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**eTable 1.** Dose to Organs at Risk for Patients Treated with IMPT vs IMRT  
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This supplemental material has been provided by the authors to give readers additional information about their work.
**eTable 1. Dose to Organs at Risk for Patients Treated with IMPT vs IMRT**

| Dosimetry Parameter\(^a\)  | IMPT (n=28), GyE | IMRT (n=49), GyE | P value\(^b\) |
|-----------------------------|-----------------|-----------------|----------------|
| Oral Cavity (Mean)          | 15.4 (12.3, 21.4) | 32.8 (30.2, 37.1) | <.001          |
| Larynx (Mean)               | 16.0 (12.9, 20.2) | 29.6 (22.8, 33.1) | <.001          |
| Larynx (Max)                | 53.8 (48.2, 58.4) | 57.6 (52.2, 62.7) | .06            |
| Parotid Gland (Mean)        | 22.5 (19.8, 25.6) | 25.2 (23.0, 26.5) | .01            |
| Optic Chiasm (D\(0.05\text{cc}\)) | 37.2 (27.1, 48.3) | 43.1 (20.8, 52.2) | .64            |
| Optic Nerve (D\(0.05\text{cc}\)) | 48.6 (34.1, 55.2) | 40.5 (24.9, 53.5) | .14            |
| Brainstem (D\(0.05\text{cc}\)) | 58.5 (55.6, 59.3) | 59.0 (55.3, 59.8) | .27            |
| Temporal Lobe (D\(2\text{cc}\)) | 64.5 (58.5, 68.6) | 59.4 (50.0, 61.6) | .02            |
| Cochlea (Mean)              | 43.0 (41.1, 44.9) | 43.8 (42.0, 46.2) | .47            |
| Spinal Cord (D\(0.1\text{cc}\)) | 44.3 (41.7, 48.4) | 44.3 (42.9, 46.0) | .61            |

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity modulated radiation therapy; GyE, Gray equivalent.

\(^a\) Statistics presented: median and interquartile range (IQR)

\(^b\) P value was obtained from Wilcoxon rank sum test

\(^c\) D\(x\text{cc}\), the minimal dose to the highest irradiated \(x\ \text{cm}^3\) of corresponding OARs.
### eTable 2. Comparison of Specific Acute Adverse Events for Patients Treated with IMPT vs IMRT

| Toxicities   | Acute Adverse Events\(^a\) (%) | \(P\) value\(^b\) |
|--------------|---------------------------------|------------------|
|              | None | Grade 1 | Grade 2 | Grade 3 |
| Oral Pain    | IMPT | 14.3 | 75.0 | 10.7 | 0 | .66 |
|              | IMRT | 12.2 | 69.4 | 18.4 | 0 |
| Dysphagia    | IMPT | 21.4 | 60.7 | 14.3 | 3.6 | .05 |
|              | IMRT | 10.2 | 42.9 | 42.9 | 4.1 |
| Fatigue      | IMPT | 25.0 | 64.3 | 10.7 | 0 | .02 |
|              | IMRT | 4.1 | 73.5 | 22.4 | 0 |
| Xerostomia   | IMPT | 50.0 | 42.9 | 7.1 | 0 | .002 |
|              | IMRT | 14.3 | 63.3 | 22.4 | 0 |
| Dysgeusia    | IMPT | 39.3 | 53.6 | 7.1 | 0 | .004 |
|              | IMRT | 12.2 | 57.1 | 30.6 | 0 |
| Dermatitis   | IMPT | 7.1 | 64.3 | 25.0 | 3.6 | .45 |
|              | IMRT | 10.2 | 46.9 | 40.8 | 2.0 |
| Mucositis    | IMPT | 10.7 | 64.3 | 21.4 | 3.6 | .03 |
|              | IMRT | 8.2 | 32.7 | 49.0 | 10.2 |
| Weight Loss  | IMPT | 39.3 | 25.0 | 35.7 | 0 | <.001 |
|              | IMRT | 4.1 | 36.7 | 49.0 | 10.2 |
| Hoarseness   | IMPT | 92.9 | 7.1 | 0 | 0 | .007 |
|              | IMRT | 63.3 | 32.7 | 4.1 | 0 |
| Nausea       | IMPT | 30.6 | 55.1 | 12.2 | 2.0 | .03 |
|              | IMRT | 30.6 | 55.1 | 12.2 | 2.0 |

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity modulated radiation therapy.

\(a\). No grade 4 or 5 acute AEs occurred in the entire cohort.

\(b\). \(P\) value was obtained from Chi-square test for trend (Cochran-Armitage Test).
eTable 3. Univariable and Multivariable Analyses for Locoregional Failure-Free Survival Before and After Matching

| Variable                  | Before Matching (N=77) | After Matching (N=48) |
|---------------------------|------------------------|------------------------|
|                           | Univariable            | Multivariable          | Univariable            | Multivariable          |
|                           | HR (95% CI)            | P                      | HR (95% CI)            | P                      |
|                           |                        |                        |                        |                        |
| RT Modality               |                        |                        |                        |                        |
| IMRT                      | Reference              |                        |                        |                        |
| IMPT                      | 0.00 (0.00-inf)        | >.99                   | 0.00 (0.00-inf)        | >.99                   |
| Sex                       | Female Reference       |                        |                        |                        |
| Male                      | 1.28 (0.25-6.61)       | .77                    | 1.17 (0.20-6.82)       | .86                    |
| Age                       | 1.00 (0.94-1.08)       | .18                    | 1.00 (0.92-1.08)       | .98                    |
| Smoking History           | No Reference           |                        |                        |                        |
| Yes                       | 1.77 (0.39-7.93)       | .46                    | 2.83 (0.55-14.7)       | .22                    |
| KPS                       | 1.06 (0.91-1.25)       | .45                    | 1.09 (0.93-1.28)       | .28                    |
| T-stage                   | T3-T4 Reference        |                        |                        |                        |
| T1-T2                     | 0.44 (0.10-2.01)       | .29                    | 0.28 (0.05-1.54)       | .14                    |
| N-stage                   | N2-N3 Reference        |                        |                        |                        |
| N0-N1                     | 1.73 (0.33-9.00)       | .51                    | 1.32 (0.25-6.88)       | .74                    |
| Stage (AJCC 8th)          | III-IVA Reference      |                        |                        |                        |
| EBV Status                | Positive Reference     |                        |                        |                        |
| Negative/Unknown          | 0.00 (0.00-inf)        | >.99                   |                        |                        |
| Concurrent Chemo          |                        |                        |                        |                        |
| Type of Concurrent Chemo | Reference | | | |
|--------------------------|-----------|---|---|
| Yes                      | 0.23 (0.02-2.23) | 0.17 (0.02-1.63) | |
| Weekly cisplatin         | Reference  | | |
| High dose cisplatin      | 1.38 (0.26-7.37) | 0.91 (0.17-4.92) | |

a. Multivariable Cox proportional hazard model included a panel of covariates determined *a priori*: radiotherapy modality, sex, age, smoking history, KPS, EBV status and disease stage. Radiotherapy modality and EBV status were removed from the model due to event=0 in one group.

b. Multivariable Cox proportional hazard model included a panel of covariates determined *a priori*: radiotherapy modality, sex, age, smoking history, KPS and disease stage. Radiotherapy modality was removed from the model due to event=0 in one group.
**eTable 4. Baseline Clinical Characteristics of Patients by Radiation Modality in Propensity Score–Matched Cohort**

| Characteristics                  | IMPT (n=24) | IMRT (n=24) | P value$^a$ |
|----------------------------------|-------------|-------------|-------------|
| Age at RT, median (IQR), yr      | 44.6 (41.1,58.7) | 53.9 (35.9,61.5) | .42         |
| Sex                              |             |             | >.99        |
| Male                             | 17 (70.8)   | 17 (70.8)   |            |
| Female                           | 7 (29.2)    | 7 (29.2)    |            |
| Smoking History                  | >.99        |             |            |
| No                               | 18 (75.0)   | 18 (75.0)   |            |
| Yes                              | 6 (25.0)    | 6 (25.0)    |            |
| KPS                              | >.99        |             |            |
| 100                              | 2 (8.3)     | 2 (8.3)     |            |
| 90                               | 19 (79.2)   | 19 (79.2)   |            |
| 80                               | 3 (12.5)    | 3 (12.5)    |            |
| T-stage                          | >.92        |             |            |
| T0                               | 1 (4.2)     | 0 (0)       |            |
| T1                               | 5 (20.8)    | 6 (25.0)    |            |
| T2                               | 2 (8.3)     | 2 (8.3)     |            |
| T3                               | 9 (37.5)    | 11 (45.8)   |            |
| T4                               | 7 (29.2)    | 5 (20.8)    |            |
| N-stage                          | >.67        |             |            |
| N0                               | 5 (20.8)    | 3 (12.5)    |            |
| N1                               | 9 (37.5)    | 12 (50.0)   |            |
| N2                               | 9 (37.5)    | 7 (29.2)    |            |
| N3                               | 1 (4.2)     | 2 (8.3)     |            |
| Stage (AJCC 8$^{th}$)            | >.83        |             |            |
| I                                | 2 (8.3)     | 1 (4.2)     |            |
| II                               | 3 (12.5)    | 4 (16.7)    |            |
| III                              | 11 (45.8)   | 13 (54.2)   |            |
| IVA                              | 8 (33.3)    | 6 (25.0)    |            |
| WHO Subtype                      | >.99        |             |            |
| Type 1 (KSCC)                    | 0           | 0           |            |
| Type 2a (NKDC)                   | 0           | 1 (4.2)     |            |
| Type 2b (NKUC)                   | 24 (100.0)  | 23 (95.8)   |            |
| Radiation Alone                  | 2 (8.3)     | 1 (4.2)     | >.99       |
| Induction Chemotherapy           | 6 (25.0)    | 3 (12.5)    | .46        |
| Concurrent Chemotherapy          | 22 (91.7)   | 23 (95.8)   | >.99       |
| Type of concurrent chemotherapy  | >.38        |             |            |
| High dose cisplatin              | 13 (59.1)   | 9 (39.1)    |            |
|                          | Weekly cisplatin | Adjuvant Chemotherapy | RT dose, median (IQR) |
|--------------------------|------------------|-----------------------|-----------------------|
|                          | 9 (40.9)         | 14 (60.9)             |                       |
| Adjuvant Chemotherapy    | 11 (45.8)        | 14 (58.3)             | .56                   |
| RT dose, median (IQR)    | 70.0 GyE (69.96-70.0) | 69.96 Gy (69.96-69.96) | >.99                  |

Abbreviations: IMPT, intensity-modulated proton therapy; IMRT, intensity modulated radiation therapy; RT, radiotherapy; IQR, interquartile range; KPS, Karnofsky Performance Score; AJCC, American Joint Committee on Cancer; WHO, World Health Organization; KSCC, keratinizing squamous cell carcinoma; NKDC, non-keratinizing differentiated carcinoma; NKUC, non-keratinizing undifferentiated carcinoma; GyE, Gray equivalent.

a. Categorical variables were assessed by Chi-squared test or Fisher's exact test. Continuous variables were compared by Wilcoxon rank sum test.
eTable 5. Univariable and Multivariable Analyses for Progression-Free Survival in Propensity Score–Matched Cohort

| Variable                  | Univariable          | Multivariable<sup>a</sup> |
|---------------------------|----------------------|----------------------------|
|                           | HR (95% CI)          | P             | HR (95% CI)          | P             |
| RT Modality               |                      |                |                      |                |
| IMRT Reference            |                      |                |                      |                |
| IMPT                      | 0.31 (0.07-1.47)     | .14            | 0.33 (0.07-1.68)     | .18            |
| Sex                       |                      |                |                      |                |
| Female Reference          |                      |                |                      |                |
| Male                      | 3.55 (0.76-16.7)     | .11            | 3.55 (0.72-17.5)     | .12            |
| Age                       | 1.00 (0.96-1.05)     | .97            | 0.98 (0.94-1.03)     | .48            |
| Smoking History           |                      |                |                      |                |
| No Reference              |                      |                |                      |                |
| Yes                       | 5.69 (1.43-22.7)     | .01            | 6.33 (1.16-34.6)     | .03            |
| KPS                       | 0.92 (0.80-1.05)     | .20            | 1.00 (0.85-1.17)     | .96            |
| T-stage                   |                      |                |                      |                |
| T3-T4 Reference           |                      |                |                      |                |
| T1-T2                     | 0.45 (0.12-1.69)     | .24            | 0.36 (0.08-1.67)     | .19            |
| N-stage                   |                      |                |                      |                |
| N2-N3 Reference           |                      |                |                      |                |
| N0-N1                     | 0.59 (0.18-1.87)     | .37            |                      |                |
| Stage (AJCC 8<sup>th</sup>) |          |                |                      |                |
| III-IVA                   | Reference            |                |                      |                |
| I-II                      | 0.56 (0.12-2.58)     | .46            |                      |                |
| Concurrent Chemo          |                      |                |                      |                |
| No Reference              |                      |                |                      |                |
| Yes                       | 0.45 (0.06-3.63)     | .45            |                      |                |
| Type of Concurrent Chemo  |                      |                |                      |                |
| Weekly cisplatin Reference|                      |                |                      |                |
| High dose cisplatin       | 1.41 (0.43-4.58)     | .57            |                      |                |

<sup>a</sup> Multivariable Cox proportional hazard model included a panel of covariates determined <sup>a priori</sup>: radiotherapy modality, sex, age, smoking history, KPS and disease stage.
eMethods. Details of Pretreatment Evaluation, Radiation Technique, Chemotherapy Regimen, and Follow-up Strategy

Pretreatment Workup

Pretreatment evaluation included history and physical examination, endoscopic evaluation of the nasopharynx, computed tomography (CT) and/or magnetic resonance imaging (MRI) of the nasopharynx including the neck, pre-treatment EBV status (plasma/tissue), baseline audiogram and dental evaluation, pre-chemotherapy laboratory tests including complete blood count, renal and hepatic function tests. Positron emission tomography (PET)/CT was done to rule out distant metastasis.

Treatment

Patients with stage I disease were treated with radiation alone. Stage II-IVA patients were treated with either concurrent chemoradiation followed by adjuvant chemotherapy or per protocol if patient is enrolled in NRG-HN001: Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA). In brief, after concurrent chemoradiation with cisplatin, patients on NRG-HN001 (ClinicalTrials.gov ID: NCT02135042) were reassessed using post-chemoradiation plasma EBV DNA to determine adjuvant therapy options. Induction chemotherapy was allowed in off-protocol patients.

Radiation therapy

Planning CT and MRI were acquired in the supine position with five-point thermoplastic mask immobilization and co-registered with baseline PET/CT. Gross tumor volume (GTV) was delineated based on imaging studies and clinical exam findings for both primary disease (GTVp) and involved lymph nodes (GTVn). Three-millimeter (mm) margin was added to the GTV to generate clinical target volume (CTV). High-risk CTVs including areas at risk of subclinical disease were generated as CTVp and CTVn. High-risk CTVp included the GTVp along with all the normal areas of spread, i.e skull base, parapharyngeal fat, posteriorly maxillary sinus. High-risk CTVn included GTVn and encompassed bilateral nodal level II-V and bilateral retropharyngeal nodal regions. Low-risk subclinical areas including level IV, VB and supraclavicular area without grossly involved low-lying nodes may be treated with the next lower dose level. Level IB was not included for node negative patients. Inclusion of IB level was at the discretion of the treating radiation oncologist for node positive patients. For IMRT planning, PTVs were generated from CTVs plus 3-5 mm margin to account for daily setup variation. For IMPT, CTV evaluated was generated from CTVs plus 2-3 mm margin for optimization. The prescription doses were delivered to PTVs in IMRT and to CTV evaluated in IMPT. The prescription doses to the gross disease/high-risk areas/low-risk subclinical areas were 69.96/56-59.4/54.12 GyE in 33 fractions or 70/59-63/56 GyE in 35 fractions. Radiation therapy was delivered once daily, five days per week. All target volumes were treated simultaneously in IMRT with integrated boost and sequentially in IMPT.

Chemotherapy

Concurrent chemotherapy was administered with cisplatin, either weekly (40mg/m²) up to 7 cycles or every three weeks (100mg/m²) up to 3 cycles. Induction chemotherapy regimen was administered at the discretion of treating medical oncologist and included cisplatin, carboplatin, gemcitabine, paclitaxel, 5-fluorouracil (5-FU). Adjuvant chemotherapy for patients on NRG-HN001 included cisplatin/5-FU or gemcitabine/paclitaxel. Adjuvant chemotherapy for off-protocol patients was administered at the discretion of treating medical oncologist.

Follow up

All patients were seen by treating radiation oncologist weekly for toxicity evaluation during treatment. Patients were subsequently followed at 8-12 weeks post radiation, then at 3-month interval for the first 2 years, then every 6-12 months thereafter. Follow up imaging included MRI of the nasopharynx and the neck, and PET/CT at appropriate intervals determined by the treating physician. Fiberoptic nasolaryngoscopy examination, focused head and neck physical examination, and toxicity evaluation were done at every radiation oncology follow up visit.