Radiotherapy and Oncology 134 (2019) 81–88

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Radiation therapy dose de-escalation compared to standard dose radiation therapy in definitive treatment of HPV-positive oropharyngeal squamous cell carcinoma

Prashant Gabani [a], Alexander J. Lin [a], Justin Barnes [b], Peter Oppelt [c], Douglas R. Adkins [c], Jason T. Rich [d], Jose P. Zevallos [d], Mackenzie D. Daly [a], Hiram A. Gay [a], Wade L. Thorstad [a,*]

[a] *Department of Radiation Oncology, Washington University School of Medicine;* [b] *Saint Louis University School of Medicine;* [c] *Division of Medical Oncology, Washington University School of Medicine; and* [d] *Department of Otolaryngology, Washington University School of Medicine, Saint Louis, United States*

ARTICLE INFO

Article history:
Received 25 October 2018
Received in revised form 9 January 2019
Accepted 11 January 2019
Available online 4 February 2019

Keywords:
HPV
Oropharyngeal cancer
Radiation therapy
Chemotherapy
Dose de-escalation

ABSTRACT

Background: Despite existing evidence that human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) has a favorable prognosis compared to HPV-negative OPSCC, randomized studies have yet to report the effect of de-escalating radiation therapy (RT) dose for definitive treatment. The aim of this study was to assess the effectiveness of dose de-escalated RT (DDRT) vs. standard dose RT (SDRT) in patients with HPV-positive OPSCC.

Methods: This was an observational study using the National Cancer Database (Year 2010–2014) to identify patients who had HPV-positive OPSCC and were treated with definitive RT or chemo-RT. Patients undergoing surgery were excluded. Patients receiving ≥50 Gy, but <66 Gy were categorized as receiving DDRT. Patients receiving ≥66 Gy were categorized as receiving SDRT. Inverse probability of treatment weighting (IPTW) using propensity scores was used to balance the two groups. Kaplan–Meier analysis was used to estimate overall survival (OS). Subset analyses in patients receiving RT alone and concurrent chemo-RT were also performed. Multivariable Cox proportional hazards modeling was used to evaluate factors associated with OS.

Results: 759 patients with HPV-positive OPSCC were identified: 104 received DDRT and 655 received SDRT. The median follow-up was 30.5 (2.4–81.4) months. After IPTW-adjusted analysis, there was no difference in the 3-yr OS between the two groups (82.2% vs. 79.3%; $P = 0.85$). In the subset of patients receiving concurrent chemoradiotherapy, IPTW-adjusted analysis also did not show a difference in the 3-yr OS between the two groups (83.1% vs. 79.6%; $P = 0.83$). On multivariable analysis, DDRT was not associated with an inferior OS (HR 0.88; 95% CI, 0.53–1.47; $P = 0.63$).

Conclusions: In this study, DDRT was not associated with an inferior OS compared to SDRT in patients with HPV-positive OPSCC. Randomized clinical trials to address DDRT in this patient population are currently ongoing.

Summary

In this observational study of 759 patients with HPV-positive oropharyngeal squamous cell carcinoma, the receipt of dose de-escalated radiation therapy was not associated with an inferior overall survival compared to standard dose radiation therapy. If confirmed in randomized studies, dose de-escalated radiation therapy may become the new standard of care and provide for the same overall survival while decreasing the radiation therapy associated long term toxicities such as dysphagia and xerostomia.

The incidence of HPV-related oropharyngeal cancer has been rapidly increasing over the last several decades, comprising of approximately two-thirds of all oropharyngeal cancers [1]. The initial identification of HPV as a causative agent for oropharyngeal cancer suggested that these cancers may behave differently from the traditional squamous cell cancers that are linked to smoking and alcohol [2,3]. This difference in the clinical and molecular characteristics has been shown to affect prognosis, with HPV-positive cancer patients having superior overall survival (OS) compared to those with HPV-negative cancers [4,5].

* Corresponding author at: 4921 Parkview Place, LL. Saint Louis, MO 63110, United States.

E-mail address: thorstad@wustl.edu (W.L. Thorstad).

https://doi.org/10.1016/j.radonc.2019.01.016
0167-8140/

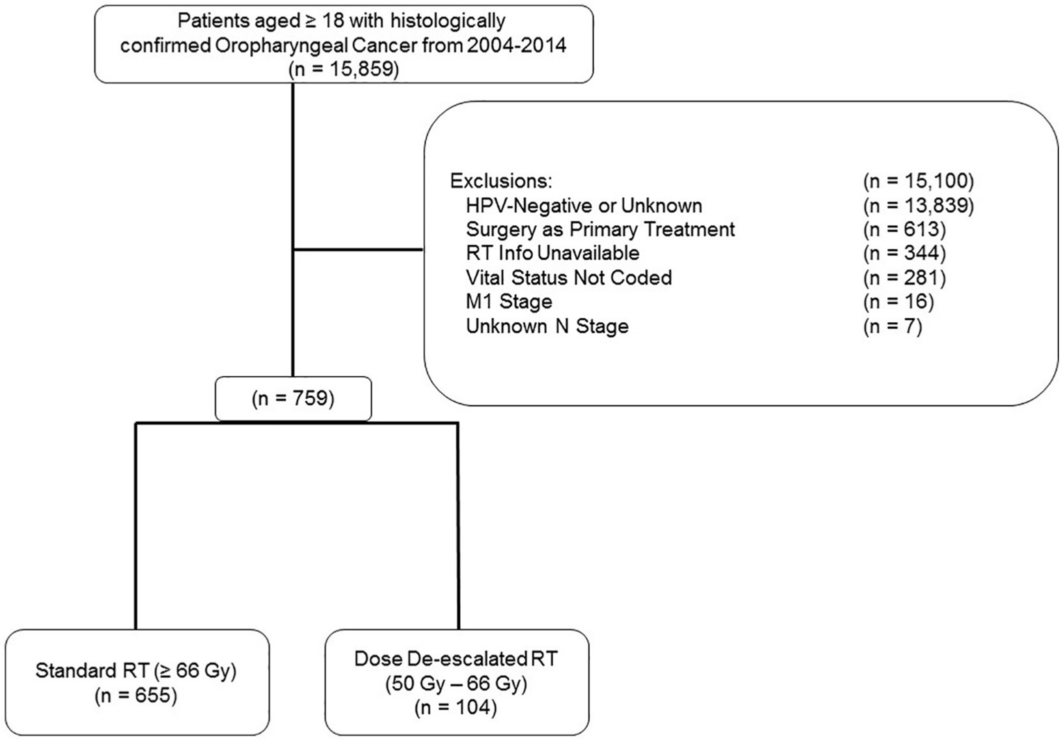

Fig. 1. CONSORT diagram describing the selection of patient who received standard dose radiation therapy and dose de-escalated radiation therapy in patients with HPV-positive oropharyngeal squamous cell carcinoma from the National Cancer Database (2010–2014).

Table 1
Baseline characteristics.

	Standard RT (%)	De-escalated RT (%)	P-value
Age			
Median (range)	59 (27–90)	58 (36–89)	0.49
Sex			
Male	565 (86.3)	88 (84.6)	0.65
Female	90 (13.7)	16 (15.4)	
Year of diagnosis			
2010	65 (9.9)	9 (8.7)	0.52
2011	91 (13.9)	16 (15.4)	
2012	144 (22.0)	16 (15.4)	
2013	160 (24.4)	31 (29.8)	
2014	195 (29.8)	32 (30.8)	
Charlson/Deyo score			
0	559 (85.3)	85 (81.7)	0.21
1	79 (12.1)	18 (17.3)	
≥2	17 (2.6)	1 (1.0)	
Race			
White	596 (91.0)	93 (89.4)	0.49
African American	46 (7.0)	7 (6.7)	
Other	13 (2.0)	4 (3.8)	
Facility type			
Community Cancer Program	65 (10.1)	11 (10.7)	0.04
Comprehensive Community Cancer Program	246 (38.1)	43 (41.7)	
Academic/Research Program	236 (36.6)	44 (42.7)	
Integrated Network Cancer Program	98 (15.2)	5 (4.9)	
Facility location			
East	283 (43.9)	51 (49.5)	0.21
Central	249 (38.6)	41 (39.8)	
West	113 (17.5)	11 (10.7)	
Insurance Status			
Uninsured	37 (5.7)	3 (2.9)	0.36
Private	366 (56.1)	66 (64.1)	
Medicaid	51 (7.8)	4 (3.9)	

Table 1 (*continued*)

	Standard RT (%)	De-escalated RT (%)	P-value
Medicare	182 (27.9)	27 (26.2)	
Other government	16 (2.5)	3 (2.9)	
Income level			
<$48,000	241 (36.9)	34 (32.7)	0.44
≥48,000	413 (63.1)	70 (75.3)	
Without high school education			
≥13%	233 (35.6)	26 (25.0)	0.04
<13%	421 (64.4)	78 (75.0)	
Clinical T category			
T1	129 (21.6)	30 (42.3)	0.002
T2	199 (33.4)	15 (21.1)	
T3	129 (21.6)	12 (16.9)	
T4	139 (23.3)	14 (19.7)	
Clinical N category			
N0	79 (12.1)	6 (5.8)	<0.001
N1	90 (13.7)	22 (21.2)	
N2a	59 (9.0)	23 (22.1)	
N2b	216 (33.0)	32 (30.8)	
N2c	125 (19.1)	10 (9.6)	
N2 NOS	47 (7.2)	7 (6.7)	
N3	39 (6.0)	4 (3.8)	
Chemotherapy			
No	64 (10.0)	26 (27.4)	<0.001
Yes	574 (90.0)	69 (72.6)	
RT dose (cGy)			
Median (range)	7000 (6600–7920)	6000 (5000–6510)	<0.001
RT dose per fraction (cGy)			
Median (range)	200 (180–212)	200 (180 – 201.6)	<0.001

Table 2
Univariable and multivariable logistic regression analyses for the receipt of DDRT.

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P-value	OR (95% CI)	P-value
Age				
Continuous	0.99 (0.97–1.02)	0.6	NS	
Sex				
Male	Ref		Ref	
Female	1.14 (0.64–2.03	0.65	NS	
Year of diagnosis				
2010	Ref		Ref	
2011	1.27 (0.53–3.05)	0.59	NS	
2012	0.80 (0.34–1.91)	0.62	NS	
2013	1.40 (0.63–3.10)	0.41	NS	
2014	1.18 (0.54–2.61)	0.67	NS	
Charlson/Deyo score				
0	Ref		Ref	
1	1.50 (0.86–2.62)	0.16	NS	
≥2	0.39 (0.05–2.94)	0.36	NS	
Race				
White	Ref		Ref	
African American	0.98 (0.43–2.22)	0.95	NS	
Other	1.97 (0.63–6.18)	0.24	NS	
Facility type				
Community Cancer Program	Ref		Ref	
Comprehensive Community Cancer Program	1.03 (0.51–2.11)	0.93	NS	
Academic/Research Program	1.10 (0.54–2.25)	0.79	NS	
Integrated Network Cancer Program	0.30 (0.10–0.91)	0.03	NS	
Facility location				
East	Ref		Ref	
Central	0.91 (0.59–1.43)	0.69	NS	
West	0.54 (0.27–1.07)	0.08	NS	

(*continued on next page*)

Table 2 (*continued*)

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	P-value	OR (95% CI)	P-value
Insurance status				
Uninsured	Ref		Ref	
Private	2.22 (0.67–7.42)	0.19	NS	
Medicaid	0.97 (0.20–4.58)	0.97	NS	
Medicare	1.83 (0.53–6.35)	0.34	NS	
Other government	2.31 (0.42–12.71)	0.34	NS	
Income level				
<$48,000	Ref		Ref	
≥48,000	1.20 (0.77–1.86)	0.41	NS	
Without high school education				
≥13%	Ref		Ref	
<13%	1.66 (1.04–2.66)	0.04	2.41 (1.26–4.61)	0.008
Clinical T category				
T1	Ref		Ref	
T2	0.32 (0.17–0.63)	0.001	0.37 (0.19–0.73)	0.01
T3	0.40 (0.20–0.82)	0.01	0.38 (0.17–0.84)	0.02
T4	0.43 (0.22–0.85)	0.02	0.45 (0.21–0.93)	0.03
Clinical N category				
N0	Ref		Ref	
N1	3.22 (1.24–8.34)	0.02	NS	
N2a	5.13 (1.97–13.4)	0.001	NS	
N2b	1.95 (0.79–4.84)	0.15	NS	
N2c	1.05 (0.37–3.01)	0.92	NS	
N2 NOS	1.96 (0.62–6.19)	0.25	NS	
N3	1.35 (0.36–5.07)	0.66	NS	
Chemotherapy				
No	Ref		Ref	
Yes	0.30 (0.18–0.50)	<0.001	0.43 (0.21–0.88)	0.02

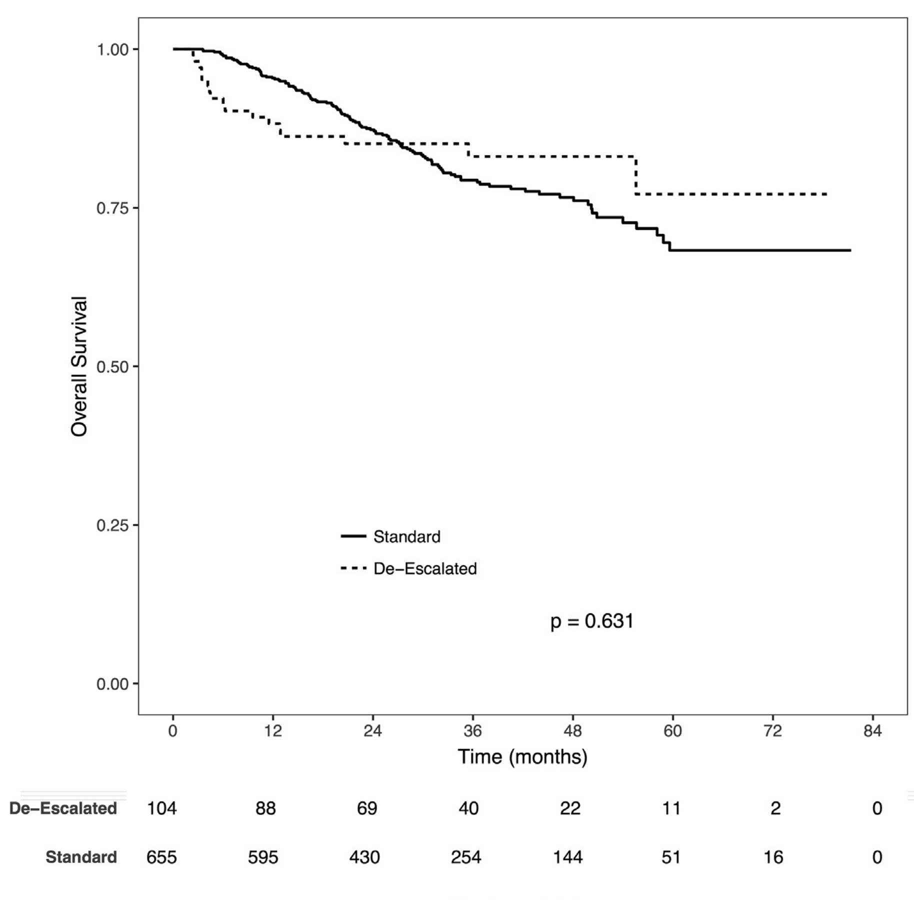

Fig. 2A. Kaplan–Meier analysis of overall survival for patients with HPV-positive oropharyngeal squamous cell carcinoma who received dose de-escalated radiation therapy and standard dose radiation therapy.

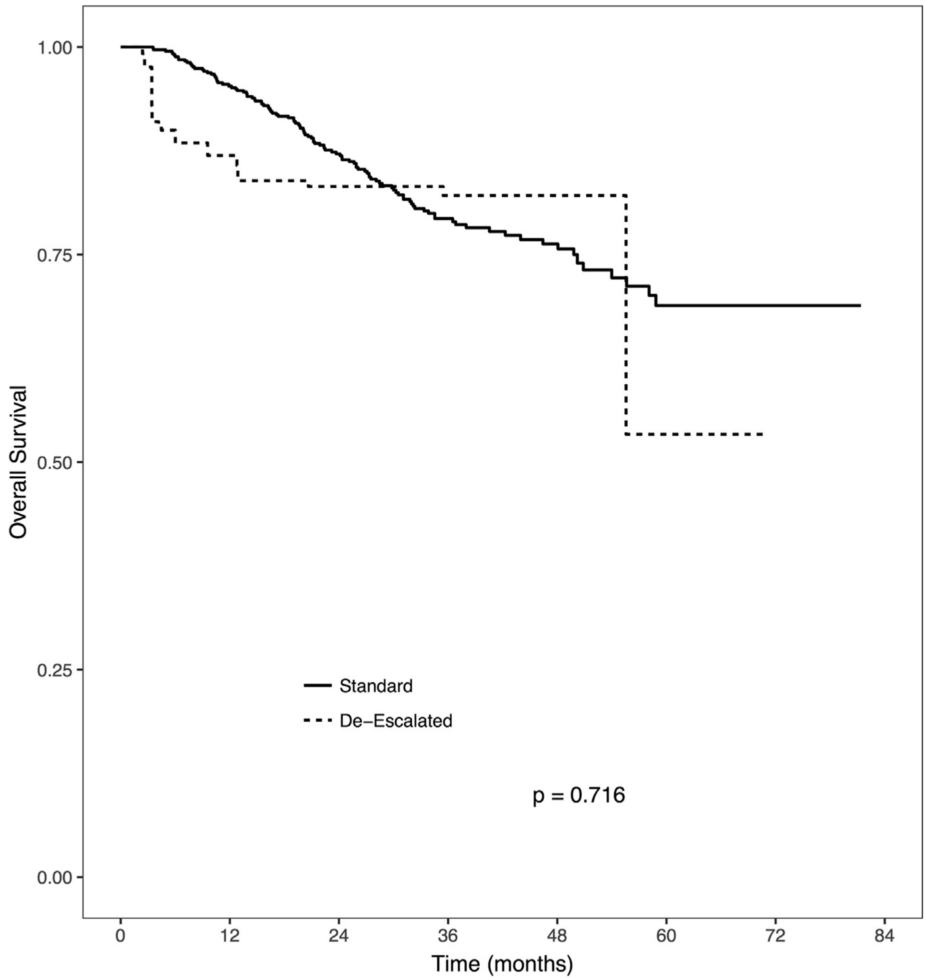

Fig. 2B. Inverse probability of treatment weighting-adjusted Kaplan-Meier analysis of overall survival for patients with HPV-positive oropharyngeal squamous cell carcinoma who received dose de-escalated radiation therapy and standard dose radiation therapy. Data are weighted proportions and not absolute numbers.

Based on these studies, it is believed that HPV-positive oropharyngeal cancer may respond favorably to radiation therapy (RT) and chemotherapy. This has prompted the suggestion that the use of conventional RT doses (≥66 Gy) might lead to overtreatment and unnecessary toxicity, such as dysphagia and xerostomia, both of which can be reduced by lowering the RT dose [6,7]. However, randomized studies comparing outcomes of standard RT dose and lower RT dose in HPV-positive oropharyngeal squamous cell carcinoma have not been reported. Here, we use the National Cancer Database (NCDB) to investigate the effects of lowering the RT dose in patients receiving definitive RT or chemo-RT for the treatment of HPV-positive oropharyngeal squamous cell carcinoma.

Materials and methods

The NCDB was used as the primary dataset for this study. The NCDB is a joint project of the American Cancer Society and the American College of Surgeons Commission on Cancer. The American College of Surgeons has executed a Business Associate Agreement that includes a data use agreement with each of its Commission on Cancer accredited hospitals. The NCDB, established in 1989, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the US annually. Data elements are collected and submitted to the NCDB from commission-accredited oncology registries using standardized coding and data item definitions, including details not available from Surveillance, Epidemiology, and End Results (SEER) registry, such as RT dose/technique, chemotherapy use/timing, and comorbidities [8]. Data were de-identified and therefore IRB approval was not needed.

From a population of 15,859 with oropharyngeal squamous cell carcinoma, we identified 759 patients who met our inclusion criteria (Fig. 1). Patients with HPV-negative or unknown status, patients who received surgery as the primary treatment, patients who had unknown RT information, patients with unknown N-category, and those with metastatic disease were excluded. Patients receiving ≥50 Gy, but less than 66 Gy were considered as receiving dose de-escalated RT (DDRT). Patients receiving ≥66 Gy were considered as receiving standard dose RT (SDRT) (Supplemental Fig. 1). Due to the retrospective nature of this study, the reason patients received DDRT was unclear, but it is likely due to either patients stopping treatment early because of side effects or institutional protocols of DDRT. Patients who underwent surgery were excluded. Patients were staged using the American Joint Committee on Cancer (AJCC) 7th edition TNM staging.

To account for potential selection bias in the SDRT and DDRT groups, we performed inverse probability of treatment weighting (IPTW) to balance the two groups, where the weights were derived from the predicted values of a multivariable logistic regression model. IPTW is a statistical method aiming to minimize bias due

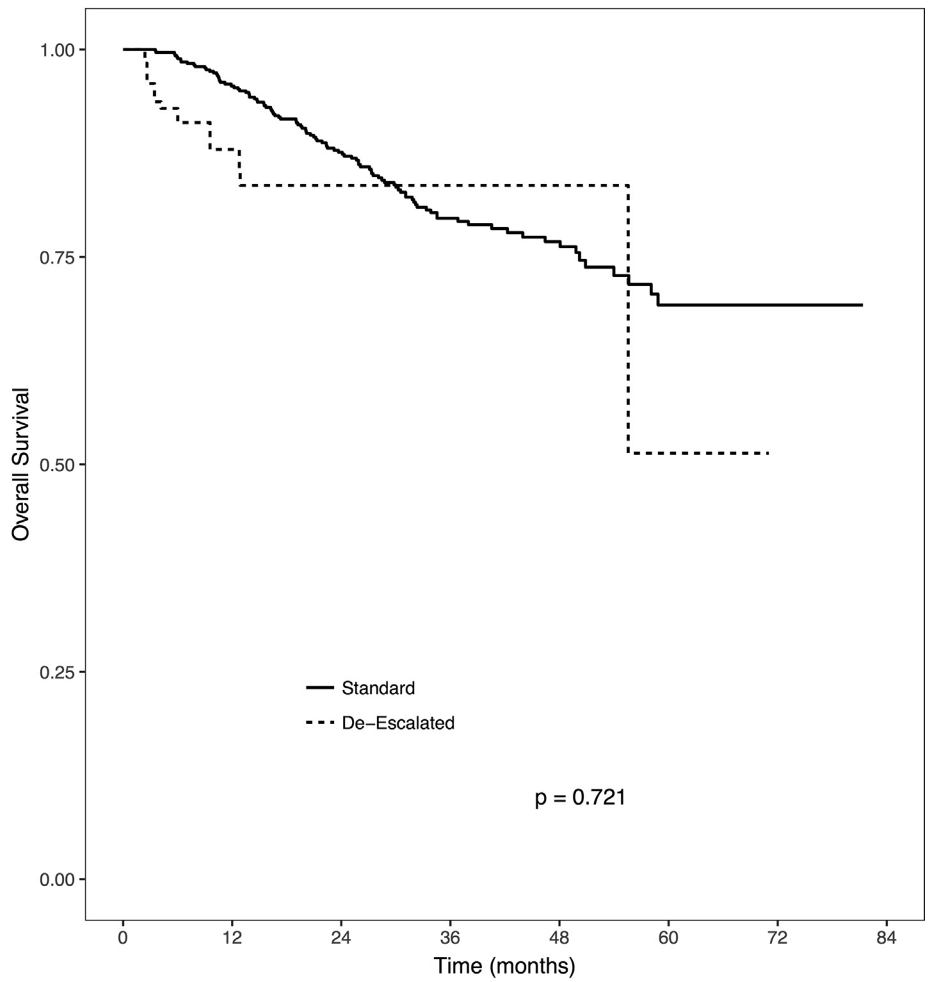

Fig. 2C. Inverse probability of treatment weighting-adjusted Kaplan–Meier analysis of overall survival for patients with HPV-positive oropharyngeal squamous cell carcinoma who received dose de-escalated radiation therapy combined with chemotherapy and standard dose radiation therapy combined with chemotherapy. Data are weighted proportions and not absolute numbers.

to treatment selection, where under-represented individuals are "up-weighted" and over-represented individuals are "down-weighted" in order to balance the patient characteristics [9]. The goodness-of-fit of the propensity score model was assessed using the Hosmer and Lemeshow test. In this analysis, we utilized logistic regression model to estimate the probability of receiving de-escalated treatment using the following covariates: sex, age, year of diagnosis, charlson/deyo score, insurance type, facility location and type, race, N-group, T-group, zip code level income, education information, and receipt of chemotherapy status. Covariate balance was evaluated by evaluating standardized mean differences and kernel density plots (Supplemental Figs. 2–3). Kaplan–Meier method was used to estimate the OS. Multivariable Cox proportional hazards modeling was used to evaluate factors associated with OS. Logistics regression modeling was used to evaluate factors associated with the receipt of DDRT. Analyses were performed in R 3.3.2 using the IPW survival package.

Results

A total of 759 patients were included in the analysis: 104 received DDRT and 655 received SDRT. Baseline patient characteristics stratified by DDRT and SDRT are reported in Table 1. The two groups differed most significantly in regards to type of treatment facility, high school education, T-category, chemotherapy, and the RT dose. The median dose of RT per fraction was 200 cGy per fraction for both groups. On multivariable analysis, higher education level was associated with a higher likelihood for the receipt of DDRT, whereas factors that were associated with a lower likelihood for the receipt of DDRT were treatment at integrated network cancer program, higher T-category, and use of chemotherapy (Table 2).

At the time of analysis, 143 (18.8%) patients had died. The median follow-up was 30.5 months (range, 2.4–81.4 months). The 3-yr OS in patients receiving DDRT was 83.1% vs. 79.4% in patients receiving SDRT ($P = 0.63$, Fig. 2A). In the IPTW population, the 3-yr OS was 82.1% in DDRT vs. 79.3% in SDRT ($p = 0.85$, Fig. 2B). A subset analysis in patients who received both chemotherapy and radiation therapy was performed. In this subset analysis, the IPTW-adjusted analysis showed the 3-yr OS of 78.8% in DDRT vs. 79.2% in SDRT ($P = 0.83$, Fig. 2C). Kernel density plots, dot plots, and Kaplan-Meier curve of unmatched data are included in Supplemental Figs. 4–6. We also performed a subset analysis of survival in patients who received RT alone. In this subset cohort, the 3-yr OS was 79.1% in DDRT vs. 77.3% in SDRT ($P = 0.61$, supplemental Fig. 7).

On multivariable analysis, factors that were associated with inferior OS were increasing age (HR, 1.03; 95% CI, 1.005–1.05; $P = 0.02$) and higher T-category (T2: HR, 2.36; 95% CI, 1.19–4.69; $P = 0.01$; T3: HR, 3.94; 95% CI, 1.99–7.81; $P < 0.001$; T4: HR, 6.17; 95% CI, 3.20–11.92; $P < 0.001$). Conversely, factors that were

Table 3
Univariable Multivariable cox proportional hazards model for overall survival.

	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P-value	HR (95% CI)	P-value
Age				
Continuous	1.04 (1.03–1.06)	<0.001	1.03 (1.005–1.05)	0.02
Sex				
Male	Ref		Ref	
Female	1.10 (0.71–1.73)	0.66	NS	
Year of diagnosis				
2010	Ref		Ref	
2011	0.82 (0.48–1.41)	0.48	NS	
2012	0.77 (0.45–1.31)	0.33	NS	
2013	0.65 (0.37–1.13)	0.13	NS	
2014	0.87 (0.49–1.53)	0.63	NS	
Charlson/Deyo score				
0	Ref		Ref	
1	1.59 (1.03–2.45)	0.04	NS	
≥2	1.61 (0.66–3.95)	0.29	NS	
Race				
White	Ref		Ref	
African American	1.75 (1.04–2.95)	0.04	NS	
Other	0.61 (0.15–2.47)	0.49	NS	
Facility type				
Community Cancer Program	Ref			
Comprehensive Community Cancer Program	0.72 (0.40–1.28)	0.26	Ref	
Academic/Research Program	1.02 (0.59–1.77)	0.95	NS	
Integrated Network Cancer program	1.23 (0.64–2.34)	0.53	NS	
Facility Location				
East	Ref		Ref	
Central	0.88 (0.61–1.27)	0.5	NS	
West	0.84 (0.52–1.35)	0.47	NS	
Insurance Status				
Uninsured	Ref		Ref	
Private	0.39 (0.20–0.78)	0.01	0.48 (0.24–0.97)	0.04
Medicaid	1.56 (0.73–3.36)	0.25	NS	
Medicare	1.42 (0.73–2.77)	0.3	NS	
Other Government	0.41 (0.09–1.86)	0.25	NS	
Income Level				
<$48,000	Ref		Ref	
≥48,000	0.56 (0.40–0.78)	<0.001	NS	
Without high school education				
≥13%	Ref		Ref	
<13%	0.61 (0.44–0.85)	0.003	0.70 (0.49–0.99)	0.04
Clinical T stage				
T1	Ref		Ref	
T2	2.55 (1.29–5.05)	0.007	2.36 (1.19–4.69)	0.01
T3	4.55 (2.31–8.96)	<0.001	3.94 (1.99–7.81)	<0.001
T4	6.88 (3.59–13.19)	<0.001	6.17 (3.20–11.92)	<0.001
Clinical N stage				
N0	Ref		Ref	
N1	0.72 (0.37–1.38)	0.32	NS	
N2a	0.43 (0.18–1.00)	0.05	NS	
N2b	0.67 (0.39–1.22)	0.20	NS	
N2c	1.47 (0.84–2.59)	0.18	NS	
N2 NOS	0.76 (0.35–1.67)	0.50	NS	
N3	0.90 (0.39–2.08)	0.8	NS	
Chemotherapy				
No	Ref		Ref	
Yes	0.92 (0.55–1.55)	0.75	NS	
Radiation Therapy				
Standard RT	Ref		Ref	
De-escalated RT	0.88 (0.53–1.47)	0.63	NS	

associated with improved OS were having private insurance (HR, 0.48; 95% CI, 0.24–0.97; $P = 0.04$) and higher education (HR, 0.70; 95% CI, 0.49–0.99; $P = 0.04$). DDRT was not associated with OS on univariable or multivariable analysis (Table 3). Interestingly, N-category (N2 or N3) was not associated with inferior OS.

Discussion

The results of this population based study suggest that the use of DDRT is not associated with inferior OS compared to patients treated with SDRT in the definitive treatment of HPV-positive oropharyngeal squamous cell carcinoma. Since the publication by Ang et al. [4] it has been proposed that this cancer is more sensitive to RT and chemotherapy than HPV-negative oropharyngeal cancer. If validated in randomized trials, DDRT has the potential to alter the standard of care in the treatment of head and neck cancers due to the substantial toxic effects that are associated with the standard dose chemoradiotherapy [6].

Since HPV data have only been used for prognostic purposes, the literature describing treatment de-escalation in HPV-positive cancer is sparse. The findings of the present study are comparable to the historical controls established in clinical trials of SDRT in HPV-positive oropharyngeal cancer [4,10]. A recent phase II trial of de-escalating therapy using 60 Gy showed a 2-yr OS of 98% (95% CI 85−100%), which is consistent with the findings of the present study [11]. A non-randomized trial of dose de-escalation from the Mayo Clinic in post-operative patients reported similar outcomes in an abstract form [12]. A large randomized trial, HN-002 has completed the enrollment phase with results scheduled to be reported over the next several years.

Radiation dose de-escalation is of interest as there is a strong relationship between RT dose delivered to organs at risk, and the long term toxicities, such as dysphagia and xerostomia. Studies have shown that dysphagia increases with every 10 Gy above 55 Gy delivered to the pharyngeal constrictors [13]. Similarly, feeding tube dependence and risk of aspiration has also been shown to increase when the volume of pharyngeal constrictors receiving 70 Gy exceed 30–50% [14,15]. A small study of 44 patients with HPV-positive oropharynx cancer treated with 60 Gy and concurrent cisplatin chemotherapy showed excellent 3 year outcomes with an improved quality of life [16]. Our study further supports excellent 3-yr OS with use of DDRT.

The results of this study need to be interpreted with caution as this is a population based observational study from a large national database. Foremost, this study is subject to a high degree of selection bias, as illustrated by the difference in T-category between the two groups. We attempted to balance important clinical covariates with the IPTW-adjusted approach. Per the AJCC 7th edition TNM staging, patients with N3 disease should have inferior survival compared to N1 disease. However, in this study, we did not observe this. This was likely due to a small sample size of 44 patients in the entire cohort having N3 disease. Additionally, there are multiple unmeasured confounding factors, such as the type of chemotherapy agent utilized and the number of chemotherapy cycles, patient performance status, as well as treating physician bias that goes into recommending SDRT versus DDRT. Additionally, the NCDB only reports on OS and we could not comment of the rates of local failure or distant failure. And lastly, treatment related toxicity data are also not available in this database.

Conclusion

To summarize, we observed no differences in OS between DDRT and SDRT in the definitive treatment of HPV-positive oropharyngeal squamous cell carcinoma. If these findings are confirmed by recently completed and ongoing de-escalation studies, which include quality of life measures, a new standard of care will be established for patients with HPV-positive oropharyngeal cancer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.016.

References

[1] Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294–301.
[2] Weinberger PM, Yu Z, Haffty BG, Kowalski D, Harigopal M, Brandsma J, et al. Molecular classification identifies a subset of human papillomavirus–associated oropharyngeal cancers with favorable prognosis. J Clin Oncol 2006;24:736–47.
[3] Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008;100:407–20.
[4] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
[5] Lassen P, Eriksen JG, Hamilton-Dutoit S, Tramm T, Alsner J, Overgaard J. Effect of HPV-associated p16INK4A expression on response to radiotherapy and survival in squamous cell carcinoma of the head and neck. J Clin Oncol 2009;27:1992–8.
[6] Caudell JJ, Schaner PE, Meredith RF, Locher JL, Nabell LM, Carroll WR, et al. Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2009;73:410–5.
[7] Ang KK, Zhang Q, Rosenthal DI, Nguyen-Tan PF, Sherman EJ, Weber RS, et al. Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 2014;32:2940–50.
[8] Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. Ann Surg Oncol 2008;15:683–90.
[9] Mansournia MA, Altman DG. Inverse probability weighting. BMJ 2016;352.
[10] Li H, Torabi SJ, Yarbrough WG, Mehra S, Osborn HA, Judson B. Association of human papillomavirus status at head and neck carcinoma subsites with overall survival. JAMA Otolaryngol Head Neck Surg 2018;144:519–25.
[11] Chen AM, Felix C, Wang PC, Hsu S, Basehart V, Garst J, et al. Reduced-dose radiotherapy for human papillomavirus-associated squamous-cell carcinoma of the oropharynx: a single-arm, phase 2 study. Lancet Oncol 2017;18:803–11.
[12] Ma DJ, Price K, Moore EJ, Patel SH, Hinni ML, Chintakuntlawar AV, et al. Two year results for MC1273, a phase II evaluation of aggressive dose de-escalation for adjuvant chemoradiation in HPV+ oropharynx squamous cell carcinoma (OPSCC). ASTRO 2017;2017.
[13] Eisbruch A, Schwartz M, Rasch C, Vineberg K, Damen E, Van As CJ, et al. Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 2004;60:1425–39.
[14] Levendag PC, Teguh DN, Voet P, van der Est H, Noever I, de Kruijf WJ, et al. Dysphagia disorders in patients with cancer of the oropharynx are significantly affected by the radiation therapy dose to the superior and middle constrictor muscle: a dose-effect relationship. Radiother Oncol 2007;85:64–73.
[15] Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M, Worden FP, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 2007;68:1289–98.
[16] Chera BS, Amdur RJ, Tepper JE, Tan X, Weiss J, Grilley-Olson JE, et al. Mature results of a prospective study of deintensified chemoradiotherapy for low-risk human papillomavirus-associated oropharyngeal squamous cell carcinoma. Cancer 2018;124:2347–54.