regression analysis was also conducted separately within each propensity score quintile. Alternatively, propensity score 1:1 matching using a greedy algorithm was used to pair each patient in the RT alone group with one patient in the CRT group whose propensity score was within the designated caliper size. The matched cohort was then used for OS and CSS analysis with the Kaplan–Meier method. Statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R (http://www.r-project.org). All statistical tests were two sided, and a *p*-value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient demographics and tumor characteristics

Between 1998 and 2010, a total of 812 newly-diagnosed, biopsy-proven NPC cases were identified among Asian Americans residing in California. Overall, 91 (11.2%) underwent RT alone and 721 (88.8%) underwent CRT. There were more men (67.9%) than women (32.1%), with a ratio of approximately 2:1. The majority of cases occurred in individuals of Chinese descent (51.6%), followed by those of Southeast Asian origin (22.5%) and Filipinos (21.1%). Over half of the patients (52.0%) resided in neighborhoods with higher levels of SES (levels 4 and 5). The majority of the cases were WHO type II or III histology, with 81.3% in the RT alone group and 78.4% in the RT + chemotherapy group ($p = 0.13$).

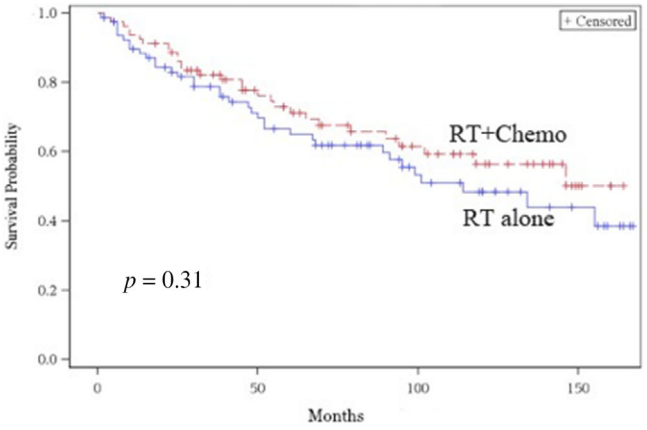

FIGURE 1 Overall survival for patients treated by radiation therapy (RT) alone versus chemoradiation

Patient demographics and tumor characteristics of the two treatment groups are reported in Table 1. Those treated with RT alone were older than those treated with CRT (mean age 60.2 vs. 50.1 years, $p < 0.0001$), with 34.0% patients in the RT alone group aged older than 70 years versus 5.8% in the CRT group. A significantly greater proportion of patients in the CRT group were diagnosed in the latter years of this case series, and were diagnosed with more advanced disease at presentation with tumor extending outside the nasopharynx and positive lymph nodes (25.3% vs. 44.8%). To control for selection bias, we constructed propensity scores for the likelihood of chemotherapy receipt based on age, year of diagnosis, sex, SES, WHO histology, and Surveillance, Epidemiology, and End Results stage. When adjusted for propensity score, all variables were balanced among patients treated with RT alone and CRT with propensity score-adjusted $p > 0.05$ (Table 1).

3.2 | Survival analysis

Figure 1 shows the OS curves of patients who did and did not receive chemotherapy using the propensity score matched cohort. With a median follow-up time of 6.6 years, the OS at 5 years was 65% with RT alone, and 72% with addition of chemotherapy. The OS difference was not statistically significant between the two groups ($p = 0.31$). The mean follow-up was 6.5 years (range 0.5–12.2 years).

Multivariate Cox proportional hazards regression analysis showed that the addition of chemotherapy was not associated with improved OS after adjustment for year of diagnosis, age, sex, SES, WHO

TABLE 1 Demographics and tumor characteristics

	RT only		RT + chemotherapy			PS adjusted
Characteristics	No. patients	(%)	No. patients	(%)	*p*-value	*p*-value
Year of diagnosis					0.001	0.77
1998–2001	50	54.9	259	35.9		
2002–2005	27	29.7	282	39.1		
2006–2010	14	15.4	180	25.0		
Age (years)					<0.0001	0.77
Mean age	60.2		50.1			
<40	10	11.0	139	19.3		
40–55	32	35.2	348	48.3		
56–70	18	19.8	192	26.6		
>70	31	34.0	42	5.8		
Sex					0.79	0.998
Male	63	69.2	489	67.8		
Female	28	30.8	232	32.2		
Asian American	91	11.2	721	88.8	0.92	0.72
Northeast Asian	3	3.3	22	3.1		
Chinese	44	48.4	375	52.0		
Southeast Asian	20	22.0	163	22.6		
Filipino	22	24.0	149	20.5		
Others	2	2.4	12	1.8		
SES					0.84	0.95
SES 1 LOW	14	15.4	88	12.2		
SES 2	17	18.7	118	16.4		
SES 3	17	18.7	136	18.8		
SES 4	21	23.0	176	24.4		
SES 5	22	24.2	203	28.2		
WHO histology					0.13	0.99
WHO I	17	18.7	156	21.6		
WHO II/III	74	81.3	565	78.4		
SEER stage					<0.0001	0.90
Extended tumor, N0	27	29.7	93	12.9		
Localized tumor, N+	41	45.0	305	42.3		
Extended tumor, N+	23	25.3	323	44.8		
AJCC T stage					0.45	0.85
T1	41	45.1	305	42.3		
T2-4	50	54.9	416	57.7		

Abbreviations: AJCC, American Joint Committee on Cancer; PS, propensity score; RT, radiation therapy; SEER, Surveillance, Epidemiology, and End Results Program; SES, Social Economic status; WHO, World Health Organization.

histology, and stage (HR 0.88, 95% CI 0.62–1.25, $p = 0.37$). In line with the aforementioned result, the Cox proportional hazards regression analysis adjusted for propensity score also yielded similar results when using the entire cohort (HR 0.89, 95% CI 0.63–1.27, $p = 0.66$), as shown in Table 2. Furthermore, when data were analyzed separately within each propensity score quintile, no statistically significant association was found between treatment and the OS within any of the stratum, with a *p*-value of 0.13 for the middle stratum (Table 2). By design, patients in the middle stratum had near-random propensity scores centered at 0.5, and represented the subgroup with the greatest adjustment for bias.

For CSS, there was no significant difference between the two treatment groups using the propensity score matched cohort ($p = 0.35$; Figure 2). Multivariate Cox proportional hazards regression analysis

TABLE 2 Propensity score analysis: risk of death for patients treated with radiation therapy + chemotherapy

	Overall survival		
Quintile	HR	95% CI	*p*-value
1, lowest probability of RT + chemotherapy	0.66	0.42–1.04	0.07
2,	0.86	0.39–1.91	0.70
3,	0.45	0.16–1.25	0.13
4,	2.47	0.60–10.13	0.21
5, highest probability of RT + chemotherapy	0.43	0.06–3.19	0.41
Entire sample*	0.89	0.63–1.27	0.66

Abbreviations: CI, confidence interval; PS, propensity score; RT, radiation therapy.
Quintiles represent patients grouped on the basis of propensity score. *The hazard ratio for the entire sample is adjusted for the propensity score.

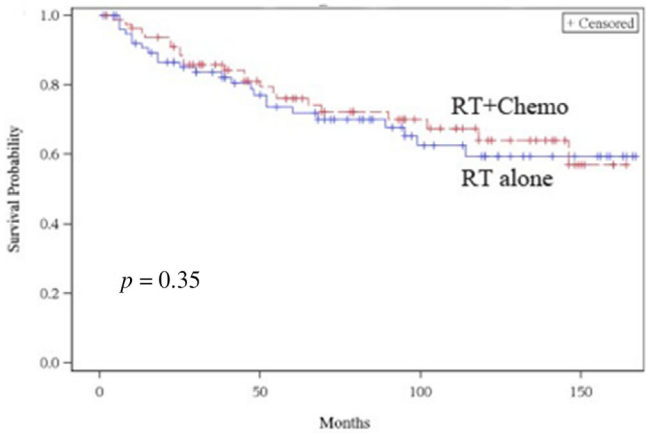

FIGURE 2 Cancer-specific survival for patients treated by radiation therapy (RT) alone versus chemoradiation

showed that the addition of chemotherapy to RT was not associated with improved CSS after adjustment for year of diagnosis, age, sex, SES, WHO histology, and stage (HR 1.08, 95% CI 0.71–1.65, $p = 0.72$).

Potential interactions between the addition of chemotherapy to RT and year of diagnosis, age, stage, and WHO histology were examined separately. No statistically significant correlations were identified, and we were unable to identify any subgroups with an OS or CSS benefit with the receipt of CRT compared to RT alone ($p > 0.05$, for all).

4 | DISCUSSION

The results of the present study, representing data from a large series of cases using a population-based cancer registry, are notable, because they show a small but non-significant OS benefit with the use of CRT over RT alone for Asian Americans with NPC. This finding is consistent with the outcomes of several randomized trials published from endemic areas in Asia showing non-significant improvements in OS between the two approaches.[3–12] For instance, in one of the largest studies conducted in Asia, Lee et al. reported 5-year OS rates of 64% and 68% among 348 patients treated by RT alone and CRT for NPC, respectively, on a large randomized trial from a multicenter study from Hong Kong using essentially the same CRT backbone as from the Intergroup trial.[3] In another prospective trial involving 189 NPC patients, Lee et al. reported 3-year OS rates of 87% and 83%, respectively, for patients treated by RT and CRT using conventionally fractionated regimens.[5] Kwong et al. similarly reported a difference in 3-year OS rates of 86% and 77% among 222 patients randomized to CRT and RT for NPC, respectively[9].

While other groups have conversely shown a survival advantage with the addition of concurrent chemotherapy to RT, the selection criteria, RT details, rates of treatment compliance, and choice of chemotherapy agents have varied widely, resulting in difficulty in drawing definitive conclusions. For instance, while the OS benefit associated with concurrent was initially confirmed by a randomized trial from Taiwan in an endemic population using concurrent cisplatin and 5-fluorouracil, a re-analysis of the data suggested that concurrent CRT is only beneficial for "low-risk" advanced stage patients.[10,11] Others, to the contrary, have suggest that the OS benefit may be limited to patients with T3 or T4 disease.[8] It must be noted, however, that classification systems for this disease have evolved greatly over the years, and the inclusion of histology and race has been proposed.[8,13–15]

There have been at least nine phase III randomized trials comparing RT alone with CRT in NPC.[3–12] Table 3 summarizes the outcomes of these trials. Despite the seemingly conflicting results, the use of concurrent CRT is, nevertheless, considered standard of care, largely based on the results of the North American Intergroup Trial, which was the first to show an OS benefit.[4] More recently, the Meta-Analysis of Chemotherapy in Nasopharynx Carcinoma (MAC-NPC) collaborative group analyzed data from 4806 patients treated in 19 trials, and found that the addition of chemotherapy to RT significantly improved OS with an absolute benefit of 6.3% at 5 years[16].

The present results are particularly noteworthy given the significant toxicity traditionally observed with this more aggressive approach. In the Intergroup trial, the incidence of high-grade hematologic toxicity, stomatitis, nausea/vomiting, and hearing impairment was higher among the CRT versus RT alone group.[4] Similarly, in the NPC 99-01 trial, the incidence of grade 4 or higher acute toxicity was 12% versus 1% for patients treated by CRT and RT alone, respectively[3]. Additionally, deaths due to toxicity or incidental causes was increased by 7%

TABLE 3 Published randomized trials comparing concurrent chemoradiation with radiation therapy alone for nasopharyngeal carcinoma

Author	Location	Year	No. pts	Chemo (CRT)	Adjuvant	OS (CRT)	OS (RT)	End-point	*p*
Al-Saraff et al.	North America	1998	147	CDDP q3 weeks	CDDP/5-FU	67	37	5 years	0.001
Lin et al.	Taiwan	2003	284	CDDP q4 weeks	5-FU	72	54	5 years	0.0022
Kwong et al.	Hong Kong	2004	219	Uracil/Tegafur	CDDP*	86	77	3 years	0.06
Wee et al.	Singapore	2005	221	CDDP q3 weeks	CDDP/5-FU	80	65	3 years	0.0061
Chan et al.	Hong Kong	2005	350	CDDP weekly	None	72	59	5 years	0.048
Lee et al.	Hong Kong#	2010	348	CDDP q3 weeks	CDDP/5-FU	68	64	5 years	0.22
Sharma et al.	India	2010	153	CDDP weekly	None	62	42	3 years	0.02
Lee et al.	Multi-national†	2011	189	CDDP q3 weeks	CDDP/5-FU	87	83	3 years	0.84
Zhang et al.	China	2013	115	Oxaliplatin	None	73	60	5 years	0.03
Chen et al.	China	2013	316	CDDP weekly	CDDP/5-FU	72	62	5 years	0.043

Abbreviations: CRT, concurrent chemoradiation; OS, overall survival; RT, radiation therapy alone; pts, patients.
*Included alternating cisplatin, fluorouracil, vincristine, bleomycin, and methotrexate, which was received by only half the patients; #Included patients from Canada; †Hong Kong, China, Canada, and Singapore.

with the addition of chemotherapy to RT. In the study from Sun Yat-Sen University in Guangzhou, China, the incidence of grade 3 or higher acute toxicity was nearly doubled (63% vs. 32%) for patients receiving concurrent CRT compared with RT alone.[7] These same studies have also showed that patients treated by CRT for NPC are more likely to have difficulties with compliance given the more intensive toxicity profile. For instance, even among the patients randomized to the CRT arm in the Intergroup trial, just 63% received all three cycles of concurrent cisplatin.[4] Although newer RT techniques, such as intensity-modulated radiotherapy, have improved the toxicity profile, the use of CRT is still associated with significant toxicity.[17,18] A recently published meta-analysis of five randomized trials additionally showed that concurrent CRT was associated with a nearly two-fold increase in the likelihood of late hearing loss and/or deafness compared with RT alone among patients treated for NPC.[23]

The present study was limited by a lack of rigorous information on chemotherapy, most notably regarding regimen and timing. Before the publication in 1998 of the Intergroup trial, multiple prospective trials tested sequential chemoradiation in the form of induction or adjuvant chemotherapy for NPC.[19–22] However, both strategies failed to improve survival compared with RT alone. Although the CCR database only recorded the first course of chemotherapy and did not provide specific logistical details regarding the sequence of chemotherapy in relation to RT, it could be reasonably presumed that the majority of CRT patients received concurrent chemotherapy, given that all cases were diagnosed in the contemporary era after the publication of the landmark Intergroup trial. Similarly, it could be presumed that patients received single-agent cisplatin with RT in accordance with details of the Intergroup trial. How the addition or omission of adjuvant and/or induction chemotherapy with concurrent CRT may have affected observed outcomes also remains uncertain. Additionally, it was not possible to determine with certainty whether all CRT patients received all planned chemotherapy, a particularly relevant consideration given the historical difficulties with compliance that have affected this group.

The potential role of technology as a confounding factor must also be acknowledged, given that studies have suggested that patients treated by intensity-modulated techniques for NPC benefit from improved outcomes with respect to local control and overall survival.[24,25] This is especially notable given that more patients in the CRT group were diagnosed in the latter years of this series and presumably received intensity-modulated radiotherapy. Although the exact type of RT received by patients could not be determined with certainty, the influence of technique must be considered in the interruption of the present results. Furthermore, information on EBV, an increasingly recognized prognostic factor when measured in plasma, was not available through the CCR and may have influenced outcomes.[26] Finally, several recently published studies have attempted to develop nomograms to better elucidate which populations may benefit the most from concurrent CRT, and have the potential to better optimize treatment selection in the future.[27–29]

In conclusion, the results of the present study, showing a small but non-significant benefit associated with CRT compared with RT alone for Asian Americans with NPC, have hypothesis-generating implications. Although we acknowledge the limitations inherent in a population-based registry analysis of this nature, our findings showing a moderate improvement of outcomes for Asian Americans with NPC suggest that concurrent CRT is a reasonable option. However, the optimal regimen remains to be defined and a phase III trial specific for this population should be considered.

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CONFLICT OF INTEREST

The authors declare that they have read the article and there are no competing interests.

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