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original reports abstract

Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002)

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PURPOSE Reducing radiation treatment dose could improve the quality of life (QOL) of patients with good-risk human papillomavirus–associated oropharyngeal squamous cell carcinoma (OPSCC). Whether reduced-dose radiation produces disease control and QOL equivalent to standard chemoradiation is not proven.

PATIENTS AND METHODS In this randomized, phase II trial, patients with p16-positive, T1-T2 N1-N2b M0, or T3 N0-N2b M0 OPSCC (7th edition staging) with ≤ 10 pack-years of smoking received 60 Gy of intensity-modulated radiation therapy (IMRT) over 6 weeks with concurrent weekly cisplatin (C) or 60 Gy IMRT over 5 weeks. To be considered for a phase III study, an arm had to achieve a 2-year progression-free survival (PFS) rate superior to a historical control rate of 85% and a 1-year mean composite score ≥ 60 on the MD Anderson Dysphagia Inventory (MDADI).

RESULTS Three hundred six patients were randomly assigned and eligible. Two-year PFS for IMRT + C was 90.5% rejecting the null hypothesis of 2-year PFS ≤ 85% ($P = .04$). For IMRT, 2-year PFS was 87.6% ($P = .23$). One-year MDADI mean scores were 85.30 and 81.76 for IMRT + C and IMRT, respectively. Two-year overall survival rates were 96.7% for IMRT + C and 97.3% for IMRT. Acute adverse events (AEs) were defined as those occurring within 180 days from the end of treatment. There were more grade 3-4 acute AEs for IMRT + C (79.6% *v* 52.4%; $P < .001$). Rates of grade 3-4 late AEs were 21.3% and 18.1% ($P = .56$).

CONCLUSION The IMRT + C arm met both prespecified end points justifying advancement to a phase III study. Higher rates of grade ≥ 3 acute AEs were reported in the IMRT + C arm.

J Clin Oncol 39:956-965. © 2021 by American Society of Clinical Oncology

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PURPOSE

More than 70% of oropharyngeal squamous cell carcinomas (OPSCCs) are associated with human papillomavirus (HPV).[1] HPV appears to be the primary causative agent in OPSCC patients with minimal smoking history.[2,3] This population has less comorbidity and increased responsiveness to curative-intent radiation and cisplatin.[4] Because of these patients' lower competing risks of death, long-term effects of chemoradiation (CRT) may be more likely to manifest.[5,6]

Standard therapy for locoregionally advanced OPSCC is a combination of 70 Gy of radiation therapy (RT) with concurrent platinum chemotherapy.[7,8] However, this treatment may be associated with severe short- and long-term toxicities.[9,10] One approach to deintensification of treatment is reduction of RT dose based on preclinical data and single-arm clinical trials.[11-14] Retrospective data and one clinical trial indicate that nonsmokers with small-volume HPV-positive OPSCC can do well without chemotherapy.[15-17]

Major risk factors for relapse and death in OPSCC patients include a lack of HPV or p16 staining (as a surrogate marker for HPV), extensive smoking history, and advanced T or N categories.[18] In the Radiation Therapy Oncology Group (RTOG) 0129 phase III trial testing standard versus intensified RT with concurrent cisplatin, the HPV-positive OPSCC patients with smoking history ≤ 10 pack-years or N0-2a disease (by 7th edition staging) had the lowest risk for death on recursive partitioning analysis.[19] These patients achieved a 3-year overall survival (OS) of 93% compared with 46.2% for those with HPV-negative OPSCC and smoking history > 10 pack-years or T4 disease. Similarly, in the Eastern Cooperative Group (ECOG) 1308 phase II trial of induction chemotherapy followed by reduced-dose RT and chemotherapy, HPV-positive OPSCC patients with > 10 pack-years of smoking or T4 or N2c-N3 disease had worse 2-year progression-free survival (PFS) and OS rates.[20]

NRG-HN002 (ClinicalTrials.gov identifier: NCT02254278) focused on patients with p16-positive OPSCC likely to

ASSOCIATED CONTENT
See accompanying editorial on page 947
Appendix
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 4, 2020 and published at ascopubs.org/journal/jco on January 28, 2021: DOI https://doi.org/10.1200/JCO.20.03128

attain long-term survivorship. We evaluated the efficacy and acceptability of two curative-intent platforms incorporating reduced-dose RT with or without cisplatin, evaluated against PFS benchmarks obtained from previous NRG Oncology trials. This trial was designed to select the arm(s) achieving PFS (primary objective) and swallowing-related quality of life (QOL) as measured by the M. D. Anderson Dysphagia Inventory (MDADI; co-primary objective) justifying advancement to a phase III study.

PATIENTS AND METHODS

Trial Design and Patients

In this phase II, randomized, parallel-group trial, patients were recruited who had histologically proven OPSCC and were ≥ 18 years of age with Zubrod performance status 0-1 from 93 sites in four countries. Patients had T1-2 N1-N2b M0 or T3 N0-N2b M0 staging (by the 7th edition of the American Joint Committee on Cancer Staging Manual) and ≤ 10 pack-year smoking history. Renal, hepatic, and hematologic functions adequate for cisplatin administration were required.

Tumors were scored as p16-positive if strong and diffuse nuclear and cytoplasmic immunohistochemical staining was present in ≥ 70% of tumor cells, or if the H-score was > 30.[21]

Exclusion criteria included oral cavity or unknown primary cancer; radiographically matted, supraclavicular, or infraclavicular lymph nodes; other simultaneous invasive malignancy; or severe medical comorbidity precluding protocol-based therapy.

Permuted block random assignment was stratified by intent to deliver unilateral versus bilateral RT. Patients were randomly assigned (1:1) to 60 Gy of intensity-modulated radiation therapy (IMRT) in 30 fractions, at five fractions per week, concurrent with cisplatin at 40 mg/m^2 weekly (IMRT + C), versus 60 Gy of IMRT alone, at six fractions per week. An intermediate-risk volume around the primary site, the neck levels involved by gross disease, and immediately adjacent uninvolved levels of the neck were prescribed to 54 Gy. The remaining uninvolved, electively treated neck levels were prescribed to 48 Gy. All IMRT doses were delivered over 30 fractions.

On the IMRT + C arm, cisplatin doses were adjusted to manage treatment-related toxic effects. Substitution of cisplatin by alternative therapies was not allowed. Cisplatin was discontinued after more than two high-grade events requiring dose reduction.

After the end of RT, follow-up was reported at 1 and 3 months and then every 3 months through the end of year 2, then every 6 months for the following 3 years, and annually thereafter. Adverse events (AEs) were monitored throughout and after cessation of trial treatment. Grade 4-5 AEs were subject to expedited reporting.

Trial Oversight

The trial was sponsored by the National Cancer Institute. NRG Oncology directed the collection, analysis, and interpretation of data. The trial was conducted in accordance with International Conference on Harmonization Good Clinical Practice Guideline and principles of the Declaration of Helsinki of 1964. An independent, unblinded data, and safety monitoring committee reviewed available safety and efficacy data at predefined time points. Patients provided written informed consent before undergoing any trial-related procedures.

MDADI Testing and Trial Definitions

All patients, if able, were required to complete one global item and 19 other items used to calculate the composite score of the MDADI. The MDADI was usable if the composite score could be calculated (all 19 items answered) and was completed within 3 months of the 1-year time point.

Failure to maintain PFS was defined as local, regional, or distant progression, or death because of any cause. Locoregional failure (LRF) was defined as local or regional progression, salvage surgery of the primary tumor with the tumor present or the outcome unknown, salvage neck dissection with the tumor present or the outcome unknown at more than 20 weeks after the end of RT, death because of the study cancer without documented progression, or death because of any unknown cause without documented progression. Distant metastasis (DM) or death because of other causes was considered competing risks. LRF and death were considered competing risks for the DM end point.

The primary end point was the 2-year PFS, defined as the percentage of patients free of disease progression and alive at 2 years. The co-primary end point of swallowing QOL was based on the mean of the composite MDADI scores at 1 year. Secondary end points included LRF, DM, OS, and high-grade acute and late AEs.

Statistical Analysis

The 2-year PFS for patients treated with standard-of-care radiotherapy and cisplatin in this population was estimated to be 91% on the basis of the observed PFS of a similar population of patients in the RTOG 0522 clinical trial. The null hypothesis was that the 2-year PFS rate of both the de-intensified arms of this trial would be 85%. The alternative hypothesis was that one or both arms would achieve a PFS > 85%, with a target 2-year PFS of 91%. This target 2-year PFS rate for the de-intensified arms was deemed the clinically relevant rate as this would be the expected figure for patients treated with the standard of care (ie, no de-intensification) in this population. To obtain 80% power and a one-sided type I error rate of 10%, assuming a binomial distribution, 140 randomly assigned and eligible patients per arm were required. A sample size of 296 patients was

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set to account for 5% loss after random assignment. The primary efficacy analyses included all patients who underwent random assignment and were considered eligible (modified intention-to-treat population).

The binomial 2-year PFS estimates and exact 90% lower confidence bound (LCB) were calculated and the null hypothesis of PFS ≤ 85% was tested against the alternative of > 85% with a one-sided binomial exact test at the 0.10 level. In addition, the PFS and OS rates were estimated by the Kaplan-Meier method and the groups were compared by the two-sided log-rank test. The LRF and DM rates were estimated by the cumulative incidence method, and the groups were compared by the two-sided cause-specific log-rank test (two-sided alpha of .10). Hazard ratios were estimated by the Cox proportional hazards model for PFS and OS and by the cause-specific Cox model for LRF and DM.

The MDADI requirement for the 1-year mean composite score for an arm was ≥ 60. This minimum level was based on previous studies of patients with oropharyngeal cancer receiving primary CRT, which yielded a median MDADI total score of 76 for one population[22] and a range of mean subscale scores from 64.5 to 86.4 in another population.[23] Thus, a minimally acceptable composite score was considered to be at least 60. The MDADI composite score change at 1 year from baseline was compared between arms with two-sided two-sample *t* test. Assuming an effect size of 0.33, two-sided alpha of .20, and that 168 patients would complete the MDADI questionnaire at 1 year (40% attrition), there was 80% power to detect a ≥ 5 point difference, the minimum importance difference, in 1-year mean composite score change between arms.[24]

For either arm to move to a phase III study, a statistical decision on a PFS > 85% and a 1-year mean total MDADI score ≥ 60 were required. If PFS and MDADI goals were met by both the arms, then selection was decided on the basis of a PFS comparison between the arms. If the two arms were not statistically different in terms of PFS, the best arm was to be selected on the basis of the MDADI mean change score from baseline at 1-year and a 5-point within-group decline from baseline to 1-year of the MDADI scores. If these differences could not be established between the arms, then both arms would be selected.

AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4 and were analyzed without regard to attribution. The acute and late periods were defined as ≤ 180 and > 180 days after the end of the treatment. Overall acute and late grade 3-4 AE rates between the arms were compared by two-sided Fisher's exact test, and 95% CIs based on the exact binomial method were reported. For grade 3-4 AE rates and feeding tube rates at specific time points, 95% CIs based on the same method were reported.

Role of the Funding Source

NRG Oncology was responsible for data collection, statistical analysis, study design, and preparation of the manuscript. The National Cancer Institute sponsored the study. No commercial support was provided. The corresponding author (S.S.Y.) had full access to all of the data and the final responsibility to submit for publication. This study is registered at ClinicalTrials.gov identifier: NCT02254278.

RESULTS

Patients

From October 27, 2014, to February 7, 2017, a total of 316 patients were enrolled and 308 were randomly assigned, of whom two were subsequently determined to be ineligible (Fig 1).

Among 306 randomly assigned and eligible patients, the median age was 59 years (range, 31-84); 84.0% were male, 52.6% had tonsil primary site, 62.4% had T2-T3 disease, 75.5% had N2 disease, and 67.6% were stratified as having bilateral IMRT planning, although ultimately 85.3% on review had bilateral IMRT (Table 1).

Five patients on the IMRT + C arm and two patients on the IMRT arm received no RT. All patients who started RT completed 60 Gy (Appendix Table A1, online only). Five patients assigned to the IMRT + C arm did not receive cisplatin. Of patients receiving cisplatin, 127 of 157 patients (80.9%) received 5-6 cycles and 72.6% received at least 200 mg/m^2 (Appendix Table A2, online only).

On the IMRT + C arm, 87.3% had an overall RT compliance score indicating that RT was delivered per protocol or with acceptable variation compared with 87.9% on the IMRT arm (Appendix Table A3, online only). For patients assigned to IMRT + C, 141 of 157 patients (89.8%) had an overall score indicating that cisplatin was delivered per protocol or with acceptable variation (Appendix Table A4, online only).

Efficacy

The median follow-up for censored patients was 2.6 years (range, 0.003-4.1). On the IMRT + C and IMRT arms, 147 and 145 patients were evaluable for 2-year PFS (see Fig 1 for exclusions). Fourteen and 18 patients on the IMRT + C and IMRT arms, respectively, experienced a PFS event in the first 2 years. The two-year PFS estimates were 90.5% (90% LCB, 86.6%; $P = .04$) for IMRT + C and 87.6% (90% LCB, 83.3%; $P = .23$) for IMRT (Fig 2A). The estimated hazard ratio (IMRT + C *v* IMRT) for PFS was 0.67 (95% CI, 0.36 to 1.24), and there was no significant difference between arms ($P = .20$). The Kaplan-Meier estimates of the 2-year PFS rates were 90.7% (95% CI, 86.1 to 95.4) and 87.7% (95% CI, 82.4 to 93.0) on the IMRT + C and IMRT arms, respectively.

Figure 2B shows the LRF results. The estimated 2-year LRF rates were 3.3% (95% CI, 1.2 to 7.1) and 9.5% (95% CI, 5.5 to 15.0) on the IMRT + C and IMRT arms, respectively. The estimated hazard ratio (IMRT + C *v* IMRT) for LRF was 0.39 (95% CI, 0.17 to 0.90). The LRF difference between arms was significant ($P = .02$).

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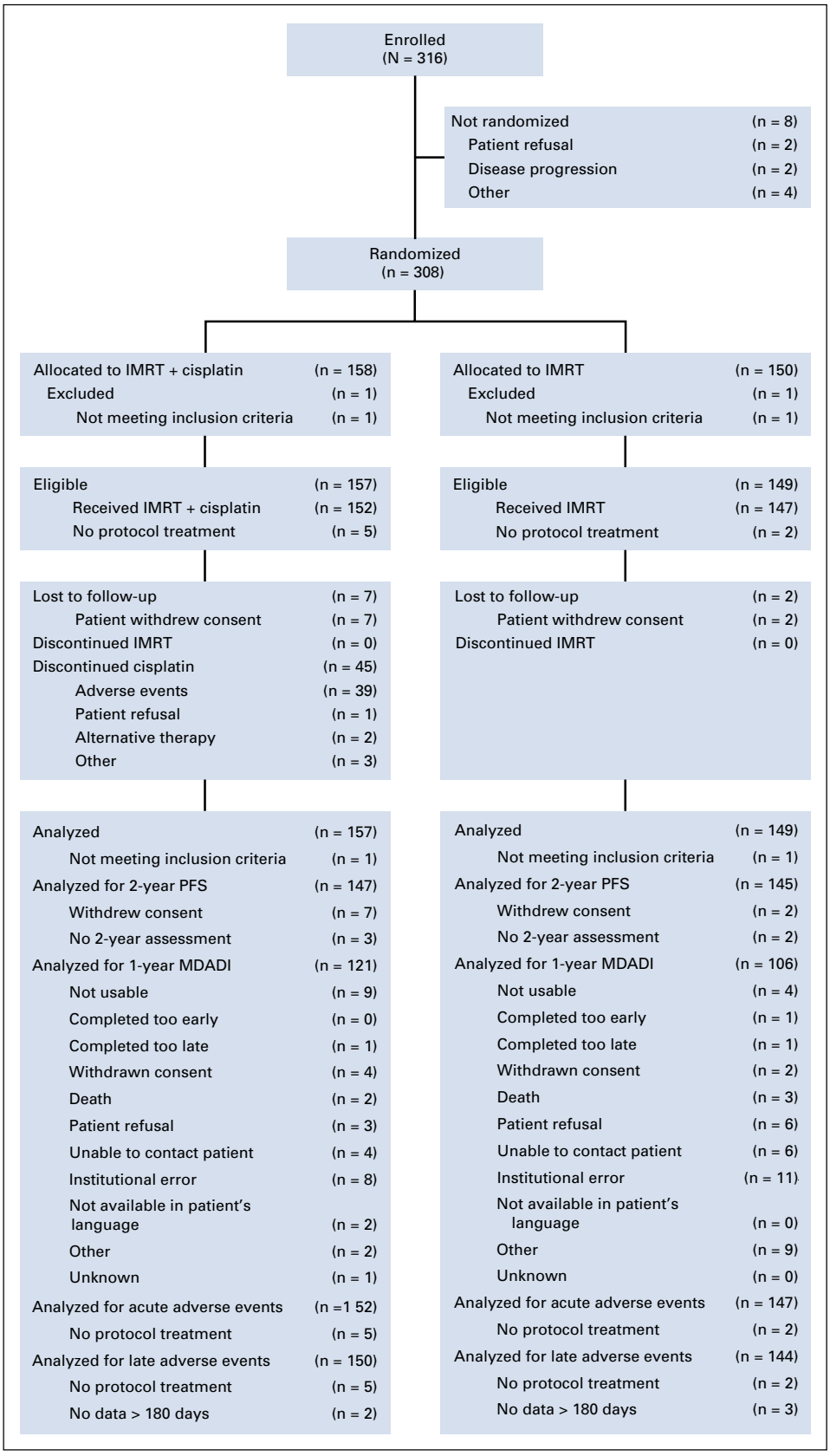

FIG 1. CONSORT Flow Diagram for NRG-HN002. IMRT, intensity-modulated radiation therapy; MDADI, MD Anderson Dysphagia Inventory; PFS, progression-free survival.

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TABLE 1. Patient and Tumor Characteristics in NRG-HN002

Patient or Tumor Characteristic	IMRT + Cisplatin (n = 157)		IMRT (n = 149)		Total (N = 306)	
	n	%	n	%	n	%
Age (years)						
≤ 49	28	17.8	14	9.4	42	13.7
50-59	56	35.7	60	40.3	116	37.9
60-69	46	29.3	55	36.9	101	33.0
≥ 70	27	17.2	20	13.4	47	15.4
Sex						
Male	133	84.7	124	83.2	257	84.0
Female	24	15.3	25	16.8	49	16.0
Race						
American Indian or Alaska Native	1	0.6	1	0.7	2	0.7
Asian	0	0.0	4	2.7	4	1.3
Black or African American	1	0.6	2	1.3	3	1.0
White	151	96.2	130	87.2	281	91.8
Unknown or not reported	4	2.5	12	8.1	16	5.2
Ethnicity						
Hispanic or Latino	3	1.9	7	4.7	10	3.3
Not Hispanic or Latino	143	91.1	130	87.2	273	89.2
Unknown	11	7.0	12	8.1	23	7.5
Zubrod performance status						
0	132	84.1	113	75.8	245	80.1
1	25	15.9	36	24.2	61	19.9
Smoking history: pack-years						
0	112	71.3	101	67.8	213	69.6
> 0 to < 5	26	16.6	32	21.5	58	19.0
5-10	19	12.1	16	10.7	35	11.4
Primary site						
Oropharynx NOS	4	2.5	13	8.7	17	5.6
Tonsillar fossa, tonsil	83	52.9	78	52.3	161	52.6
Base of tongue	68	43.3	58	38.9	126	41.2
Pharyngeal oropharynx	1	0.6	0	0.0	1	0.3
Posterior pharyngeal wall	1	0.6	0	0.0	1	0.3
T stage, clinical						
T1	64	40.8	51	34.2	115	37.6
T2	67	42.7	80	53.7	147	48.0
T3	26	16.6	18	12.1	44	14.4
N stage, clinical						
N0	6	3.8	7	4.7	13	4.2
N1	28	17.8	34	22.8	62	20.3
N2a	24	15.3	19	12.8	43	14.1
N2b	99	63.1	89	59.7	188	61.4

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TABLE 1. Patient and Tumor Characteristics in NRG-HN002 (continued)

Patient or Tumor Characteristic	IMRT + Cisplatin (n = 157) n	IMRT + Cisplatin (n = 157) %	IMRT (n = 149) n	IMRT (n = 149) %	Total (N = 306) n	Total (N = 306) %
RT planning (as stratified)						
Unilateral	52	33.1	47	31.5	99	32.4
Bilateral	105	66.9	102	68.5	207	67.6
RT planning (per central review)						
Unilateral	16	10.2	21	14.1	37	12.1
Bilateral	136	86.6	125	83.9	261	85.3
Unknown	5	3.2	3	2.0	8	2.6

Abbreviations: IMRT, intensity-modulated radiation therapy; NOS, not otherwise specified; RT, radiation therapy.

The most common site of first failure in the IMRT + C arm was DM (35.3% of the failures), and the most common site in the IMRT arm was local (41.7% of the failures). Appendix Table A5 (online only) shows the sites of first disease failure, and Appendix Table A6 (online only) shows the LRF rates by T and N categories.

The estimated 2-year DM rates were 4.0% (95% CI, 1.6 to 8.0) and 2.1% (95% CI, 0.6 to 5.5) on the IMRT + C and IMRT arms, respectively. The estimated hazard ratio for DM (IMRT + C *v* IMRT) was 1.43 (95% CI, 0.40 to 5.08). The difference between the arms was not significant ($P = .58$) (Fig 2C). Sites of first DM are given in Appendix Table A7, online only.

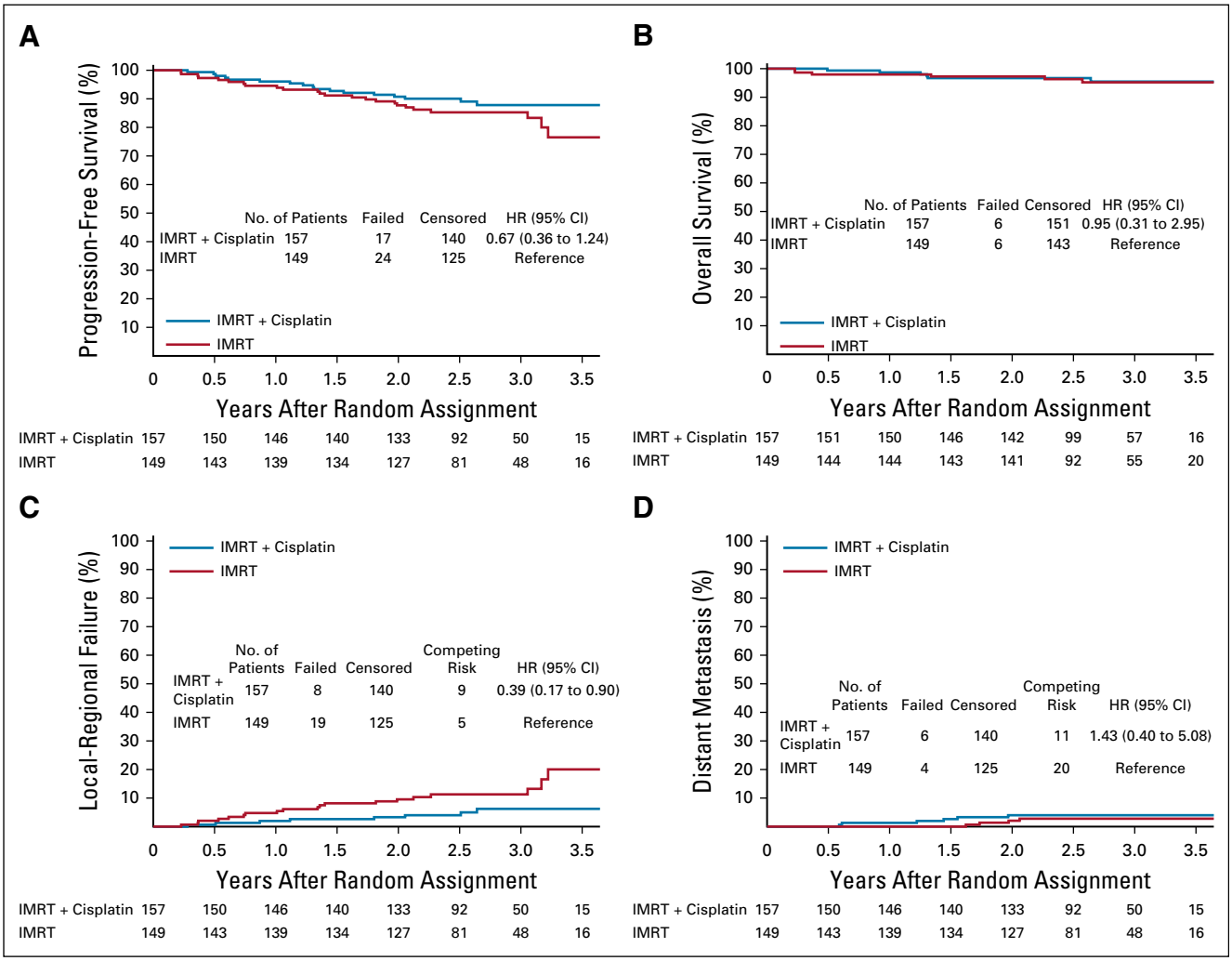

FIG 2. NRG-HN002 progression-free (A) and overall survival (B), local-regional failure (C), and distant metastasis (D). HR, hazard ratio; IMRT, intensity-modulated radiation therapy.

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TABLE 2. MDADI Composite Scores in NRG-HN002

Analysis	Assigned Treatment	Statistic	Time Point	
			Baseline	One Year[a]
Cross-sectional	IMRT + cisplatin	n	132	121
		Mean	90.82	85.30
		95% CI	89.10 to 92.55	82.53 to 88.07
		SD	10.02	15.41
	IMRT	n	134	106
		Mean	87.94	81.76
		95% CI	85.75 to 90.14	78.98 to 84.54
		SD	12.84	14.44
Change from baseline	IMRT + cisplatin	n	—	106
		Mean	—	−5.62
		95% CI	—	−8.64 to −2.60
		SD	—	15.66
	IMRT	n	—	100
		Mean	—	−6.22
		95% CI	—	−9.34 to −3.11
		SD	—	15.70
		P value[b]	—	.78

Abbreviations: IMRT, intensity-modulated radiation therapy; RT, radiation therapy; SD, standard deviation.
[a]After end of RT, ± 3 months.
[b]Two-sided two-sample *t* test for between-arm difference.

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The estimated 2-year OS rates were 96.7% (95% CI, 93.9 to 99.5) and 97.3% (95% CI, 94.6 to 99.9) on the IMRT + C and IMRT arms, respectively (Fig 2D). The estimated treatment effect hazard ratio (IMRT + C *v* IMRT) was 0.95 (95% CI, 0.31 to 2.95), and there was no significant difference between the arms ($P = .93$). Causes of death are shown in Apendix Table A8, online only.

Swallowing (MDADI) and AEs

Table 2 summarizes the MDADI composite scores by arm. The 1-year means were 85.30 (95% CI, 82.53 to 88.07) and 81.76 (95% CI, 78.98 to 84.54) for the IMRT + C and IMRT arms, respectively. The 1-year mean changes from baseline were − 5.62 (95% CI, − 8.64 to − 2.60) and − 6.22 (95% CI, − 9.34 to − 3.11) ($P = .78$), respectively.

Table 3 summarizes high-grade AEs that occurred in ≥ 5% of patients on either arm. The grade 3-4 acute AE rate on the IMRT + C arm was higher than that on the IMRT arm (79.6% [95% CI, 72.3 to 85.7] *v* 52.4% [95% CI, 44.0 to 60.7]; $P < .001$). The grade 4 acute AE rates were 15.1% and 2.0%. Late grade 3-4 rates were 21.3% (95% CI, 15.1 to 28.8) on IMRT + C and 18.1% (95% CI, 12.2 to 25.3) on IMRT ($P = .56$). Two patients on each arm (1.3% and 1.4%) experienced one or more late grade 4 AEs. No grade 5 AEs were reported.

During RT, 73.7% of the patients on the IMRT + C arm and 46.3% of the patients on the IMRT arm had one or more grade 3-4 AEs. These rates were 17.9% and 11.1%, respectively, at 6 months from RT and continued to drop at 1 and 2 years (Appendix Fig A1, online only). Before treatment, 1.3% and 0% of the patients on the IMRT + C and IMRT arms had feeding tubes. These rates were 2.8% and 3.8% at 6 months from RT (Appendix Fig A2, online only) on the IMRT + C and IMRT arms, respectively.

DISCUSSION

In this study testing a reduced dose of curative-intent radiotherapy, the arm of 60 Gy of IMRT with concurrent weekly cisplatin satisfied acceptability criteria for 2-year PFS and MDADI at 1 year. The accelerated radiation arm did not meet statistical conditions for PFS acceptability. These results demonstrate the greater certainty of go/no-go decision making derived from a large randomized trial as opposed to retrospective or prospective single-arm studies.[25]

Although the IMRT-cisplatin combination resulted in a higher rate of acute AEs compared with IMRT alone, the rates of grade 3-4 late AEs and, importantly, the 1-year change from baseline MDADI were not significantly different. This is consistent with findings of other clinical trials that have demonstrated substantial quality-of-life recovery in CRT-treated patients by 1 year.[26-28]

TABLE 3. Adverse Events (Without Regard to Attribution) Occurring in at Least 5% of Patients on Either Arm of NRG-HN002

Grade of Adverse Event	IMRT + Cisplatin	IMRT
Acute period patient total	152	147
Grade 3-4 overall	121 (79.6%)	77 (52.4%)
Grade 3-4 lymphocyte count decreased	83 (54.6%)	35 (23.8%)
Grade 2-3 dry mouth	78 (51.3%)	67 (45.6%)
Grade 3 mucositis oral	32 (21.1%)	31 (21.1%)
Grade 3 dysphagia	27 (17.8%)	11 (7.5%)
Grade 3-4 WBC decreased	23 (15.1%)	1 (0.7%)
Grade 3-4 neutrophil count decreased	17 (11.2%)	0 (0.0%)
Grade 3 nausea	15 (9.9%)	1 (0.7%)
Grade 3 anorexia	13 (8.6%)	6 (4.1%)
Grade 3 vomiting	11 (7.2%)	1 (0.7%)
Grade pain	10 (6.6%)	9 (6.1%)
Grade 3 weight loss	9 (5.9%)	5 (3.4%)
Grade 3 fatigue	9 (5.9%)	1 (0.7%)
Grade 3 dermatitis radiation	4 (2.6%)	8 (5.4%)
Late period patient total	150	144
Grade 3-4 overall	32 (21.3%)	26 (18.1%)
Grade 2-3 dry mouth	39 (26.0%)	28 (19.4%)
Grade 3-4 lymphocyte count decreased	16 (10.7%)	7 (4.9%)
Grade 3 weight loss	4 (2.7%)	8 (5.6%)

NOTE. Adverse events were graded with CTCAE version 4. Acute: ≤ 180 days from end of treatment. Late: > 180 days from end of treatment.
Abbreviations: CTACE, Common Terminology Criteria for Adverse Events; IMRT, intensity-modulated radiation therapy.

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As HPV-positive OPSCC patients may experience lengthy survival after cancer progression,[5] detection of differences in survival is challenging, and the survival in this study's two arms was similar. Nonetheless, the patterns of disease failure in this study are instructive. The IMRT patients, using a lower-than-standard dose in a radiotherapy-alone regimen, experienced a higher rate of LRF, and two thirds of these patients were at the primary site. In these radiation-only patients, there was a suggestion of increased LRF in concert with tumor stage, suggesting the need for more treatment with increasing tumor burden. Although some relapsed patients may be salvageable,[29] the morbidity of locoregional recurrence is a concern.[30] No such patterns were observed in the patients who received concurrent cisplatin.

Cisplatin scheduling remains controversial. One phase III study of mostly postoperative oral cavity cancer patients indicated that bolus cisplatin dosing at 100 mg/m^2 as compared with weekly dosing at 30 mg/m^2 produced superior locoregional control but similar survival.[31] Although it is frequently asserted that weekly cisplatin is less toxic,[32] an early report from a phase III nasopharyngeal cancer study showed increased hematologic AEs using weekly cisplatin.[33] Others hypothesize that it is the overall cumulative dose, not the schedule, that produces negative effects.[34] In this study, the majority (56%) of the patients received six cycles of weekly chemotherapy, but 19% received fewer than five cycles. Notably, the results of this study's CRT arm matched the PFS estimated from RTOG 0522, a high-dose radiation study that used bolus cisplatin.[35] Furthermore, the hematologic AEs in this study were not dissimilar from those of RTOG 1016, which only used two cycles of bolus cisplatin.[26]

Cisplatin may enact subtle long-term effects.[36,37] In a laryngeal cancer phase III clinical trial more noncancer-related deaths were observed at long-term follow-up in patients receiving concurrent CRT as compared with those treated with induction chemotherapy followed by radiation or radiation alone.[38] However, in the HPV-positive OPSCC population, two phase III randomized trials failed to confirm the noninferiority of substituting cetuximab, a blocking antibody of the epidermal growth factor receptor, for cisplatin.[26,27] A regimen of carboplatin and paclitaxel was substituted for cisplatin in one single-arm trial,[13] but the efficacy of this regimen has never been compared with cisplatin. Immunotherapy is being combined with radiation (ClinicalTrials.gov identifier: NCT03258554) and CRT (ClinicalTrials.gov identifier: NCT03040999), but at least one phase III trial has shown no benefit (ClinicalTrials.gov identifier: NCT02952586). Initial induction chemotherapy or upfront surgical intervention followed by adjuvant therapy may reduce either radiation dosage[39] (ClinicalTrials.gov identifier: NCT01898494) or radiation

volume[40] or the necessity for radiation[41] or concurrent cisplatin (ClinicalTrials.gov identifier: NCT02215265) in certain patients, but these approaches remain at the phase II level.

Deintensification balances a reduction in high-grade toxicity against the opportunity for cure. Although both the arms in this study performed relatively well, there is high confidence that the CRT arm did not compromise PFS. The next step as determined within NRG Oncology is a randomized phase II and III trial (ClinicalTrials.gov identifier: NCT03952585) that directly compares 70 Gy against 60 Gy given with the same bolus cisplatin regimen and against 60 Gy with nivolumab, with co-primary end points of PFS and swallowing QOL.

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SUPPORT

Supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP), U24CA196067 (NRG Specimen Bank), U24CA180803 (IROC) from the National Cancer Institute (NCI).

ETHICS COMMITTEE APPROVAL

This research has been officially reviewed by an institutional review board and does meet requirements for protection of human subjects.

DATA SHARING STATEMENT

All data used in the publication will be de-identified and available for data sharing via NCI's NCTN/NCORP Data Archive at least 6 months from the publication date. Data dictionaries are provided with the data. Information about the archive and how to access the data can be found in ref. 42.

CLINICAL TRIAL INFORMATION

NCI; NRG-HN002, NCT02254278.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.20.03128.

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ACKNOWLEDGMENT

The authors thank Thien Nu Do (Protocol development), Vanita Patel (data management), Nancy Linnemann and Marsha Radden (Radiation Therapy Quality Assurance), and Jonathan Harris (statistical input).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reduced-Dose Radiation Therapy for HPV-Associated Oropharyngeal Carcinoma (NRG Oncology HN002)

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Sue S. Yom
Research Funding: Genentech, Merck, Bristol-Myers Squibb, BioMimetix
Patents, Royalties, Other Intellectual Property: UpToDate, Springer

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Consulting or Advisory Role: Varian Medical Systems
Research Funding: Varian Medical Systems

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Consulting or Advisory Role: Bristol-Myers Squibb, Merck, EMD Serono, Roche, Kura Oncology, BioNTech, Shattuck, Bayer, Debiopharm Group, Ipsen, Gilead Sciences, Bicara Therapeutics, BioNTech AG
Research Funding: Bristol-Myers Squibb, Genocea Biosciences, Cullinan Oncology

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No other potential conflicts of interest were reported.

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APPENDIX

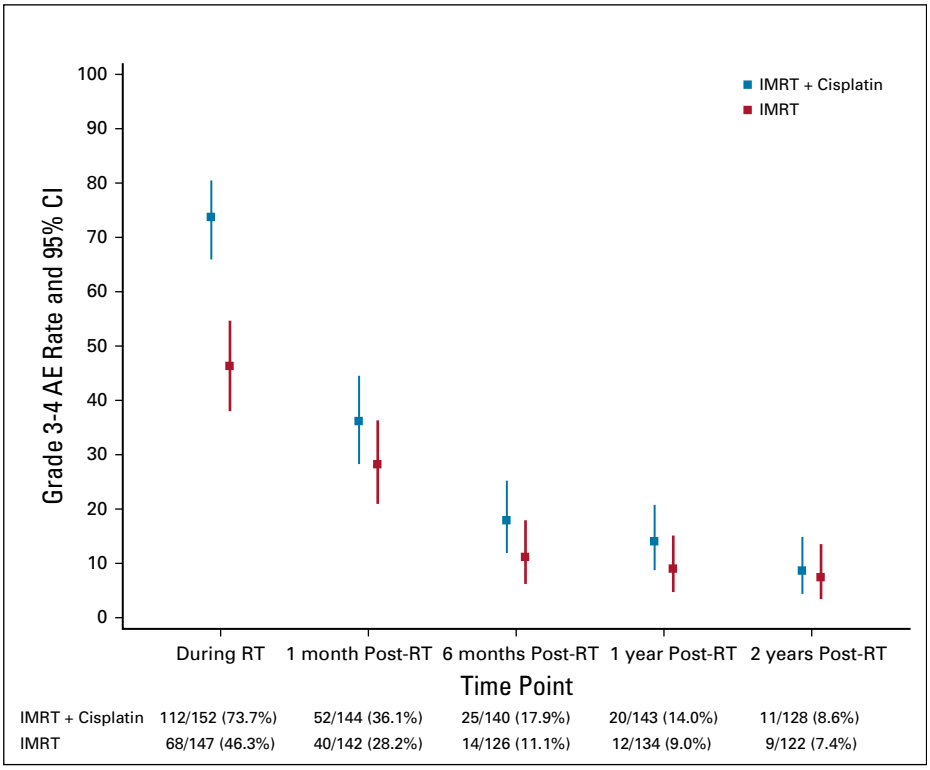

FIG A1. High-grade adverse event rates over time by treatment arm.

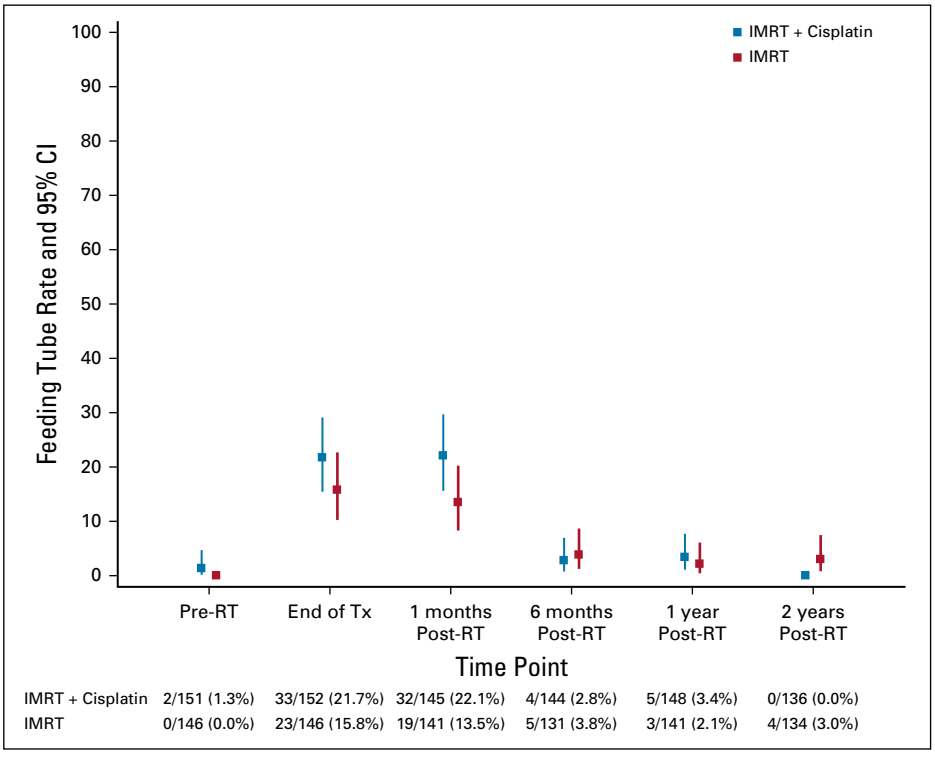

FIG A2. Feeding tube rates over time by treatment arm.

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TABLE A1. Radiation Therapy Delivered in NRG-HN002

RT Delivered	IMRT + Cisplatin (N = 157)	IMRT (N = 149)
RT given		
No	5 (3.2%)	2 (1.3%)
Yes	152 (96.8%)	147 (98.7%)
Reason RT not started or discontinued		
Treatment completed	152 (96.8%)	147 (98.7%)
Patient withdrawal or refusal	4 (2.5%)	1 (0.7%)
Alternative therapy	1 (0.6%)	1 (0.7%)
RT dose (Gy)		
Mean	58.1	59.2
SD	10.6	6.9
Median	60.0	60.0
Min-max	0.0-60.0	0.0-60.0
Q1-Q3	60.0-60.0	60.0-60.0
0.00	5 (3.2%)	2 (1.3%)
60.00	152 (96.8%)	147 (98.7%)
PTV_6000 D95% (Gy)		
Mean	58.3	59.3
SD	10.6	6.9
Median	60.1	60.0
Min-max	0.0-61.5	0.0-61.4
Q1-Q3	60.0-60.3	59.9-60.3
PTV_6000 D99.9% (Gy)		
Mean	55.0	56.5
SD	10.6	7.3
Median	57.5	57.9
Min-max	0.0-60.1	0.0-60.7
Q1-Q3	56.0-58.6	56.9-58.5
PTV_6000 max (Gy)		
Mean	62.6	63.7
SD	11.5	7.6
Median	64.6	64.6
Min-max	0.0-69.1	0.0-68.9
Q1-Q3	63.5-65.4	63.6-65.4
PTV_6000 mean (Gy)		
Mean	59.9	61.0
SD	10.9	7.2
Median	61.8	61.8
Min-max	0.0-63.9	0.0-64.4
Q1-Q3	61.4-62.2	61.4-62.1
GTVp_6000 D95% (Gy)	n = 155	n = 148
Mean	59.2	60.3
SD	10.9	7.1
Median	61.1	61.0

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TABLE A1. Radiation Therapy Delivered in NRG-HN002 (continued)

RT Delivered	IMRT + Cisplatin (N = 157)	IMRT (N = 149)
Min-max	0.0-64.3	0.0-64.2
Q1-Q3	60.6-61.6	60.5-61.4
GTVp_6000 D99.9% (Gy)	n = 155	n = 148
Mean	58.5	59.6
SD	10.8	7.0
Median	60.4	60.4
Min-max	0.0-63.6	0.0-62.4
Q1-Q3	60.0-60.9	59.9-60.8
GTVp_6000 max (Gy)	n = 155	n = 148
Mean	61.7	62.9
SD	11.4	7.5
Median	63.8	63.6
Min-max	0.0-69.0	0.0-68.9
Q1-Q3	62.7-64.5	62.8-64.6
GTVp_6000 mean (Gy)	n = 155	n = 148
Mean	60.2	61.3
SD	11.1	7.3
Median	62.1	62.0
Min-max	0.0-66.8	0.0-66.2
Q1-Q3	61.5-62.7	61.4-62.6
GTVn_6000 D95% (Gy)	n = 156	n = 148
Mean	57.1	57.8
SD	15.0	13.9
Median	60.9	61.0
Min-max	0.0-64.8	0.0-63.5
Q1-Q3	60.5-61.4	60.5-61.5
GTVn_6000 D99.9% (Gy)	n = 156	n = 148
Mean	56.4	57.1
SD	14.9	13.7
Median	60.2	60.3
Min-max	0.0-63.2	0.0-63.0
Q1-Q3	59.9-60.7	59.8-60.9
GTVn_6000 max (Gy)	n = 156	n = 148
Mean	59.7	60.3
SD	15.7	14.5
Median	63.5	63.6
Min-max	0.0-69.1	0.0-68.2
Q1-Q3	62.6-64.6	62.8-64.6
GTVn_6000 mean (Gy)	n = 156	n = 148
Mean	58.1	58.8
SD	15.3	14.1
Median	62.0	62.1
Min-max	0.0-66.1	0.0-66.0
Q1-Q3	61.4-62.6	61.5-62.6

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TABLE A1. Radiation Therapy Delivered in NRG-HN002 (continued)

RT Delivered	IMRT + Cisplatin (N = 157)	IMRT (N = 149)
RT fractions		
Mean	29.0	29.6
SD	5.3	3.5
Median	30	30
Min-max	0-30	0-30
Q1-Q3	30-30	30-30
0	5 (3.2%)	2 (1.3%)
29	1 (0.6%)	1 (0.7%)
30	151 (96.2%)	146 (98.0%)
RT elapsed days	n = 152	n = 147
Mean	41.1	33.3
SD	2.6	1.7
Median	41	33
Min-max	36-55	30-41
Q1-Q3	39-43	32-35

Abbreviations: IMRT, intensity-modulated radiation therapy; Q1, 1st quartile; Q3, 3rd quartile; RT, radiation therapy; SD, standard deviation.

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TABLE A2. Cisplatin Delivered for Patients Assigned to IMRT + Cisplatin in NRG-HN002 (N = 157)

Cisplatin Delivered	No. (%, if applicable)
Cisplatin given	
No	5 (3.2%)
Yes, terminated early	45 (28.7%)
Yes, terminated per protocol	107 (68.2%)
Reason cisplatin not started or discontinued	
Treatment completed	107 (68.2%)
Adverse events(s)	39 (24.8%)
Patient withdrawal or refusal	5 (3.2%)
Alternative therapy	3 (1.9%)
Other	3 (1.9%)
Cisplatin number of doses given	
Mean	5.2
SD	1.4
Median	6
Min-max	0-6
Q1-Q3	5-6
0	5 (3.2%)
1	2 (1.3%)
3	8 (5.1%)
4	15 (9.6%)
5	39 (24.8%)
6	88 (56.1%)
Cisplatin total dose (mg/m^2)	
Mean	205.7
SD	56.0
Median	238.3
Min-Max	0.0-249.1
Q1-Q3	197.4-242.1
< 200	43 (27.4%)
≥ 200	114 (72.6%)

Abbreviations: IMRT, intensity-modulated radiation therapy; Q1, 1st quartile; Q3, 3rd quartile; SD, standard deviation.

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TABLE A3. Radiation Therapy Reviews in NRG-HN002

RT Quality Score	IMRT + Cisplatin (N = 157)	IMRT (N = 149)
Tumor volume contouring score		
Per protocol	85 (54.1%)	80 (53.7%)
Acceptable variation	51 (32.5%)	49 (32.9%)
Unacceptable variation	16 (10.2%)	18 (12.1%)
Not evaluable	5 (3.2%)	2 (1.3%)
Organs at risk contouring score		
Per protocol	133 (84.7%)	131 (87.9%)
Acceptable variation	18 (11.5%)	11 (7.4%)
Unacceptable variation	1 (0.6%)	5 (3.4%)
Not evaluable	5 (3.2%)	2 (1.3%)
Tumor volume and organs at risk contouring score		
Per protocol	90 (57.3%)	88 (59.1%)
Acceptable variation	46 (29.3%)	44 (29.5%)
Unacceptable variation	16 (10.2%)	15 (10.1%)
Not evaluable	5 (3.2%)	2 (1.3%)
Tumor volume dose volume analysis score		
Per protocol	113 (72.0%)	110 (73.8%)
Acceptable variation	38 (24.2%)	33 (22.1%)
Unacceptable variation	1 (0.6%)	4 (2.7%)
Not evaluable	5 (3.2%)	2 (1.3%)
Organs at risk dose volume analysis score		
Per protocol	146 (93.0%)	141 (94.6%)
Acceptable variation	6 (3.8%)	6 (4.0%)
Not evaluable	5 (3.2%)	2 (1.3%)
Total dose score		
Per protocol	152 (96.8%)	147 (98.7%)
Not evaluable	5 (3.2%)	2 (1.3%)
Fractionation score		
Per protocol	152 (96.8%)	147 (98.7%)
Not evaluable	5 (3.2%)	2 (1.3%)
Elapsed days score		
Per protocol	151 (96.2%)	145 (97.3%)
Acceptable variation	1 (0.6%)	2 (1.3%)
Not evaluable	5 (3.2%)	2 (1.3%)
Overall score		
Per protocol	87 (55.4%)	84 (56.4%)
Acceptable variation	50 (31.8%)	47 (31.5%)
Unacceptable deviation	15 (9.6%)	16 (10.7%)
No RT given	4 (2.5%)	2 (1.3%)
Not evaluable	1 (0.6%)	0 (0.0%)

Abbreviations: IMRT, intensity-modulated radiation therapy; RT, radiation therapy.

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TABLE A4. Cisplatin Reviews for Patients Assigned to IMRT + Cisplatin in NRG-HN002 (N = 157)

Cisplatin Quality Score	No. (%)
Overall review	
Per protocol	133 (84.7%)
Acceptable variation	8 (5.1%)
Unacceptable deviation	11 (7.0%)
Not evaluable	5 (3.2%)
Dose	
85%-115%	96 (61.1%)
< 85% because of protocol-specified reasons	40 (25.5%)
70 to < 85% because of non–protocol-specified reasons	5 (3.2%)
< 70% because of non–protocol-specified reasons	7 (4.5%)
> 115%	1 (0.6%)
Wrong drug or agent given	1 (0.6%)
85%-115% not per protocol because of failure to dose reduce	2 (1.3%)
Not evaluable	5 (3.2%)
Treatment delays	
No delays	98 (62.4%)
≤ 1 wk	48 (30.6%)
> 1 week because of protocol-specified reasons	1 (0.6%)
> 1 to ≤ 2 weeks because of non–protocol-specified reasons	2 (1.3%)
> 2 weeks because of non–protocol-specified reasons	3 (1.9%)
Not evaluable	5 (3.2%)

Abbreviation: IMRT, intensity-modulated radiation therapy.

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TABLE A5. Patterns of First Failure or Death in NRG-HN002

Mode of Failure or Death	IMRT + Cisplatin (n = 17)	IMRT (n = 24)	Total (N = 41)
Local	1 (5.9%)	10 (41.7%)	11 (26.8%)
Regional	5 (29.4%)	5 (20.8%)	10 (24.4%)
Local and regional	1 (5.9%)	1 (4.2%)	2 (4.9%)
Distant	6 (35.3%)	4 (16.7%)	10 (24.4%)
Death, COD this disease	0 (0.0%)	1 (4.2%)	1 (2.4%)
Death, COD second primary	1 (5.9%)	0 (0.0%)	1 (2.4%)
Death, COD other	2 (11.8%)	1 (4.2%)	3 (7.3%)
Death, COD unknown	1 (5.9%)	2 (8.3%)	3 (7.3%)

Abbreviations: COD, cause of death; IMRT, intensity-modulated radiation therapy.

TABLE A6. Local-Regional Failure by T and N Categories in NRG-HN002

Failed/Total	N0	N1	N2a	N2b	Total
IMRT + cisplatin					
T1	N/A	1/6	1/11	3/47	5/64
T2	N/A	1/16	0/12	2/39	3/67
T3	0/6	0/6	0/1	0/13	0/26
Total	0/6	2/28	1/24	5/99	8/157
IMRT					
T1	N/A	2/10	0/8	2/33	4/51
T2	N/A	2/19	2/11	6/50	10/80
T3	2/7	1/5	0/0	2/6	5/18
Total	2/7	5/34	2/19	10/89	19/149

Abbreviation: IMRT, intensity-modulated radiation therapy.

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TABLE A7. First Site(s) of Distant Metastasis in NRG-HN002

Site of First Metastasis	IMRT + Cisplatin (n = 6)	IMRT (n = 4)	Total (N = 10)
Left lower rib	1 (16.7%)	0 (0.0%)	1 (10.0%)
Liver	0 (0.0%)	1 (25.0%)	1 (10.0%)
Liver; bone	0 (0.0%)	1 (25.0%)	1 (10.0%)
Liver; thoracic spinal cord	1 (16.7%)	0 (0.0%)	1 (10.0%)
Lung	4 (66.7%)	2 (50.0%)	6 (60.0%)

Abbreviation: IMRT, intensity-modulated radiation therapy.

TABLE A8. Cause of Death in NRG-HN002

Cause of Death	IMRT + Cisplatin (n = 6)	IMRT (n = 6)	Total (N = 12)
Because of this disease	2 (33.3%)	3 (50.0%)	5 (41.7%)
Because of second primary or other malignancy	1 (16.7%)	0 (0.0%)	1 (8.3%)
Because of other cause	2 (33.3%)	1 (16.7%)	3 (25.0%)
Unknown	1 (16.7%)	2 (33.3%)	3 (25.0%)

Abbreviation: IMRT, intensity-modulated radiation therapy.