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Nasopharyngeal carcinoma

Metastatic nasopharyngeal carcinoma: Patterns of care and survival for patients receiving chemotherapy with and without local radiotherapy

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ABSTRACT

Background and purpose: Radiotherapy (RT) to the primary nasopharyngeal tumor is frequently offered to patients with metastatic nasopharyngeal carcinoma (mNPC). However, only limited data exist to support RT in this setting. We used the National Cancer Database (NCDB) to evaluate outcomes for mNPC patients receiving chemotherapy with and without local RT.

Methods: The NCDB was queried for patients with mNPC with synchronous metastatic disease at diagnosis who received chemotherapy. Overall survival (OS) was analyzed using the Kaplan–Meier method, Cox proportional hazards models, and propensity score-matched analyses.

Results: From 2004 to 2013, 718 cases were identified (39% chemotherapy-alone, 61% chemotherapy + RT). At a median follow-up of 4.4 years, RT was associated with improved survival on univariate analysis (median OS 21.4 vs 15.5 months; 5-year OS 28% vs 10%; $p < 0.001$) and multivariate analyses (HR, 0.61; CI, 0.51–0.74; $p < 0.001$). Propensity score analysis with matched baseline characteristics demonstrated a similar OS advantage with RT (HR, 0.68; CI, 0.55–0.84; $p < 0.001$). The benefits of RT remained consistent in models controlling for single vs multi-organ metastases and anatomic sites of metastatic involvement. RT dose was an independent prognostic factor as both a continuous and categorical variable, with OS benefits observed among patients receiving ≥50 Gy. Long-term survival of >10 years was only observed in the RT cohort.

Conclusions: This analysis supports strategies incorporating local RT with chemotherapy for mNPC. Prospective trials evaluating RT integration for mNPC are warranted.

Worldwide, approximately 86,000 cases of nasopharyngeal carcinoma (NPC) are diagnosed annually, with roughly 6–8% of patients presenting with synchronous metastatic disease (mNPC) [1,2]. Platinum-based chemotherapy represents the primary treatment modality for mNPC [3–5]. Strategies incorporating radiation therapy (RT) to the primary nasopharyngeal tumor and regional lymph nodes are also included as options in the contemporary National Comprehensive Cancer Network (NCCN) guidelines [5], although only limited data exist to support RT in this setting. Moreover, available series to support RT for mNPC come almost exclusively from endemic populations in China and Southeast Asia, where the incidence and biologic composition of NPC are distinct from non-endemic western populations [3].

In this analysis, we used the NCDB to evaluate the patterns-of-care and overall survival (OS) for mNPC patients receiving chemotherapy with and without RT in the United States (US).

Methods

The NCDB is ahospital-based cancer registry sponsored by the American College of Surgeons (ACoS) and American Cancer Society (ACS) and includes approximately 70% of malignancies diagnosed in the US [6]. Demographics, comorbidities, tumor characteristics, and OS are recorded, as well as therapies including chemotherapy, RT, and surgery. The ACoS and the Commission on Cancer are not responsible for the analyses or conclusions drawn by investigators. The following NCDB analysis was performed with approval from our local institutional review board.

Eligibility criteria included patients ≥18 years old with newly-diagnosed NPC with metastatic disease (M1) at diagnosis, all treated with chemotherapy, with known vital status at last follow up

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and known status for the use of radiotherapy and surgery (Supplemental Fig. 1). Patients dying within the first month from diagnosis and those undergoing surgical resection or surgery-NOS were excluded. Treatment coding in the NCDB is limited to the first course of treatment, defined as all methods of therapy recorded in the treatment plan and administered to the patient before disease progression or recurrence [7]. Available coding for local nasopharyngeal RT includes external beam radiation to the head and neck or sinuses. Because the NCDB records RT data for only one anatomic site per patient, it is not possible to determine which patients received both local RT and RT to distant metastatic sites. Patients coded to receive RT to distant sites were analyzed in the chemotherapy without local RT cohort. Data regarding specific chemotherapy agents and cycle numbers are not available.

Tumor histology was categorized in a manner similar to prior publications [8], including keratinizing squamous cell carcinoma (ICD-O codes 8070/8071), non-keratinizing differentiated carcinoma (codes 8072/8073), and non-keratinizing undifferentiated carcinoma (codes 8020/8021/8082 and any non-keratinizing carcinomas assigned an undifferentiated grade). Data regarding histologic and serum Epstein-Barr virus (EBV) testing are not available. Available surrogates for EBV-associated disease included non-keratinizing histology and a study-defined Chinese/Southeast Asian category encompassing races from endemic populations with near-uniform EBV-positive disease [3,9]. It was not possible to further stratify Southern Chinese or other endemic groups such as North Africans or Arctic natives.

The primary objective for analysis was the comparison of OS outcomes for patients with mNPC treated with chemotherapy with and without local RT. Survival was estimated using the Kaplan–Meier method and compared using Cox proportional hazards models. Multivariate Cox models were adjusted for factors selected *a priori* including RT, age, sex, year of diagnosis, treatment center, insurance status, comorbidity scores, T-classification (T), N-classification (N), tumor histology, and race. Separate multivariate models including the above cofactors, with the exception of RT administration, were used to analyze RT-specific factors including RT dose, treatment technique (intensity-modulated radiotherapy [IMRT] vs other), and the sequencing of chemotherapy and RT. For analytic purposes, induction-chemotherapy and subsequent RT was defined as chemotherapy initiation $\geq$21 days prior to RT initiation. Concurrent-chemotherapy included initiation $\leq$20 days prior to and $\leq$ 42 days (6 weeks) after RT initiation. Adjuvant-chemotherapy included initiation $\geq$43 days after RT initiation. Due to the coding of only one chemotherapy start date in the NCDB, it is unknown what percentage of patients receiving induction-chemotherapy continued to receive chemotherapy concurrently with subsequent RT. Metastatic sites including lung, liver, bone, and brain metastases were available among patients diagnosed in the year 2010 or later; the impact of RT was assessed in this subset controlling for metastatic spread (single vs multi-organ and individual anatomic sites) in addition to the aforementioned multivariate factors. The proportional hazards assumption was assessed for all covariates and returned no significant results [10]. Median follow up was assessed using the reverse Kaplan–Meier method [11]. Baseline characteristics were compared using the χ^2 and Mann–Whitney U test for categorical and continuous variables, respectively.

Propensity score-matched analyses were performed comparing outcomes with chemotherapy vs chemotherapy plus local RT. One-to-one matching without replacement was completed using the nearest-neighbor match on the logit of the propensity score for therapeutic approach (derived from age, sex, year, treatment center, insurance status, comorbidity score, T, N, tumor histology, and race). The caliper width was 0.05x the standard deviation of the logit of the propensity score [12], which is estimated to eliminate over 99% of the bias due to cofounding variables [13].

Sequential landmark analyses for patients surviving $\geq$1, $\geq$2, and $\geq$3 years and sensitivity analyses limited to patients starting RT within 120, 90, 60, 30, and 10 day of chemotherapy initiation were performed to account for potential selection biases favoring RT delivery in patients with more favorable prognoses and potential immortal-time biases among patients receiving delayed RT [14]. Subgroup analyses evaluating the impact of RT were performed for covariates selected *a priori* including age, year, sex, treatment center, comorbidities, T, N, histology, and race. A recursive-partitioning analysis (RPA) was performed, using the methods described by Ciampi [15], stratifying patients into prognostic tiers with common clinical variables identified as significant on multivariate analysis. Survival outcomes with and without RT were assessed within each prognostic tier.

Results

Our search criteria for patients with newly-diagnosed mNPC treated with chemotherapy returned 718 cases from 2004–2013, including 281 (39.1%) receiving chemotherapy alone and 437 (60.9%) receiving chemotherapy and local RT. Regional differences in racial composition were observed, with Chinese and Southeast Asian patients representing the majority of cases in the Pacific region of the US and non–hispanic whites representing the majority in all other regions (Map displayed in Supplemental Fig. 2).

Patient and treatment characteristics are displayed in Table 1. RT use was associated with lower comorbidity scores, T4 disease, and treatment at non-academic centers. The median and mode RT doses were 66 Gy and 70 Gy, respectively (interquartile range [IQR], 51.6–70 Gy).

The median follow up was 4.4 years. At last follow up, 74% (528) of the analyzed patients were deceased. The median OS for the entire cohort was 18.1 months. On univariate analysis, the addition of RT to chemotherapy was associated with longer median OS compared to chemotherapy alone (21.4 vs 15.5 months), as well as improved 1-year (67% vs 58%), 3-year (37% vs 20%), 5-year (28% vs 10%), and 8-year OS (18% vs 5%) (HR 0.63; CI 0.54–0.75; $p < 0.001$) (Fig. 1A). Survival > 10 years was only observed in the RT cohort (18% vs 0%).

On multivariate analysis, RT remained independently associated with improved OS (HR 0.61; CI 0.51–0.74; $p < 0.001$) (Table 2). Additional prognostic factors for OS observed on multivariate analysis included younger age, treatment at an academic center, private insurance, lower comorbidity scores, lower T-classification, and non-keratinizing histology. A trend toward improved OS was observed for Chinese/Southeast Asian patients compared to white patients.

A propensity score analysis was performed matching 225 patients receiving chemotherapy alone with 225 patients receiving chemotherapy and RT. Patient characteristics were well-balanced across all covariates (Supplemental Table 1). This matched analysis redemonstrated an association between RT and improved OS, with comparable benefits to the overall analysis (median OS 22.7 vs 16.0 months; 5-year OS 27% vs 13%; HR 0.68; CI 0.55–0.84; $p < 0.001$) (Fig. 1B).

On analyses of RT dose (Table 2), increasing dose was associated with improved OS as a continuous variable ($p < 0.001$). When analyzed in dose groups of <30, 30–49.9, 50–69.9, and $\geq$70 Gy, the survival advantage of RT was observed with doses $\geq$50 Gy (Fig. 2). The use of RT with both induction and concurrent chemotherapy strategies was associated with improved OS over chemotherapy alone (Table 2), with no significant differences between strategies.