

Intensity-Modulated Radiation Therapy With or Without Chemotherapy for Nasopharyngeal Carcinoma: Radiation Therapy Oncology Group Phase II Trial 0225

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A B S T R A C T

Purpose

To investigate the feasibility of intensity-modulated radiation therapy (IMRT) with or without chemotherapy, and to assess toxicities, failure patterns, and survivals in patients with nasopharyngeal carcinoma (NPC).

Patients and Methods

Radiation consisted of 70 Gy given to the planning target volumes of primary tumor plus any N+ disease and 59.4 Gy given to subclinical disease, delivered over 33 treatment days. Patients with stage T2b or greater or with N+ disease also received concurrent cisplatin (100 mg/m²) on days 1, 22, and 43 followed by adjuvant cisplatin (80 mg/m²) on day 1; fluorouracil (1,000 mg/m²/d) on days 1 through 4 administered every 4 weeks for three cycles. Tumor, clinical status, and acute/late toxicities were assessed. The primary objective was to test the transportability of IMRT to a multi-institutional setting.

Results

Between February 2003 and November 2005, 68 patients with stages I through IVB NPC (of which 93.8% were WHO types 2 and 3) were enrolled. Prescribed IMRT (target delineation) was given to 83.8%, whereas 64.9% received chemotherapy per protocol. The estimated 2-year local progression-free (PF), regional PF, locoregional PF, and distant metastasis-free rates were 92.6%, 90.8%, 89.3%, and 84.7%, respectively. The estimated 2-year PF and overall survivals were 72.7% and 80.2%, respectively. Acute grade 4 mucositis occurred in 4.4%, and the worst late grade 3 toxicities were as follows: esophagus, 4.7%; mucous membranes, 3.1%; and xerostomia, 3.1%. The rate of grade 2 xerostomia at 1 year from start of IMRT was 13.5%. Only two patients complained of grade 3 xerostomia, and none had grade 4 xerostomia.

Conclusion

It was feasible to transport IMRT with or without chemotherapy in the treatment of NPC to a multi-institutional setting with 90% LRPF rate reproducing excellent reports from single institutions. Minimal grade 3 and lack of grade 4 xerostomia were encouraging.

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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INTRODUCTION

Although rare among whites, nasopharyngeal carcinoma (NPC) is rather common among Asians.¹ Standard treatment for NPC is radiotherapy (RT) for early-stage lesions or chemoradiotherapy for more advanced lesions.^{2,3} Historical local control (LC) rates for patients who undergo conventional RT range from 64% to 95% for T1-2 tumors but decrease to 44% to 68% in T3-4 lesions.⁴⁻⁹ Modern series, including recent phase II/III trials have shown an improvement in LC (up to 95%), which is likely attributed to major advances in imaging, radiation techniques, and the incorporation of chemotherapy into standard management.^{2,10-13}

Retrospective studies that used RT alone for NPC suggest a correlation between LC and the dose delivered to the tumor.^{8,14} One study showed that LC was significantly improved when greater than 67 Gy were delivered to the tumor. In another retrospective series, improved LC was also attributed to improvements in technical accuracy. Because the nasopharynx is surrounded by normal critical structures, accuracy in dose delivery is essential in any dose-escalation studies.

Intensity-modulated RT (IMRT) modulates the radiation beams so that a high dose can be delivered to the tumor while the dose to the normal tissues is reduced.¹⁵ Investigators compared dosimetric plans of IMRT with conventional

techniques for NPC and concluded that IMRT provided improved tumor coverage and spared normal tissues.^{16,17} Lee et al¹⁸ reported that the clinical experience of IMRT for NPC showed considerable recovery of salivary function with time. The authors also reported an excellent local progression-free rate of 97%. Two recent, phase III trials also showed improvements in salivary function in patients treated with IMRT versus conventional RT for early-stage NPC.^{19,20}

Although IMRT for NPC is promising in terms of improvement of salivary function from different single institutions,¹⁸⁻²³ the data still need to be validated in a multi-institutional setting. Therefore, the Radiation Therapy Oncology Group (RTOG) conducted this multicenter, phase II trial to test the feasibility of IMRT with or without chemotherapy for all stages of NPC. Preliminary results are reported in this article. This trial accrued patients before the publication of the two phase III trials that established improvement in salivary function by IMRT.

PATIENTS AND METHODS

Study Objectives/Patient Eligibility

Patients with previously untreated stages I to IVB NPC, with an Eastern Cooperative Oncology Group performance status of 0 or 1, who met criteria for blood counts and other tests (ie, WBC \geq 4,000/ μ L; platelets \geq 100,000/ μ L; serum creatinine \leq 1.6 mg/dL) were eligible. Patients younger than 18 years old or those with a prior (ie, within 5 years) or synchronous malignancy, other than nonmelanoma skin cancer, were excluded. Pretreatment evaluations consisted of history and physical, dental, nutritional, audiogram, and laboratory studies. Magnetic resonance imaging (MRI) of the nasopharynx/neck was required unless there was a contraindication (ie, pacemaker); a computed tomography (CT) scan of the nasopharynx/neck was required if there was a contraindication to MRI. Additional tests to evaluate the extent of disease included chest x-ray, alkaline phosphatase, liver function tests, lactate dehydrogenase, and—when indicated—liver or bone scans. Positron emission tomography (PET) was optional. The disease was staged according to the 1997 American Joint Committee on Cancer Staging. All patients signed written informed consents, and the study was approved by participating centers' institutional review boards.

The primary objective was to test the feasibility of delivering IMRT in a multi-institutional setting. Other objectives were to determine rates of late xerostomia, locoregional (LR) control, distant metastasis (DM), progression-free survival (PFS), and overall survival (OS) and to determine compliance to combined modality.

Treatment

Computerized optimization was used with fusion of MRI and/or PET with treatment planning CT images, when possible, to accurately delineate the gross tumor volume (GTV), which included the primary disease and nodes greater than 1 cm in diameter or nodes with necrotic centers. The clinical target volume (CTV) denoted the subclinical regions at risk for involvement. Different CTVs were defined, as follows: CTV₇₀ = GTV + 5-mm margin; CTV_{59.4} = CTV₇₀ + 5 mm margin plus areas at risk for microscopic involvement, including the entire nasopharynx, retropharyngeal nodal regions, skull base, clivus, pterygoid fossae, parapharyngeal space, sphenoid sinus, the posterior third of the nasal cavity/maxillary sinuses that includes the pterygopalatine fossae, and levels I through V nodal regions. To account for organ motion/daily treatment set-up uncertainties, a planning target volume (PTV) was added (ie, additional margin of 3 to 5 mm) to each of the above CTVs. In areas where the GTV or the CTV was adjacent to critical normal structures (ie, brainstem) the margin could be reduced to 1 mm.

RT was delivered by using a simultaneous-integrated IMRT boost technique. PTV₇₀ received 70 Gy in 2.12 Gy/fraction, and PTV_{59.4} received 59.4 Gy in 1.8 Gy/fraction, over 33 days. The lower neck could be included in the IMRT fields by using proper contours of CTVs (1.8 Gy/fraction) and by keeping the

dose to the larynx to as low as possible without compromising target coverage. Alternatively, split-field IMRT technique was used, in which the low neck was treated with conventional anterior-posterior or anterior-posterior/posterior-anterior fields and received a total of 50.4 Gy. However, all involved nodes received a total dose of 70 Gy.

Patients with stage T2b or greater and/or N+ disease also received concurrent cisplatin (CDDP; 100 mg/m²) on days 1, 22, and 43 followed by adjuvant CDDP (80 mg/m²) on day 1; fluorouracil (FU; 1,000 mg/m²/d) on days 1 through 4 every 4 weeks for three cycles, as per Intergroup 0099. Guidelines for dose modifications were specified in the protocol.

Follow-Up/Statistical Considerations

Patients underwent weekly examinations during treatment. Follow-up evaluations occurred every 3 months during the first 2 years; every 6 months during years 3 to 5; then annually. In addition to tumor/clinical status, acute/late (ie, occurring > 90 days after start of RT) normal tissue effects were graded. Systemic/acute RT adverse effects were scored by using the National Cancer Institute Common Toxicity Criteria, version 2.0, whereas late RT effects were scored according to the RTOG/European Organisation for Research and Treatment of Cancer criteria. Whole salivary flows, both unstimulated and stimulated, also were collected at pretreatment and at 3, 6, and 12 months after treatment. No validated instruments were used in this protocol.

All treatment plans were reviewed by the Image-Guided Therapy Center, Washington University (St Louis, MO). All target volumes were evaluated by study chairs. Patients who were scored as having no or minor variations were considered compliant; those who had major variations or were not evaluable were considered noncompliant. Noncompliance could result from inaccurate target volume delineation (eg, not contouring of neck level V, 93% of the isodose surface covering less than 95% of the target volumes, greater than 5% of the PTV₇₀ receiving greater than 115%, and/or greater than 60% of each parotid glands receiving greater than 30 Gy). An important aspect of this study was the determination that the locoregional progression-free (LRPF) rate—in which failure was defined as local and/or regional progression, death as a result of study cancer without documented site of failure, or death as a result of unknown causes—was not compromised by the use of IMRT. The sample size was estimated on the basis of this end point. A rate of 80% was targeted, and 65% was considered unacceptable. By using Fleming's one-sample, multiple-testing procedure with type I and type II errors both set at 0.10, 57 evaluable patients were required.²⁴ The sample size was adjusted by 10% to allow for ineligible patients and loss to follow-up, so the total sample size was 64 patients. If 15 of the first 57 evaluable patients failed, the LRPF rate would be considered unacceptable. For the feasibility end point, a compliance rate of 90% was targeted, and 75% was considered unacceptable. If 10 or more of the first 57 patients were noncompliant, the treatment was deemed nontransportable to a multi-institutional setting.

Another end point was the rate of grade 2 or greater xerostomia 1 year (\pm 3 months) after the start of IMRT. A rate of 30% was targeted, and 55% (eg, if 27 of 57 patients experienced this toxicity) was considered unacceptable. Other secondary end points were acute/late effects; DM-free rates, in which failure was DM; PFS, in which failure was local, regional, or distant progression or death as a result of any cause; overall survival (OS), in which failure was death as a result of any cause. All percentages reported for the sites of first failures were based on all 68 patients.

OS and PFS were estimated by using the Kaplan-Meier method,²⁵ and local, regional, LRPF, and DM-free rates were calculated by using the method of cumulative incidence²⁶ to account for the competing risk of death without failure. All time-to-failure end points were calculated from the date of registration to the date of failure/last follow-up for patients who did not experience failure. Patients who developed DM were still observed for LR failure.

RESULTS

Patient Characteristics/Treatment Compliance

From February 2003 to November 2005, 68 patients were accrued from 17 centers in North America, and nine centers accrued

Table 1. Distribution of Patient Demographic and Clinical Tumor Characteristics

Characteristic	Patients	
	No.	%
Age, years		
Median		48.5
Range		18-73
Sex		
Male	51	75.0
Female	17	25.0
Ethnicity		
White	37	54.4
Asian	23	33.8
Black	5	7.4
Native Hawaiian or other Pacific Islander	1	1.5
Unknown	2	2.9
Zubrod performance scale		
0	47	69.1
1	21	30.9
Primary site		
Nasopharynx NOS	35	51.5
Posterior superior wall	24	35.3
Lateral wall	9	13.2
T stage		
1	17	25.0
2a	12	17.6
2b	16	23.5
3	10	14.7
4	13	19.1
N stage		
0	18	26.5
1	21	30.9
2	21	30.9
3a	2	2.9
3b	6	8.8
AJCC stage grouping		
I	9	13.2
IIA	2	2.9
IIB	17	25.0
III	21	30.9
IVA	11	16.2
IVB	8	11.8
WHO histology		
I	6	8.8
II or IIA	24	35.3
III or IIB	37	54.4
Unknown	1	1.5

Abbreviations: NOS, not otherwise specified; AJCC, American Joint Committee on Cancer.

greater than two patients who were eligible for analysis. Table 1 lists the pretreatment patient demographic and clinical tumor characteristics. Fifty-seven patients (83.8%) had stages IIB to IVB disease that required chemotherapy.

Only one patient was deemed not evaluable for assessment of target delineation, because digital radiation planning data was not received. Major target variation was noted in 10 patients overall and in nine of the first 57 patients. Reasons were incorrect contouring of CTV_{59,4}, missing the posterior third of the maxillary sinus; or incomplete coverage of the level-V nodal region. The estimated compliance

rate was 83.8% (95% CI, 72.9 to 91.6). A total of 89.7% of the patients received 70 Gy.

Chemotherapy was given to all 57 patients who had stages IIB to IVB disease. Thirty-seven patients (64.9%) were scored by the medical oncology chair per protocol, 19 (33.3%) of whom had deviations, and one (1.8%) of whom was not evaluable. Fifty patients (87.7%) received all three concurrent CDDP cycles, whereas an additional six patients (10.5%) received two concurrent cycles. Only 26 patients (45.6%) received all three cycles of adjuvant CDDP/FU. Overall, only 25 patients (43.9%) received all cycles of concurrent and adjuvant chemotherapy. Only 13 patients (22.8%) received all cycles with at least 80% of the planned dose.

Failure Pattern

Median follow-up for surviving patients was 2.6 years (range, 0.5 to 4.6 years). There were seven patients who experienced LR failure: one was local only, two were regional only, three were local and regional, and one was death as a result of study cancer without documented site of failure. All seven failures occurred in the first 57 evaluable patients, and all had T2b-4 and/or N+ and WHO disease types 2 to 3. Only one patient had WHO type 1 disease. Some regional failures were attributed to incorrect contouring of level V. Almost all patients were treated with a single IMRT technique. Ten patients developed DM; sites of failure were liver (n = 3), bone (n = 2), lung (n = 2), liver and lung (n = 1), epidural space of spine (n = 1), and trachea (n = 1). Eight of these 10 patients received all three cycles of both concurrent and adjuvant chemotherapies, but only three had at least 80% of planned dose. First failure sites were as follows: distant (n = 10; 14.7%), locoregional (n = 2; 2.9%), local (n = 1; 1.5%), regional (n = 1; 1.5%), death with no evidence of progression (n = 3; 4.4%), and death as a result of study cancer without documented site of failure (n = 1; 1.5%). This last patient failed treatment (locally, regionally, and distantly) and died. The cause of death was not clearly documented and, hence, was scored as LR failure. Two patients developed second primaries (one each in the nasal cavity and prostate). At the time of publication, 48 patients were alive without any documented progression. Fifteen patients died; the cause of death was the study cancer in 12 of these patients; treatment complications were the cause

Table 2. 2-Year Estimates of Time-to-Event End Points

End Point	Patient Group			
	All		Stages IIB to IVB	
	2-Year Estimate	95% CI	2-Year Estimate	95% CI
Local progression-free interval	92.6	86.3 to 98.9	91.2	83.8 to 98.6
Regional progression-free interval	90.8	83.6 to 97.9	89.2	81.0 to 97.5
Locoregional progression-free interval	89.3	81.7 to 96.9	87.5	78.7 to 96.3
Distant metastases-free interval	84.7	75.9 to 93.5	82.1	72.0 to 92.3
Progression-free survival	72.7	61.9 to 83.5	68.0	55.7 to 80.2
Overall survival	80.2	70.5 to 89.8	76.7	65.6 to 87.8

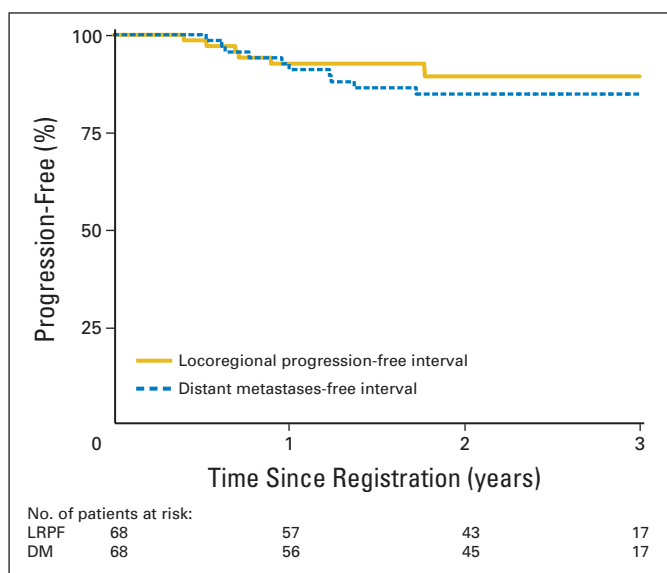


Fig 1. Locoregional progression-free (LRPF) and distant metastasis (DM) -free rates in patients with nasopharyngeal cancer treated with intensity-modulated radiation therapy with or without chemotherapy.

in three patients. Table 2 lists the 2-year estimated rates and 95% CIs for all time-to-event end points. Figures 1 and 2 show the Kaplan-Meier curves for LRP and DM-free and for PFS and OS rates, respectively. At the time of publication, the median had not been reached for any time-to-event end point.

Acute/Late Toxicity

Three patients (4.4%) died as a result of complications of protocol treatment (dysphagia/esophagitis 83 days after start of IMRT;

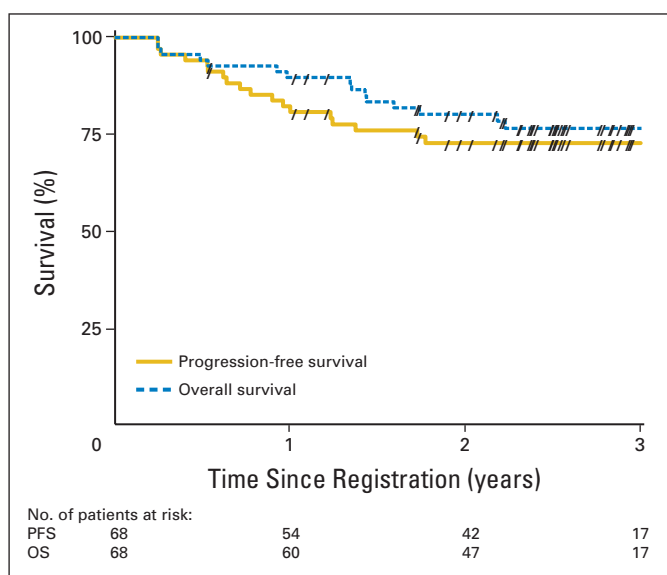


Fig 2. Progression-free survival (PFS) and overall survival (OS) in patients with nasopharyngeal cancer treated with intensity-modulated radiation therapy with or without chemotherapy. Forward slashes indicate censored patients.

Table 3. Type and Frequency of Acute Adverse Effects Observed in 68 Patients

Adverse Effect	No. of Patients by Toxicity Grade				
	1	2	3	4	5
Allergy/immunology	3	0	0	0	0
Auditory/hearing	7	20	10	0	0
Blood/bone marrow	5	14	31	4	0
Cardiovascular					
Arrhythmia	3	2	0	0	0
General	6	3	5	0	0
Constitutional symptom	17	24	16	1	0
Dermatologic/skin	16	30	9	0	0
Endocrine	1	6	1	0	0
Gastrointestinal	3	19	41	4	1
Hemorrhage	13	0	0	0	0
Hepatic	21	9	1	1	0
Infection febrile neutropenia	4	5	5	1	1
Lymphatic	2	1	0	0	0
Metabolic/laboratory	16	9	11	3	0
Musculoskeletal	1	2	2	0	0
Neurology	21	6	3	1	0
Ocular/visual	2	1	1	0	0
Pain	7	21	10	1	0
Pending	3	0	0	0	0
Pulmonary	10	7	0	1	1
Renal/genitourinary	12	7	2	0	0
Sexual/reproductive function	1	1	3	0	0
Worst nonhematologic					
No. of patients	3	13	43	6	3
% of total patients	4.4	19.1	63.2	8.8	4.4
Worst overall					
No. of patients	3	12	42	8	3
% of total patients	4.4	17.6	61.8	11.8	4.4

febrile neutropenia at 80 days; pneumonitis at 74 days). In addition, eight patients (11.8%) experienced grade 4 acute adverse effects, and 42 patients (61.8%) experienced grade 3 acute adverse effects. The most common acute, grade 4 adverse effects were leukopenia ($n = 4$), anorexia ($n = 3$), radiation mucositis ($n = 3$), hyponatremia ($n = 2$), and neutropenia ($n = 2$). Acute grades 2, 3, and 4 mucositis/stomatitis toxicities were 29.4%, 36.8%, and 4.4%, respectively. Table 3 summarizes the chemotherapy and acute IMRT toxicities.

Table 4 lists the type and frequency of late IMRT adverse effects. Overall, 13 patients (20.3%) had grade 3 late toxicity, most commonly hearing impairment⁵ and dysphagia.³ Of the 48 patients alive without progression of disease, two (4.2%) were still dependent on percutaneous endoscopic gastrostomy feeding at their last follow-up visits. Prophylactic percutaneous endoscopic gastrostomy placement was not mandatory for this protocol.

Xerostomia

The worst late, grade 2 and 3 xerostomia scores from start of treatment were 29.7% and 3.1%, respectively. The 1-year estimated rates of grades 1 and 2 xerostomia were 51.9% (95% CI, 37.6 to 66.0) and 13.5% (95% CI, 5.6 to 25.8), respectively. Seven patients overall and four of the first 57 had grade 2 xerostomia at 1 year. Salivary

Table 4. Type and Frequency of Late Radiotherapy Adverse Effects Observed in 64 Patients

Adverse Effect	No. of Patients by Toxicity Grade		
	1	2	3
Skin*	16	3	0
Mucous membrane	26	13	2
Subcutaneous tissue*	15	3	1
Salivary gland	29	19	2
Esophagus	14	9	3
Larynx	10	2	0
Spinal cord	3	0	0
Brain	2	0	0
Bone†	1	1	0
Joint	10	1	0
Auditory/hearing	14	4	5
Other	14	11	3
Worst overall			
No. of patients	18	28	13
% of total patients	28.1	43.8	20.3

*Within radiation therapy field.
†Including osteonecrosis.

output in grams at pretreatment and at 3, 6, and 12 months from the end of IMRT were recorded. There was minimal difference between pretreatment and post-treatment objective mean stimulated and unstimulated salivary function at 12 months, which indicated recovery of salivary flow after treatment with IMRT.

DISCUSSION

The proximity of the nasopharynx to critical normal tissues, such as the brainstem/optic structures, makes it difficult to treat the tumor with two-dimensional techniques while the dose to surrounding organs is kept within an acceptable range.^{16,17,27} As a result, portions of the tumor were often underdosed with the goal of normal tissue protection. IMRT enables coverage of irregularly shaped tumor while it limits the dose to critical organs, and several single institutions have reported greater than 90% LR control rates.^{18,21,22,23} Lee et al¹⁸ reported a remarkable LC rate of 97%, despite around 50% of the patients having T3-4 disease. It is noteworthy that other factors, such as advances in imaging for better tumor delineation, the addition of chemotherapy, and better supportive care, also contribute to the significant improvements in LR control.

Building on the result from University of California, San Francisco, RTOG conducted this phase II trial to test whether the result of IMRT can be reproduced in a multi-institutional setting. Per statistical design, the treatment was considered transportable if less than 10 patients of 57 were scored as having major variations. Because of the protocol requirement for centralized review, it was possible to assess the quality of the target delineation and, when needed, to provide feedback to participating centers on target volume specifications. Consequently, there was a lower percentage of major deviations for the second/subsequent patients entered at a given institution (31% deviation for the first patient, which diminished to 12% with subsequent patients).

Although NPC can be treated effectively with non-IMRT planning techniques, many patients complain of permanent xerostomia as a result of the delivery of a near full dose of RT to the bilateral parotid glands.^{5,6,28,29} The degree of xerostomia is dependent largely on the dose and volume of salivary gland in the radiation field. Studies have shown that salivary flows are markedly reduced after 10 to 15 Gy of RT.^{30,31} High doses to most of the gland will result in permanent xerostomia, which compromises patient quality of life.³²⁻³⁴ The degree of xerostomia is largely dependent on the dose/volume of the salivary gland in the radiation field.^{30,31} IMRT can limit the dose delivered to these glands without compromising tumor coverage. Multiple clinical studies have shown a lesser degree of xerostomia after IMRT relative to the two-dimensional technique.^{18,21-23,35} Kam et al¹⁹ showed that IMRT had lower incidence of observer-rated xerostomia versus the two-dimensional arm (39.3% v 82.1%; $P = .001$) at 1 year after treatment for early-stage NPC. There was also higher stimulated parotid flow rate ($P < .001$) as well as a higher stimulated whole saliva flow rate ($P = .001$) in patients who received IMRT. Pow et al²⁰ showed that IMRT was significantly better than conventional RT in terms of parotid sparing and improved quality of life for early-stage NPC. Although xerostomia and sticky saliva were problems reported in both groups at 2 months post-RT, there was consistent improvement over time with xerostomia-related symptoms at 12 months post-IMRT. This study also showed that only 14% of patients reported grade 2 xerostomia at 1 year from the start of IMRT and that 35% of the patients had no complaints of xerostomia at all.

One of our study end points focused on compliance to combined modality treatment. Our hypothesis was that a potential reduction in the radiation adverse effects on salivary flow by using IMRT would increase patient compliance to combined therapy. We found that 90% of the patients received the full 70 Gy and that 88% of the patients with stage T2b or greater and/or N+ disease received three cycles of concurrent cisplatin. This compares favorably to the compliance rates of 63% in the Intergroup 0099 trial,² 71% in the Singapore randomized trial,¹² and 52% in the Hong Kong NPC-9901 trial.¹¹ In addition, 98% of the patients received at least two cycles of CDDP compared with 86% in the Intergroup 0099 trial. Adjuvant chemotherapy compliance to three cycles of CDDP and FU was, however, slightly lower (46% v 55%, 57%, and 76%) in this RTOG study versus in the Intergroup 0099, Singapore, and Hong Kong NPC-9901 trials, respectively. The value of the adjuvant treatment is not clearly known, as at least one study did not include adjuvant chemotherapy also showed superb outcomes.³⁶

Because RT, whether by using IMRT or non-IMRT techniques, with chemotherapy achieved superb LR control in patients who presented with locoregionally advanced NPC, the development of DM has become the main pattern of relapse (up to 30%) and cause of death.^{18,21,22} The 2-year DM rate of patients who had T2b or greater and/or N+ disease in this series was 18%. This resulted in 2-year PFS and OS of 68% and 77%, respectively. These numbers are similar to the combined therapy arm of Intergroup 0099 trial (3-year PFS and OS rates were 69% and 78%, respectively).²

Given that the predominant pattern of failure in locoregionally advanced NPC treated with IMRT and chemotherapy is DM, and given that patients with NPC who have elevated vascular endothelial

growth factor have a higher likelihood of recurrence, DM, and decreased survival, we have embarked on testing the role of antiangiogenic agents to the treatment strategy in this study for this population.³⁷⁻³⁹ In a recently closed, phase II trial (RTOG 0615), bevacizumab (a monoclonal antibody directed against vascular endothelial growth factor) was added to the concurrent and adjuvant phases of therapy. The reason for combining bevacizumab with the concurrent phase of chemoradiotherapy is to enhance the effect of CDDP in potentially sterilizing distant micrometastases from the beginning of treatment, because compliance to the adjuvant phase has been generally low.

In summary, IMRT with or without chemotherapy produced excellent LPF, RPF, and LRPF rates for NPC. This is the first paper to demonstrate the transportability of IMRT from large institutions to multi-institutional setting. No excessive, unwarranted toxicities have been observed. High rates of compliance to concurrent chemotherapy were achieved, but compliance to adjuvant chemotherapy was poor. Late xerostomia associated with this regimen has decreased. On the basis of the excellent LR control and still-high rates of DM reported in this trial, along with other IMRT and none-IMRT studies, more effective systemic therapy is highly warranted to additionally improve the outcome for these patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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