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Outcomes of induction chemotherapy followed by concurrent chemoradiation for nasopharyngeal carcinoma

D.W. Golden [a,*], S. Rudra [a], M.E. Witt [a], T. Nwizu [b], E.E.W. Cohen [b,c], E. Blair [c,d], K.M. Stenson [c,d], E.E. Vokes [a,b,c], D.J. Haraf [a,c]

[a] Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL, USA
[b] Department of Medicine, Section of Hematology/Oncology, University of Chicago, Chicago, IL, USA
[c] Comprehensive Cancer Center, University of Chicago, Chicago, IL, USA
[d] Department of Surgery, Section of Otolaryngology/Head and Neck Surgery, University of Chicago, Chicago, IL, USA

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SUMMARY

Purpose: Current standard therapy for nasopharyngeal carcinoma (NPC) is concurrent chemoradiation based on randomized data. However, limited randomized data exist to support the addition of induction chemotherapy (ICT).
Methods: 58 Patients with NPC were treated from 1990 to 2010. All patients received platinum-based ICT. All 58 patients were treated with chemoradiation, 57 in a week-on/week-off (WOWO) fashion. Concurrent chemotherapy included hydroxyurea/5-fluorouracil for all patients. Median radiation dose was 70 Gy. No patient received adjuvant chemotherapy.
Results: AJCC 2009 stage was II = 13, III = 21, IVa = 13, and IVb = 11. Median follow-up for surviving patients was 66 months. Response to ICT was complete response (CR) 17% and partial response (PR) 64%. The CR rate after chemoradiation was 96%. Five-year actuarial freedom from local failure (FFLF), freedom from distant failure (FFDF), cause-specific survival (CSS), and overall survival (OS) was 98%, 90%, 90%, and 76%, respectively. Analysis of pediatric patients ($n = 9$) demonstrated 5-year actuarial FFLF, FFDF, CSS, and OS of 100%, 88%, 80%, and 80%, respectively.
Conclusions: ICT followed by concurrent chemoradiation demonstrates excellent FFLF, FFDF, CSS, and OS with tolerable toxicity. Induction chemotherapy followed by concurrent chemoradiation for patients with NPC should be explored further in a randomized setting.

Introduction

Locally advanced nasopharyngeal carcinoma is treated with concurrent chemoradiation followed by adjuvant chemotherapy. Multiple trials have investigated the use of concurrent chemoradiation versus radiotherapy alone and have shown a benefit in both the United States[1] and endemic regions.[2] Two recent meta-analyses showed a benefit for any combined modality therapy (neoadjuvant, concurrent, or adjuvant chemotherapy) over radiation alone for locally-advanced nasopharyngeal carcinoma.[3,4] Therefore, combined modality therapy with concurrent chemoradiation with or without adjuvant chemotherapy has become the standard of care for T3-4 or node positive nasopharyngeal carcinoma.

Chemoradiation followed by adjuvant chemotherapy is difficult for patients to tolerate, with only 55% of patients completing all three cycles of adjuvant chemotherapy in the Intergroup (INT) 0099 study.[1] Therefore, one possible method to improve the outcomes for locally advanced nasopharyngeal carcinoma is sequential combined modality therapy with induction chemotherapy followed by concurrent chemoradiation. By giving chemotherapy upfront followed by chemoradiation, patients may be more likely to receive all planned cycles of chemotherapy. Whether there is a benefit to induction chemotherapy in the treatment of nasopharyngeal carcinoma is unknown. The addition of induction chemotherapy to radiation alone in the treatment of nasopharyngeal carcinoma failed to show a significant improvement in outcomes,

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; CR, complete response; CSS, cause-specific survival; EBV, Epstein-Barr virus; FFLF, freedom from local failure; FFDF, freedom from distant failure; GORTEC, Oncology and Radiotherapy Group for Head and Neck Cancer; Gy, Gray; NPC, nasopharyngeal carcinoma; OS, overall survival; PD, progressive disease; PR, partial response; PTV, planning target volume; SD, stable disease; WHO, world health organization; WOWO, week-on/week-off.

* Corresponding author. Address: Department of Radiation and Cellular Oncology, University of Chicago, 5758 South Maryland Avenue, MC 9006, Chicago, IL 60637, USA. Tel.: +1 773 702 6870; fax: +1 773 834 7340.
E-mail address: dgolden@radonc.uchicago.edu (D.W. Golden).

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although many of the studies were underpowered.[5–8] However, multiple small studies show that induction chemotherapy followed by chemoradiation leads to excellent outcomes.[9–16] However, two randomized trials have conflicting outcomes as to whether there is a benefit to induction chemotherapy.[17,18]

The standard of care at our institution has been to treat locally advanced head and neck malignancies with combined modality therapy. Our outcomes using induction chemotherapy followed by chemoradiation for 27 patients with locally advanced nasopharyngeal carcinoma treated between 1990 and 1999 were previously reported.[12] Based on these excellent results, we continued to use this or similar treatment regimens. Here we report updated outcomes of patients with nasopharyngeal carcinoma treated at our institution with induction chemotherapy followed by chemoradiation. Patient and treatment related parameters are evaluated in relation to outcome.

Methods

All patients with nasopharyngeal carcinoma treated at the University of Chicago Medical Center from 1990 to 2010 were identified. Patients were eligible for inclusion if they had nasopharyngeal carcinoma American Joint Committee on Cancer (AJCC) Stage I–IV and were treated with induction chemotherapy followed by chemoradiation after January 1, 1990. All ages were included in the cohort, including children. Patients were required to have a histologic diagnosis of nasopharyngeal carcinoma. Patients were excluded if they had recurrent or metastatic nasopharyngeal carcinoma at the time of treatment. Stage was converted based on chart review to the AJCC 2009 nasopharyngeal carcinoma staging system.

Treatment details are summarized in Table 1. Fifty eight patients received platinum-based induction chemotherapy followed by concurrent chemoradiation using a 5-fluorouracil and hydroxyurea chemotherapy backbone. Induction chemotherapy consisted of two or three chemotherapy cycles delivered every three weeks. Response was evaluated after the final cycle of induction chemotherapy clinically and, if indicated, radiographically. Concurrent chemoradiation then commenced. Patients treated in a week-on/week-off (WOWO) fashion were admitted to the hospital for one week where they received chemotherapy and either five once-daily or 10 twice-daily radiation fractions. They were then discharged for one week and readmitted on a WOWO schedule until they had received the entire prescribed dose of radiation. Thus, daily radiation treatment resulted in seven WOWO cycles and twice-daily radiation treatment resulted in five WOWO cycles.

The median radiation dose was 70 Gy (range 60-75 Gy) delivered in either 2 Gy fractions daily ($n = 38$) or 1.5 Gy fractions twice-daily ($n = 26$). Although patients were treated over approximately 20 years and the institutional radiation treatment standards have evolved,[19] description of our current standard is representative of the majority of cases. All patients undergo computed tomography-based treatment planning. An initial low-risk volume is treated to either 50 Gy in daily 2 Gy fractions or 39 Gy in twice-daily 1.5 Gy fractions. This volume includes all areas of gross disease plus adjacent and draining lymph node regions. Thus, the planning target volume (PTV) will frequently include the nasopharynx and posterior nasal cavity, sphenoid sinus, retropharyngeal lymph nodes, and the 1b, 2, 3, 4, 5, and supraclavicular neck levels. Subsequently, an intermediate risk PTV is treated with an additional 10 Gy in daily 2 Gy fractions or 15 Gy in twice-daily 1.5 Gy fractions to a cumulative dose of 60 or 54 Gy, respectively. This treatment volume includes gross disease and lymph node levels adjacent to areas of gross disease. Areas of gross disease then receive a final boost of 10 Gy in daily 2 Gy fractions or 21 Gy in twice-daily 1.5 Gy fractions to a cumulative radiation dose of 70 or 75 Gy, respectively.

Table 1
Treatment details ($n = 58$).

Treatment	
Total treatment time days (median, range)	139 (86–175)
Surgery	
Surgery on primary	0
Surgery on neck	
None	28
Biopsy only	24
Excision of node	6
Neck dissection	0
Chemotherapy	
Induction chemotherapy regimen	
Carboplatin/Paclitaxel	32
IFN/CDDP/5FU/leucovorin	19
Carboplatin/Taxotere	1
TPF	4
Cetuximab/Carboplatin/Paclitaxel	1
CDDP	1
Concurrent chemo regimen	
TFH	23
FH	25
GFH	8
Taxotere-FH	1
CFH	1
Radiation	
RT treatment time, days (median, range)	87 (52–112)
RT prescribed dose, Gy (median, range)	70 (66–75)
RT delivered dose, Gy (median, range)	70 (64–75)
WOWO	
Yes	57
No	1
BID	
Yes	24
No	33
Converted to QD	1
IMRT	
Yes	38
No	20

(5FU = 5-fluorouracil; CDDP = cisplatin; CFH = cetuximab, 5-fluorouracil, hydroxyurea; FH = 5-fluorouracil, hydroxyurea; GFH = gefitinib, 5-fluorouracil, hydroxyurea; IFN = interferon-α2b; TFH = paclitaxel, 5-fluorouracil, hydroxyurea; TPF = docetaxel, cisplatin, 5-fluorouracil).

Response to treatment was evaluated at the end of induction chemotherapy and then again after concurrent chemoradiation. Response was assessed clinically and by radiographic study if felt to be warranted by the treating physician. Response was recorded as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). A CR was defined as disappearance of all clinically detectable disease and a PR was defined as reduction of all measurable disease by at least 50% without the appearance of new lesions. Patients were followed after completion of therapy with clinical exams and, if indicated, radiographic studies by the treating physicians. Acute and late toxicities were scored by the treating physicians.

Overall survival (OS), cause specific survival (CSS), freedom from local failure (FFLF), and freedom from distant failure (FFDF) were calculated using Kaplan–Meier actuarial analysis. OS was defined as the time from the first day of treatment (either induction chemotherapy or concurrent chemoradiation if the patient did not receive induction therapy) to the date of death. CSS was defined as the time from the first date of treatment until the date of death caused by nasopharyngeal carcinoma. FFDF was defined as the time from the first date of treatment until the date of distant failure and FFLF was defined as the time from the first date of treatment until the date of local failure. Patients alive or dead without evidence of disease were censored in the analysis for CSS, FFDF,