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Survival outcomes with concomitant chemoradiotherapy in older adults with oropharyngeal carcinoma in an era of increasing human papillomavirus (HPV) prevalence

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ABSTRACT

Background: Human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) has dramatically increased in incidence and prevalence among patients aged 70 and older. There are virtually no data regarding outcomes in this population, and thus optimal therapy, including the role of chemotherapy for those undergoing radiotherapy (RT), remains unclear.
Methods: The National Cancer Database was queried for older adults (defined as age 70 years and older) with locally advanced OPSCC (cT1-2N1-3, cT3-4N0-3) diagnosed from 2010 to 2014 with known HPV-status undergoing definitive RT alone or chemoradiation (CRT).
Results: Overall, 1,965 older adults with locally advanced OPSCC met inclusion criteria, including 1,141 HPV-positive (58%) and 824 HPV-negative (42%) patients. 1,211 patients (62%) received CRT. In multivariable analysis, CRT was associated with improved survival in older patients when compared to RT alone (hazard ratio [HR] = 0.74, 95% confidence interval [CI] 0.64–0.86, $P < 0.001$). CRT was associated with improved survival in both HPV-positive (HR = 0.80, 95% CI: 0.64–1.00, P = 0.05) and HPV-negative (HR = 0.69, 95% CI: 0.56–0.85, $P < 0.001$) subgroups. There was no significant interaction between HPV status and the impact of CRT on survival (P interaction = 0.57).
Conclusions: Despite the radiosensitivity of HPV-positive OPSCC and the challenges in delivering CRT to older adults, CRT was associated with improved survival in older patients with HPV-positive OPSCC, similar in magnitude to the benefit in HPV-negative patients. As the incidence of HPV-positive OPSCC in older patients continues to increase, further studies are needed to investigate optimal therapeutic strategies in this population.

Introduction

The epidemiologic landscape of oropharyngeal squamous cell carcinoma (OPSCC) has significantly evolved over the past decade [1]. Recent studies have shown that human papillomavirus (HPV)-positive OPSCC, which has historically been associated with younger patients, is now rapidly increasing in incidence in patients aged 70 and older [2–4]. There is very little data of any type that specifically focuses on this increasingly common population. Thus, the optimal therapeutic strategy for older patients with HPV-related OPSCC remains unclear.

For locally advanced OPSCC, concomitant chemoradiotherapy (CCRT) is the standard of care [5,6]. However, the role of CCRT in older patients with HPV-positive OPSCC is uncertain for several reasons. First, it is well-established that older patients have more difficulty tolerating standard multimodality therapy than younger patients, in part due to increased comorbidities and poorer performance status [6,10]. Moreover, older patients also have an increased risk of severe late toxicity when undergoing CCRT [11]. Unplanned secondary analysis of clinical trials have shown no improvement in survival with either chemotherapy or cetuximab in older patients [6,7], presumably due to toxicity outweighing oncologic benefit or inability to receive sufficient therapeutic doses of systemic therapy. Although there are some

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retrospective data suggesting some older adults may in fact benefit from CCRT with modern treatment [12,13], these studies do not consider HPV-status, making it uncertain how applicable this data is to HPV-positive cancers.

Given the radiosensitivity of HPV-associated tumors, which have markedly improved locoregional control and survival following radiotherapy in comparison to HPV-unrelated OPSCC [3], it is plausible that older patients with HPV-positive OPSCC derive less oncologic benefit from therapeutic intensifications like CCRT compared to those with HPV-negative disease. This could possibly result in an even narrower therapeutic window than other older adults with more radioresistant head and neck cancers.

Given the near complete absence of data regarding the effect of therapeutic intensification in older adults with HPV-associated OPSCC, in combination with the rapid increase in the incidence and prevalence of this of this disease in this population, more research is needed regarding the optimal therapeutic strategy for these patients. In the present study, we compare survival outcomes for patients 70 years and older with locally advanced OPSCC undergoing CCRT or RT alone in the era of increasing HPV-prevalence.

Materials and methods

Database information

This study used de-identified patient data from the National Cancer Database (NCDB), a database sponsored by the American College of Surgeons and the American Cancer Society. The NCDB captures data from more than 1,500 facilities and includes data for approximately 70% of new cancer diagnoses in the United States. The Commission on Cancer's NCDB and the hospitals participating in the NCDB are the source of the de-identified data used herein; they have not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by us. This study was deemed to be exempt from the full institutional review board review by Cedars-Sinai Medical Center.

Patient selection

The NCDB was queried for patients with locally advanced (American Joint Commission on Cancer (AJCC) 8th edition clinical stage T3-4N0-3 or T1-2N1-3) non-metastatic oropharyngeal cancers (International Classification of Diseases for Oncology [ICD-O]-3 codes: C01.9, C02.4, C05.1, C05.2, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.2) with squamous cell carcinoma histology (ICD-O-3 codes: 8050-8084) diagnosed from 2010 to 2014 (Supplementary Fig. 1). Patients with ambiguous anatomic site codes (C02.8, C02.9, C05.8, C05.9, C14.0, C14.8) were excluded. Included patients underwent definitive RT with or without chemotherapy. HPV status is coded in NCDB based on any type of HPV testing performed, including p16 immunohistochemistry, HPV in situ hybridization, or other methodologies. Concomitant chemoradiation was defined as receipt of chemotherapy within seven days of the start of RT. Older patients were defined as those aged 70 years and older. Clinical stage T1-2 N0 patients were excluded, as definitive RT without chemotherapy is the standard of care for this population. Patients who underwent surgery before radiation, with unknown follow-up, or with unknown timing of chemotherapy were excluded.

Statistical analysis

Baseline characteristics between patients undergoing RT alone and CCRT were assessed using Welch's *t*-test and the Pearson's chi-squared test for continuous and categorical covariates, respectively. Median follow-up was determined using the reverse Kaplan-Meier method. Survival functions were estimated using the Kaplan-Meier method and the Log-rank test was used to compare survival curves.

Univariate and multivariable survival analyses were performed with a Cox proportional hazards model. Variable selection was performed using a backwards stepwise selection on the full multivariable model optimizing for Akaike information criterion (AIC) [14]. The proportional hazards assumption was assessed using the scaled Schoenfeld residuals, and the multicollinearity was assessed using the variable inflation factor (VIF) [15].

To further account for confounding variables, propensity scores were estimated for each patient using a multivariable logistic regression model adjusting for all baseline patient clinical and demographical characteristics [16]. The propensity scores were then matched with the nearest neighbor method using a caliper of 0.2 [17]. Match diagnostics were assessed by the standardized mean differences and visually with histograms distributions of the propensity scores of the matched cohort.

Multivariable subgroup analyses were performed to assess the effect of CCRT on HPV status. A test of interaction was performed to evaluate differences in the effect of CCRT on survival among HPV-positive versus HPV-negative patients. All statistical analyses were performed using R statistical software (version 3.5.1; R Foundation, Vienna, Austria) with two-sided tests and a significance level of 0.05 [18].

Results

Overall, 1,965 patients aged 70 and older diagnosed with locally advanced OPSCC and known HPV status were included in this study, including 1,141 HPV-positive (58%) and 824 HPV-negative (42%) patients. 754 (38.4%) patients received RT alone and 1,211 (61.6%) patients received CCRT. Comparisons of baseline characteristics between patients undergoing CCRT versus RT alone are listed in Table 1. The mean age for the entire cohort was 75.5 years.

The median follow-up was 36.8 months. After adjusting for other covariates in multivariable analysis (Table 2), including HPV-status, CCRT was independently associated with improved OS in patients aged 70 years and older when compared to RT alone (HR 0.74, 95% CI 0.64–0.86; $P < 0.001$). Notably, HPV positivity was associated with significantly increased OS in multivariate analysis compared to HPV-negative disease in this population of older adults (HR 0.68, 95% CI 0.58–0.80; $P < 0.001$). In propensity score-matched cohorts (Supplementary Table 1), 3-year OS was 65.8% (95% CI, 62.0%–69.9%) versus 54.0% (95% CI, 50.0%–58.5%) in older adults receiving CCRT and RT alone, respectively ($P < 0.001$) (Fig. 1).

We then analyzed the influence of CCRT on OS based on HPV status. In subgroup analysis, CCRT was associated with improved survival in both patients with HPV-positive (HR = 0.80, 95% CI: 0.64–1.00, P = 0.05) and HPV-negative (HR = 0.69, 95% CI: 0.56–0.85, $P < 0.001$) disease. There was no significant interaction between HPV status and the magnitude of the association of CCRT with improved survival for older OPSCC patients (interaction P = 0.57) (Fig. 2A). In propensity score-matched cohorts of patients with HPV-associated disease (Figs. 2B and 2C), 3-year OS was 70.3% versus 62.0% in older adults with HPV-associated OPSCC receiving CCRT and RT alone, respectively ($P < 0.001$). In HPV-negative propensity score-matched cohorts, 3-year OS was 53.9% versus 43.0% in HPV-negative OPSCC undergoing CCRT and RT alone, respectively ($P < 0.001$) (Supplementary Tables 2 and 3).

Discussion

In this study, we found that CCRT was associated with improved survival in patients aged 70 years and older with locally advanced OPSCC compared to RT alone, even when accounting for HPV-status. In fact, the magnitude of improved survival associated with CCRT was similar among HPV-positive and HPV-negative patients, with no significant interaction between HPV-status and CCRT detected. In the subgroup of patients aged 70 and older with HPV-positive OPSCC, there

Table 1
Baseline characteristics in patients aged 70 or older with oropharyngeal squamous cell carcinoma undergoing definitive radiation with or without concurrent chemotherapy.

Characteristics	Overall N = 1965	Radiation alone N = 754	Chemoradiation N = 1211	P*
Age (years)				
Mean (SD)	75.5 (4.80)	76.5 (5.41)	74.8 (4.27)	< 0.001
Median [IQR]	74.0 [72.0; 78.0]	75.0 [72.0; 79.0]	74.0 [71.0; 77.0]	< 0.001
Sex				0.323
Male	1546 (78.7%)	584 (77.5%)	962 (79.4%)	
Female	419 (21.3%)	170 (22.5%)	249 (20.6%)	
Race				0.296
White	1804 (91.8%)	684 (90.7%)	1120 (92.5%)	
Black	127 (6.46%)	57 (7.56%)	70 (5.78%)	
Other/unknown	34 (1.73%)	13 (1.72%)	21 (1.73%)	
T-Classification				0.058
T1	260 (13.2%)	102 (13.5%)	158 (13.0%)	
T2	753 (38.3%)	262 (34.7%)	491 (40.5%)	
T3	568 (28.9%)	227 (30.1%)	341 (28.2%)	
T4	384 (19.5%)	163 (21.6%)	221 (18.2%)	
N-Classification (AJCC 8th Edition)				0.240
N0	224 (11.4%)	95 (12.6%)	129 (10.7%)	
N1	940 (47.8%)	356 (47.2%)	584 (48.2%)	
N2	730 (37.2%)	270 (35.8%)	460 (38.0%)	
N3	71 (3.61%)	33 (4.38%)	38 (3.14%)	
Charlson/Deyo comorbidity score				0.002
0	1439 (73.2%)	542 (71.9%)	897 (74.1%)	
1	371 (18.9%)	143 (19.0%)	228 (18.8%)	
2	130 (6.62%)	50 (6.63%)	80 (6.61%)	
≥3	25 (1.27%)	19 (2.52%)	6 (0.50%)	
Year of diagnosis				0.136
2010	138 (7.02%)	50 (6.63%)	88 (7.27%)	
2011	279 (14.2%)	94 (12.5%)	185 (15.3%)	
2012	404 (20.6%)	144 (19.1%)	260 (21.5%)	
2013	507 (25.8%)	210 (27.9%)	297 (24.5%)	
2014	637 (32.4%)	256 (34.0%)	381 (31.5%)	
Academic center				0.272
No	1116 (56.8%)	416 (55.2%)	700 (57.8%)	
Yes	849 (43.2%)	338 (44.8%)	511 (42.2%)	
Facility volume				0.206
Lower volume	1735 (88.3%)	675 (89.5%)	1060 (87.5%)	
High volume	230 (11.7%)	79 (10.5%)	151 (12.5%)	
Anatomic site				0.114
Tonsil	667 (33.9%)	254 (33.7%)	413 (34.1%)	
Base of tongue	1096 (55.8%)	409 (54.2%)	687 (56.7%)	
Other	202 (10.3%)	91 (12.1%)	111 (9.17%)	
Insurance status				0.143
No insurance	7 (0.36%)	1 (0.13%)	6 (0.50%)	
Private	237 (12.1%)	94 (12.5%)	143 (11.8%)	
Medicaid	24 (1.22%)	13 (1.72%)	11 (0.91%)	
Medicare	1634 (83.2%)	616 (81.7%)	1018 (84.1%)	
Other	63 (3.21%)	30 (3.98%)	33 (2.73%)	
Zip-code Median income				0.242
< $46,000	928 (47.2%)	343 (45.5%)	585 (48.3%)	
≥$46,000	1037 (52.8%)	411 (54.5%)	626 (51.7%)	
Zip-code Education				0.012
≤20% completed high school	1316 (67.0%)	479 (63.5%)	837 (69.1%)	
> 20% completed high school	649 (33.0%)	275 (36.5%)	374 (30.9%)	
Urban/rural				0.274
< 1 million people	1094 (55.7%)	432 (57.3%)	662 (54.7%)	
≥1 million people	871 (44.3%)	322 (42.7%)	549 (45.3%)	
HPV status				0.125
Negative	824 (41.9%)	333 (44.2%)	491 (40.5%)	
Positive	1141 (58.1%)	421 (55.8%)	720 (59.5%)	

*P values are calculated by Pearson's chi-square test for categorical variables and Welch's *t*-test for continuous variables.

was an approximately 20% relative decrease in mortality with CCRT versus RT alone in multivariable Cox regression, corresponding to a 8.3% absolute improvement in 3-year OS propensity score matched cohorts. Thus, this study supports the notion that CCRT should be considered in older adults deemed healthy enough for multimodality therapy irrespective of HPV-status. However, patient selection is critical for optimizing the therapeutic ratio in the heterogeneous older adult population. Unfortunately, identifying which older patients are best suited for chemoradiation is poorly understood, representing an important potential avenue for future investigation.

This is the only study we are aware of investigating the impact of concomitant systemic therapy specifically in HPV-positive OPSCC patients aged 70 and older receiving RT. Nevertheless, our results are supported by evidence from RTOG 1016, a trial enrolling patients with locally advanced HPV-positive OPSCC. In this study, which included 14% of patients aged 66 or older (maximum age 83 years old), improved survival was seen with cisplatin-based chemoradiation versus cetuximab-based bioradiation. There were essentially identical

Table 2
Univariate and multivariable Cox regression analysis of overall survival for oropharyngeal squamous cell carcinoma patients aged 70 or older undergoing definitive radiation.

Characteristics	Univariate survival analysis		Multivariable survival analysis	
	HR (95%CI)	p	HR (95%CI)	p
Age (years)	1.08 (1.065–1.095)	< 0.001	1.071 (1.056–1.087)	< 0.001
Sex				
Male	1.00	–	*	
Female	1.304 (1.104–1.539)	0.002		
Race				
White	1.00	–	*	
Black	1.555 (1.198–2.017)	0.001		
Other	1.432 (0.858–2.39)	0.169		
T-Classification				
T1	1.00	–	1.00	–
T2	1.496 (1.125–1.991)	0.006	1.45 (1.087–1.934)	0.011
T3	2.356 (1.774–3.129)	< 0.001	1.89 (1.408–2.538)	< 0.001
T4	2.784 (2.079–3.727)	< 0.001	2.46 (1.823–3.319)	< 0.001
N-Classification (AJCC 8th Edition)				
N0	1.00	–	1.00	–
N1	0.542 (0.436–0.675)	< 0.001	0.919 (0.721–1.17)	0.493
N2	0.776 (0.624–0.965)	0.023	0.992 (0.788–1.249)	0.947
N3	0.941 (0.638–1.388)	0.76	1.511 (1.013–2.255)	0.043
Charlson/Deyo comorbidity score				
0	1.00	–	1.00	–
1	1.398 (1.166–1.676)	< 0.001	1.447 (1.206–1.736)	< 0.001
2	1.854 (1.448–2.374)	< 0.001	1.748 (1.358–2.249)	< 0.001
≥3	2.175 (1.226–3.857)	0.008	2.186 (1.227–3.895)	0.008
Year of diagnosis	0.975 (0.918–1.036)	0.412	*	
Academic center				
No	1.00	–	1.00	–
Yes	1.027 (0.888–1.188)	0.717	1.114 (0.961–1.291)	0.153
Facility volume				
Lower volume	1.00	–	1.00	–
High volume	0.552 (0.425–0.718)	< 0.001	0.601 (0.461–0.784)	< 0.001
Anatomic site				
Tonsil	1.00	–	1.00	–
Base of tongue	0.883 (0.752–1.035)	0.125	0.946 (0.804–1.113)	0.505
Other	1.612 (1.284–2.023)	< 0.001	1.22 (0.963–1.544)	0.099
Insurance status				
No insurance	1.00	–	*	
Private	0.848 (0.209–3.449)	0.818		
Medicaid	1.355 (0.306–6.006)	0.689		
Medicare	0.945 (0.236–3.786)	0.936		
Other	0.706 (0.163–3.056)	0.641		
Zip-code Median income				
< $46,000	1.00	–	1.00	–
≥ $46,000	1.285 (1.11–1.486)	0.001	1.256 (1.083–1.457)	0.003
Zip-code Education				
≤20% completed high school	1.00	–	*	
> 20% completed high school	1.227 (1.056–1.425)	0.008		
Urban/rural				
< 1 million people	1.00	–	*	
≥1 million people	1.057 (0.915–1.223)	0.45		
Concurrent chemotherapy				
No	1.00	–	1.00	–
Yes	0.662 (0.573–0.765)	< 0.001	0.741 (0.639–0.859)	< 0.001
HPV status				
Negative	1.00	–	1.00	–
Positive	0.532 (0.460–0.615)	< 0.001	0.682 (0.579–0.803)	< 0.001

*Dropped from multivariable model through stepwise variable selection.

magnitudes of improvement in OS with cisplatin versus cetuximab in patients 66 and older as in younger patients (interaction P = 0.99). This implies that, at least for some older adults with HPV-positive OPSCC, systemic therapy can improve outcomes, similar to our findings.

The results of our study and RTOG 1016 contrast with previous historical studies showing no benefit to treatment intensification in older adults with head and neck cancer undergoing definitive radiotherapy [6,7,19]. This may be due to several reasons. First, there has been a significant improvement in radiation techniques over the past two decades, which may have improved the therapeutic window for older patients. For example, intensity-modulated radiotherapy (IMRT), now a standard of care, substantially reduces dose heterogeneity while limiting the dose to surrounding normal structures, thereby decreasing toxicity in multiple randomized phase III trials [20–22]. There is retrospective evidence that the use of IMRT in treatment of older patients with head and neck cancer is associated with improved survival [23]. Other advances, such as image guidance allowing the use of smaller margins for set-up error and the wider availability of contouring atlases for IMRT, may also potentially reduce toxicity. Collectively, these improvements in radiation delivery may result in better tolerance of CCRT and a more favorable side effect profile for older adults in the modern era [24]. There have also been substantial improvements in supportive

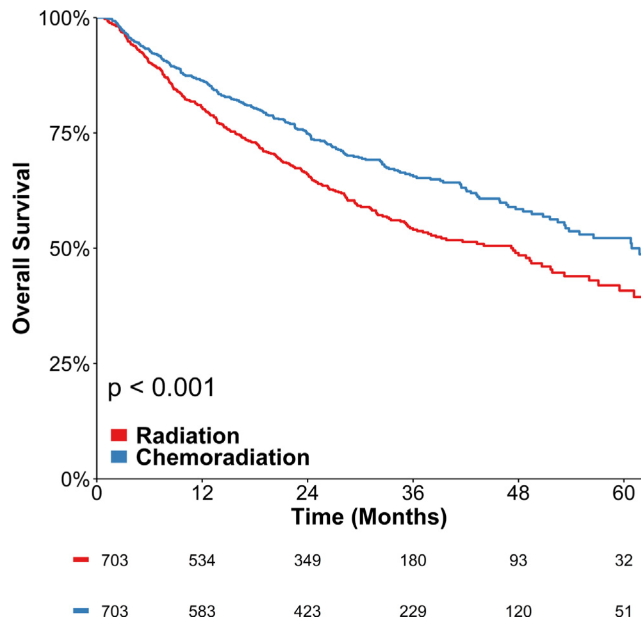

Fig. 1. Overall survival of propensity score-matched cohorts of patients with oropharyngeal squamous cell carcinoma patients aged 70 or older undergoing definitive radiation alone vs concurrent chemoradiation.

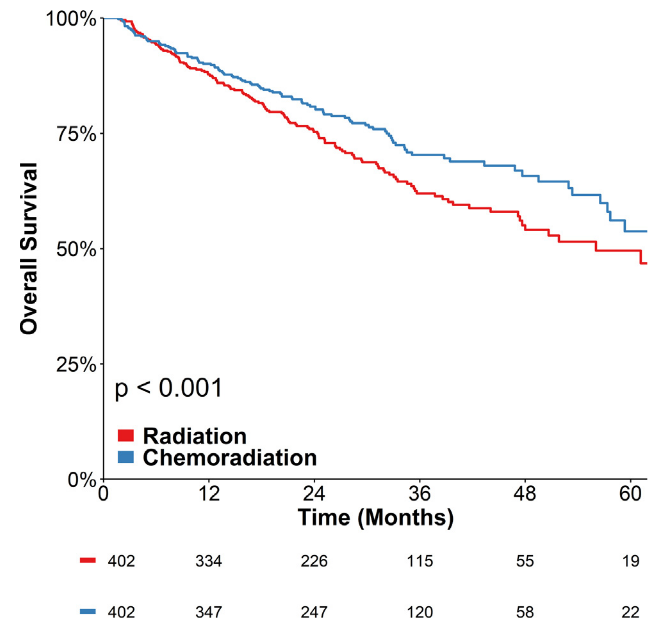

Fig. 2b. Overall survival of propensity score-matched cohorts of patients aged 70 or older with HPV-associated oropharyngeal squamous cell carcinoma patients undergoing definitive radiation with or without concurrent chemotherapy.

care, such as improved anti-nausea regimens with chemotherapy [25–27] and mucositis treatments [28–31]. Lastly, the prevalence of active smoking in North America has decreased from 1980 to 2012 [32], and thus it is likely that the prevalence of smoking among patients with OPSCC is much lower in comparison to previous eras, which may further improve toxicity profile.

There has been a dramatic increase in the prevalence and incidence of HPV-associated OPSCC among older adults since the year 2000 [2–4]. This trend is likely to accelerate over the next decade as a result of a birth cohort effect and an increase in the absolute number of older adults due to ageing of the Baby Boom generation [1]. Therefore, it is critical to understand the optimal therapeutic strategy in these patients. However, there is a lack of available high-level evidence to guide treatment decisions in older adults with HPV-positive OPSCC. Trials specific to this population are needed, given the unique challenges posed by cancer treatment in these patients. Moreover, although many older adults with HPV-associated OPSCC likely benefit from CCRT, there are some that certainly will not. Patient selection is critical, but the best determinants of fitness for CCRT are unknown. There is ongoing research investigating whether multi-domain tools, such as the geriatric assessment, are more useful in establishing fitness for multimodality treatment than more crude metrics like age, performance status, and the "eye-ball test" [33], including EGeSOR trial (NCT02025062), ELAN-FIT (NCT01864772), ELAN-UNFIT (NCT01884623) and ELAN-RT (NCT01864850). Although these studies are not specific to HPV-positive OPSCC, they may help establish principles for patient selection that are applicable to this population.

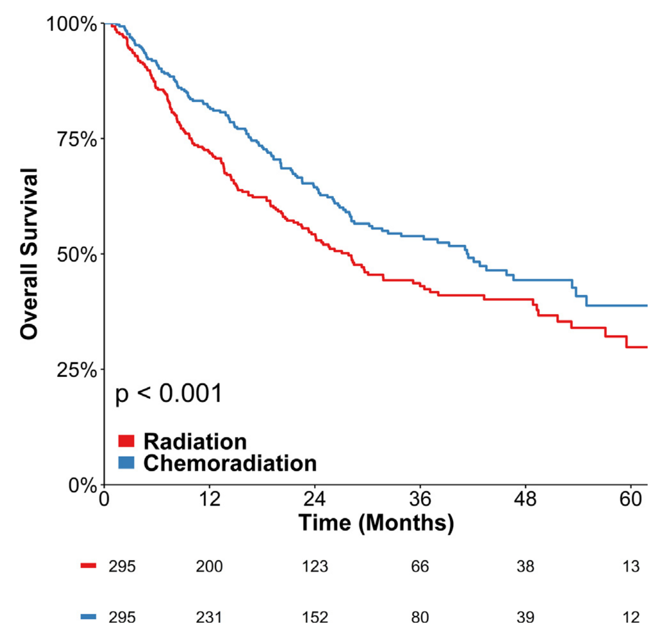

Fig. 2c. Overall survival of propensity score-matched cohorts of patients aged 70 or older with HPV-negative oropharyngeal squamous cell carcinoma undergoing definitive radiation with or without concurrent chemotherapy.

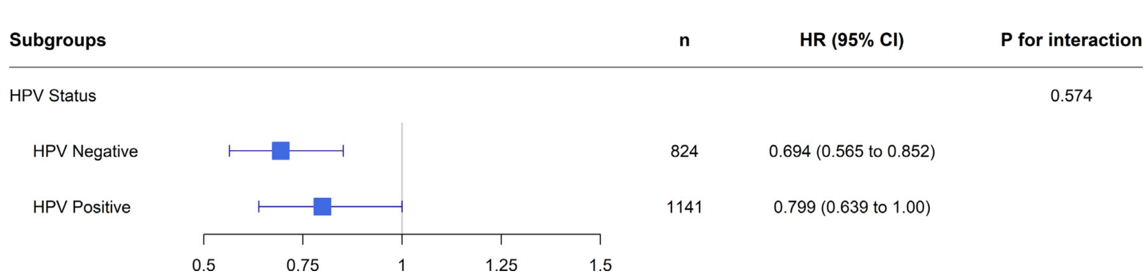

Fig. 2a. Forrest Plot of the impact of concurrent chemoradiation on overall survival in oropharyngeal squamous cell carcinoma patients aged 70 or older based on HPV status. P-values represent statistical tests of interaction.

Nevertheless, much work needs to be done to optimize treatment decisions in this relatively new and rapidly expanding population of patients.

There are several limitations in this study. First, this is a retrospective study, with all of the associated potential sources of bias that accompany such study designs. Patient-, disease- and treatment-related factors were not identical between groups undergoing CCRT and RT alone and between HPV-positive and HPV-negative patients. Specifically, patients that received CCRT were younger (mean age: 74.8 versus 76.5 years old) and had lower comorbidity (Charlson score = 0 in 74% versus 71%), although the absolute differences were relatively small. We accounted for imbalances in prognostic factors by using multivariable Cox regression and propensity score matching, but there is still a possibility that unmeasured confounders could have affected results. For example, smoking status, body mass index, performance status, and marital status are variables that could plausibly affects survival but are not captured in this database. Additionally, details regarding specific aspects of treatment, including chemotherapy agents and quality of radiation delivery, were not available, which may influence survival [34–39]. NCDB also does not provide cancer-specific outcomes, such as locoregional recurrence, distant metastasis, and cause-specific survival, which does not differentiate cancer-related events and competing risks between groups. Finally, data on toxicity and quality of life are also not reported in NCDB, which would be important and meaningful endpoints in older patients receiving multimodality therapy.

In summary, despite the radiosensitivity of HPV-associated OPSCC and the challenges in delivering CCRT to older adults, we observed significantly improved survival for locally advanced OPSCC patients aged 70 and older undergoing CCRT compared to RT alone. The benefit in survival with CCRT was similar in both HPV-positive and HPV-negative patients. Thus, CCRT should be considered in the management of older patients with locally advanced OPSCC without contraindications to treatmentirrespective of HPV-status. Ultimately, patient selection will be critical in determining which patients within the cohort of patients aged 70 and older with HPV-positive OPSCC should receive multimodality therapy, and much more research is needed. As the incidence of OPSCC in the older population is projected to continue to increase through at least 2030 [40], further randomized studies are needed specifically in this population to optimize treatment and further elucidate the benefit of CCRT in older patients.

Declaration of Competing Interest

The authors have no conflicts of interest related to this work. ZSZ was on the external advisory board for the Scripps Proton Therapy Center and has consulted for EMD Serono. All other authors have no disclosures.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.104472.

References

[1] Chaturvedi AK, Zumsteg ZS. A snapshot of the evolving epidemiology of oropharynx cancers. Cancer 2018;124:2893–6.
[2] Zumsteg ZS, Cook-Wiens G, Yoshida E, et al. Incidence of oropharyngeal cancer among elderly patients in the United States. JAMA Oncol 2016;2:1617–23.
[3] Lu DJ, Luu M, Mita A, et al. Human papillomavirus-associated oropharyngeal cancer among patients aged 70 and older: Dramatically increased prevalence and clinical implications. Eur J Cancer 2018;103:195–204.
[4] Tota JE, Best AF, Zumsteg ZS, et al. Evolution of the oropharynx cancer epidemic in the United States: Moderation of increasing incidence in younger individuals and shift in the burden to older individuals. J Clin Oncol 2019;37:1538–46.
[5] Denis F, Garaud P, Bardet E, et al. Final results of the 94–01 French head and neck oncology and radiotherapy group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. J Clin Oncol 2004;22:69–76.
[6] Pignon JP, le Maitre A, Maillard E, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
[7] Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010;11:21–8.
[8] Fentiman IS, Tirelli U, Monfardini S, et al. Cancer in the elderly: why so badly treated? Lancet 1990;335:1020–2.
[9] Reid BC, Alberg AJ, Klassen AC, et al. Comorbidity and survival of elderly head and neck carcinoma patients. Cancer 2001;92:2109–16.
[10] Sanabria A, Carvalho AL, Vartanian JG, et al. Comorbidity is a prognostic factor in elderly patients with head and neck cancer. Ann Surg Oncol 2007;14:1449–57.
[11] Machtay M, Moughan J, Trotti A, et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 2008;26:3582–9.
[12] Yoshida EJ, Luu M, David JM, et al. Postoperative chemoradiotherapy in patients with head and neck cancer aged 70 or older with positive margins or extranodal extension and the influence of nodal classification. Head Neck 2018;40:1228–36.
[13] Amini A, Jones BL, McDermott JD, et al. Survival outcomes with concurrent chemoradiation for elderly patients with locally advanced head and neck cancer according to the national cancer data base. Cancer 2016;122:1533–43.
[14] Yamashita T, Yamashita K, Kamimura R. A stepwise AIC method for variable selection in linear regression; 2007.
[15] Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.
[16] D'Agostino Jr. RB, D'Agostino Sr. RB. Estimating treatment effects using observational data. JAMA 2007;297:314–6.
[17] Austin PC. A comparison of 12 algorithms for matching on the propensity score. Stat Med 2014;33:1057–69.
[18] Statistical RCTRalaef, computing. Vienna ARFfS, [Internet]. CAfhwRo.
[19] Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006;368:843–54.
[20] Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011;12:127–36.
[21] Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006;66:981–91.
[22] Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007;25:4873–9.
[23] Beadle BM, Liao KP, Elting LS, et al. Improved survival using intensity-modulated radiation therapy in head and neck cancers: a SEER-Medicare analysis. Cancer 2014;120:702–10.
[24] Nguyen NP, Vock J, Chi A, et al. Impact of intensity-modulated and image-guided radiotherapy on elderly patients undergoing chemoradiation for locally advanced head and neck cancer. Strahlenther Onkol 2012;188:677–83.
[25] Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med 2016;375:134–42.
[26] Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol 2015;16:1079–89.
[27] Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncol 2009;10:115–24.
[28] Allison RR, Ambrad AA, Arshoun Y, et al. Multi-institutional, randomized, double-blind, placebo-controlled trial to assess the efficacy of a mucoadhesive hydrogel (MuGard) in mitigating oral mucositis symptoms in patients being treated with chemoradiation therapy for cancers of the head and neck. Cancer 2014;120:1433–40.
[29] Leenstra JL, Miller RC, Qin R, et al. Doxepin rinse versus placebo in the treatment of acute oral mucositis pain in patients receiving head and neck radiotherapy with or without chemotherapy: a phase III, randomized, double-blind trial (NCCTG-N09C6 [Alliance]). J Clin Oncol 2014;32:1571–7.
[30] Leung HW, Chan AL. Glutamine in alleviation of radiation-induced severe oral mucositis: a meta-analysis. Nutr Cancer 2016;68:734–42.
[31] Le QT, Kim HE, Schneider CJ, et al. Palifermin reduces severe mucositis in definitive chemoradiotherapy of locally advanced head and neck cancer: a randomized, placebo-controlled study. J Clin Oncol 2011;29:2808–14.
[32] Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. JAMA 2014;311:183–92.
[33] Maggiore R, Zumsteg ZS, BrintzenhofeSzoc K, et al. The older adult with locoregionally advanced head and neck squamous cell carcinoma: knowledge gaps and future direction in assessment and treatment. Int J Radiat Oncol Biol Phys 2017;98:868–83.
[34] Giralt J, Trigo J, Nuyts S, et al. Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomised, controlled, open-label phase 2 trial. Lancet Oncol 2015;16:221–32.

[35] Magrini SM, Buglione M, Corvo R, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized Phase II trial. J Clin Oncol 2016;34:427–35.
[36] Peters LJ, O'Sullivan B, Giralt J, et al. Critical impact of radiotherapy protocol compliance and quality in the treatment of advanced head and neck cancer: results from TROG 02.02. J Clin Oncol 2010;28:2996–3001.
[37] Shapiro LQ, Sherman EJ, Riaz N, et al. Efficacy of concurrent cetuximab vs. 5-fluorouracil/carboplatin or high-dose cisplatin with intensity-modulated radiation therapy (IMRT) for locally-advanced head and neck cancer (LAHNSCC). Oral Oncol 2014;50:947–55.
[38] Zumsteg ZS, Lok BH, Ho AS, et al. The toxicity and efficacy of concomitant chemoradiotherapy in patients aged 70 years and older with oropharyngeal carcinoma in the intensity-modulated radiotherapy era. Cancer 2017;123:1345–53.
[39] David JM, Ho AS, Luu M, et al. Treatment at high-volume facilities and academic centers is independently associated with improved survival in patients with locally advanced head and neck cancer. Cancer 2017;123:3933–42.
[40] Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758–65.