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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Impact of clinical complete response on treatment outcomes in patients with locally advanced HPV-negative oropharyngeal squamous cell carcinoma

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Abstract

Objective To evaluate treatment outcomes after definitive chemoradiotherapy (CRT) for human papilloma virus (HPV)-negative oropharyngeal squamous cell carcinoma (OPSCC).

Materials and methods We analyzed data concerning HPV-negative OPSCC patients treated with curative intent. All patients received concomitant high-dose cisplatin-based chemotherapy. Two different RT techniques were used: (1) sequential boost IMRT (S-IMRT) to a total dose of 70 Gy (2 Gy/fraction); (2) simultaneously integrated boost (SIB-IMRT) to a total dose of 67.5 Gy (2.25 Gy/fraction). Survival outcomes were estimated.

Results In total, 69 HPV-negative OPSCC patients were included ($n=40$ S-IMRT; $n=29$ SIB-IMRT). The median follow-up time was 40 months. The 3-year overall survival, disease-free survival, distant metastasis-free survival and locoregional-free survival were 67.1%, 63.3%, 64.5% and 66.0%, respectively. Alcohol abuse and advanced stage disease at presentation were the main risk factors for worse survival outcomes. Complete clinical response (cCR) at 3 months after CRT improved overall survival (86.3% versus 42.5%, $p<0.01$). The cCR events were greater but not statistically significant in SIB-IMRT group compared to S-IMRT patients (69% versus 47.5%, $p=0.09$).

Conclusions The positive impact of cCR at 3 months on survival needs to be confirmed in randomized clinical trials, as well as its close correlation with SIB-IMRT technique. A proper stratification of HPV-negative OPSCC patients should be paramount to tailor treatment strategy in the near future.

Keywords HPV · Oropharyngeal cancer · Survival · Complete response · IMRT

Introduction

It is now widely accepted that human papilloma virus (HPV)-negative oropharyngeal squamous cell carcinoma (OPSCC) has a worse prognosis than that for HPV-related OPSCC treated similarly (National Comprehensive Cancer Network 2019). Typically, HPV-negative OPSCC appears in old individual (> 60 years) with low socioeconomic status and a history of cigarette smoking and alcohol abuse (Leemans et al. 2011). At diagnosis, most patients present with advanced primary tumor (T) and lymph node (N) metastasis (Leemans et al. 2011). Definitive concurrent chemoradiotherapy (CRT)—using an intensity modulated technique (IMRT)—is the standard treatment, especially in locally advanced disease (National Comprehensive Cancer Network 2019). Despite, nowadays, HPV-related OPSCC draws researchers' attention, HPV-negative OPSCC maintains its identity and a cohort data analysis could be of interest in both clinical and scientific communities to define subgroups at higher risk of treatment failure.

The purpose of this study was to identify predictors of failure in HPV-negative OPSCC patients treated with definitive CRT.

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Methods and materials

Patient population

Clinical data of consecutive patients treated for newly diagnosed HPV-negative OPSCC were considered. The study was approved by the institutional review board and the scientific review committee. Data collected included demographics, stage disease at presentation, treatment details and follow-up. Patients with metastatic disease at diagnosis, those treated with induction chemotherapy or those who underwent oncologic surgery or received previous radiation to the head and neck region were not included. To assess the precise T, N, and distant (M) extent, clinical examinations (complete medical history, physical examination and nasofibrolaryngoscopy) were combined with radiologic imaging (head and neck diffusion-weighted magnetic resonance imaging (DW-MRI) and chest contrast-enhanced computed tomography (CT)). All patients underwent an accurate dental-oral evaluation, a complete nutritional counseling, a hearing test and speech/swallowing evaluation. TNM stage was updated to the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual (Lydiatt et al. 2017). The year 2017 was chosen to allow an adequate follow-up.

Treatment

After have signed informed consent, all patients underwent CRT with curative intent. Concomitant chemotherapy consisted of high-dose cisplatin (100 mg/m^2) every 3 weeks. Until November 2013, RT was delivered using a sequential boost IMRT (S-IMRT) technique to a total dose of 70 Gy (2 Gy per fraction) to the primary T and pathological N, 60 Gy (2 Gy per fraction) to the entire anatomical subsite and the involved lymph node levels and 50 Gy (2 Gy per fraction) to elective regions. After the above date, simultaneously integrated boost (SIB-IMRT) technique was used to a total dose of 67.5 Gy (2.25 Gy per fraction) to macroscopic T and N disease, 60 Gy (2 Gy per fraction) to the intermediate risk target volume and 54 Gy (1.8 Gy per fraction) to sites of suspected subclinical spread. Patient data were retrospectively collected for the S-IMRT patients and prospectively recorded for the SIB-IMRT patients.

Follow-up

During RT, patients were examined daily. Once treatment ended, follow-up program was performed according to internal algorithm (De Felice et al. 2017). Patients were followed up closely—every 3 months during first 2 years and every 6 months thereafter—to detect persistent or recurrent disease by complete physical examination and nasopharyngolaryngoscopy. Imaging was routinely performed within 3 and 9 months after the end of treatment, or where appropriate based on clinical examination findings.

Toxicity was evaluated during CRT and was recorded prospectively at each follow-up visit.

Statistical analysis

Statistical analysis was carried out using R-Studio 0.98.1091 software. Standard descriptive statistics were used to evaluate the distribution of each potential factor. Continuous variables were presented as medians and ranges, and dichotomous variables were presented as percentages.

Overall survival (OS), disease-free survival (DFS), locoregional-free survival (LRFS) and distant metastasis-free survival (DMFS), were calculated in months from the date of the end of CRT to the first event, including date of the last follow-up or death (OS) and/or relapse (DFS) and/or locoregional recurrence (LRFS) and/or distant metastasis (DMFS). OS, DFS, LRFS and DMFS were estimated by the Kaplan–Meier method, and survival curves were compared by the log-rank test. The following variables were investigated: age at diagnosis (<65 years versus ≥ 65 years), gender (male versus female), smoke (never versus current/former), alcohol abuse (no versus yes), primary tumor location (tonsil versus base of tongue versus other), clinical T classification (cT1-2 versus cT3-4), clinical N classification (cN0-1 versus cN2-3), RT technique (SIB-IMRT versus S-IMRT), complete clinical response at 3 months (cCR) (yes versus no). Variables associated with a p value <0.25 on univariate analysis were included in a multivariate survival Cox regression analysis. Results of the Cox regression analysis were presented as hazard ratio (HR) and 95% confidence interval (CI). Toxicity data at 3 months and at 1 year after treatment were analyzed. Distribution of categorical variables was compared with Chi-square tests. All reported p values were two-sided, and p values lower than 0.05 were considered significant.

Results

Patient and treatment characteristics

Overall, 69 patients were included in the analysis. Patient, tumor and treatment characteristics are listed in Table 1. Median age was 64 years (range 41–74). The vast majority of tumors were locally advanced (N2-3 in 85.5%). All patients completed the programmed CRT. Twenty-nine patients (42%) received SIB-IMRT. On the whole, there were no significant differences in baseline characteristics

Table 1 Patient, tumor and treatment characteristics

Characteristic	All (%)	S-IMRT (%)	SIB-IMRT (%)	*p* value
Gender				
Male	50 (72.5)	31 (77.5)	19 (65.5)	0.29
Female	19 (27.5)	9 (22.5)	10 (34.5)	
Age				
< 65	38 (55.1)	23 (57.5)	15 (51.7)	0.81
≥ 65	31 (44.9)	17 (42.5)	14 (48.3)	
Comorbidity				
No	44 (63.8)	26 (65)	18 (62.1)	0.80
Yes	25 (36.2)	14 (35)	11 (37.9)	
Smoke				
Never	20 (29)	15 (37.5)	5 (17.2)	0.11
Current/former	49 (71)	25 (62.5)	24 (82.8)	
Alcohol abuse				
No	59 (85.5)	35 (87.5)	24 (82.8)	0.73
Yes	10 (14.5)	5 (12.5)	5 (17.2)	
Primary T site				
Tonsil	43 (62.3)	27 (67.5)	16 (55.2)	0.29
Base of tongue	21 (30.4)	10 (25)	11 (37.9)	
Soft palate	5 (7.3)	3 (7.5)	2 (6.9)	
Clinical T classification				
T1	5 (7.3)	3 (7.5)	2 (6.9)	0.23
T2	27 (39.1)	13 (32.5)	14 (48.3)	
T3	17 (24.6)	10 (25)	7 (24.1)	
T4	20 (29)	14 (35)	6 (20.7)	
Clinical N classification				
N0	4 (5.8)	2 (5)	2 (6.9)	1.00
N1	6 (8.7)	4 (10)	2 (6.9)	
N2	30 (43.5)	16 (40)	14 (48.3)	
N3	29 (42)	18 (45)	11 (37.9)	

between S-IMRT cohort and SIB-IMRT cohort. All patients received the total prescribed dose.

Clinical outcomes

Median follow-up time was 40 months (range 24–112). In total, 30 patient deaths occurred, 24 in the S-IMRT group and 6 in the SIB-IMRT group. Six locoregional relapses (4 in the S-IMRT and 2 in the SIB-IMRT group) and 12 distant relapses (10 in the S-IMRT group and 2 in the SIB-IMRT group) were observed. The 3-year OS, DFS, DMFS and LRFS rates were 67.1% (95% CI 0.544–0.770), 63.3% (95% CI 0.507–0.736), 64.5% (95% CI 0.518–0.747) and 66.0% (95% CI 0.533–0.760), respectively.

Results from the univariate and multivariate analysis for survival outcomes are reported in Table 2. In univariate analysis, no history of alcohol abuse, early T status, early N status, SIB-IMRT and cCR were associated with increased survival outcomes.

In multivariate analysis, the cCR at 3 months was the only significant factor affecting OS, with a HR of 0.45 (95% CI 0.20–1.00, $p=0.05$). Interestingly, 39 3-month cCR events were observed, 19 (47.5%) in the S-IMRT group and 20 (69%) in the SIB-IMRT group, but with no statistically significant difference between groups ($p=0.09$). The 3-year OS rate was 86.3% in the cCR group and 42.5% in those patients who did not achieve cCR within 3 months after treatment ($p<0.01$). OS curves according to cCR are shown in Fig. 1.

Overall, in both univariate and multivariate analyses, alcohol abuse was associated with decreased DFS (HR: 6.92; 95% CI 2.69–17.84, $p<0.01$) and DMFS (HR: 5.83; 95% CI 2.19–15.53, $p<0.01$). Whereas, it was close to significance ($p=0.06$) with an HR of 2.38 (95% CI 0.98–5.76) in the multivariate analysis for LRFS.

A positive trend was found between the SIB-IMRT and S-IMRT groups with respect to 3-year OS rate (81.6%, 95% CI 61.1–92.0 versus 57.5%, 95% CI 40.8–71.0, $p=0.06$) and 3-year DMFS rate (79.0%, 95% CI 59.1–90.0 versus 55.0%, 95% CI 38.5–68.8, $p=0.06$).

No significant differences were found in severe toxicity frequencies between the S-IMRT and SIB-IMRT patients. Severe mucositis, dermatitis, dysphagia, xerostomia and feeding tube details are listed in Table 3. No severe toxicity was recorded 1 year after treatment.

Discussion

This analysis of locally advanced HPV-negative OPSCC patients demonstrated survival associations with alcohol abuse and advanced disease at presentation. In addition, our study suggested that cCR at 3 months after CRT was a significant prognostic factor for OS. An analysis of cCR events demonstrated a higher but not statistically significant proportion of cCR in patients treated with SIB-IMRT. It could be considered a sensible result, potentially affecting treatment cure rate. It is probable that SIB-IMRT could be a surrogate for more intensive total dose to primary tumor and pathological lymph nodes rather than a causal factor for disease control. Interestingly, SIB-IMRT was not associated with a higher frequencies of severe toxicity compared to S-IMRT, reflecting itself a relevant goal.

Over the years, the desire to improve cure rates while minimizing patient morbidity has driven most of the recent advances in OPSCC treatment (Moreno et al. 2019). Actually, the major point of contention has been the treatment paradigm used for HPV-related OPSCC, mainly due to the worry to over-treat these patients (De Felice et al. 2019). Focused efforts on HPV-negative disease are, therefore, warranted. While a significant correlation between complete response and survival endpoints has been detected other malignancies, such as rectal cancer (Capirci et al. 2008),

Table 2 Univariate and multivariate analyses for survival outcomes

Variable	Overall survival				Disease-free survival				Distant metastasis-free survival				Locoregional-free survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender (male vs female)	0.96 (0.42–2.18)	0.93			0.93 (0.43–2.02)	0.86			0.87 (0.39–1.97)	0.74			1.05 (0.48–2.28)	0.91		
Age (< 65 vs ≥ 65)	0.99 (0.95–1.04)	0.76			0.99 (0.95–1.04)	0.74			0.99 (0.95–1.03)	0.50			1.00 (0.96–1.05)	0.88		
Comorbidity (no vs yes)	1.05 (0.50–2.18)	0.90			1.11 (0.55–2.24)	0.77			1.25 (0.61–2.55)	0.55			0.92 (0.45–1.89)	0.82		
Smoke (never vs current/former)	1.46 (0.64–3.30)	0.37			1.36 (0.63–2.94)	0.43			0.39 (0.65–3.30)	0.35			1.35 (0.62–2.94)	0.44		
Alcohol abuse (no vs yes)	2.03 (0.87–4.74)	0.10	2.29 (0.91–5.77)	0.08	3.17 (1.46–6.85)	< 0.01	6.92 (2.69–17.84)	< 0.01	2.71 (1.21–6.07)	0.02	5.83 (2.19–15.53)	< 0.01	2.35 (1.05–5.26)	0.04	2.38 (0.98–5.76)	0.06
Primary T site (tonsil vs BoT vs other)	0.91 (0.50–1.67)	0.77			0.86 (0.48–1.53)	0.61			0.82 (0.45–1.50)	0.52			0.96 (0.54–1.71)	0.89		
Clinical T classification (T1-2 vs T3-4)	2.14 (0.99–4.59)	0.05	1.54 (0.70–3.39)	0.29	1.92 (0.94–3.90)	0.07	1.57 (0.75–3.28)	0.23	2.36 (1.11–5.03)	0.03	1.88 (0.86–4.12)	0.11	1.75 (0.86–3.60)	0.13	1.30 (0.61–2.79)	0.50
Clinical N classification (N0-1 vs N2-3)	9.17 (1.22–68.98)	0.03	6.20 (0.73–52.95)	0.09	4.55 (1.07–19.42)	0.04	2.86 (0.56–14.74)	0.21	9.47 (1.26–71.04)	0.03	6.96 (0.79–61.03)	0.08	4.38 (1.02–18.73)	0.05	2.45 (0.48–12.40)	0.28
RT technique SIB-IMRT vs S-IMRT)	0.44 (0.18–1.10)	0.07	0.47 (0.18–1.25)	0.13	0.50 (0.22–1.12)	0.09	0.40 (0.17–0.96)	0.04	0.46 (0.19–1.09)	0.08	0.37 (0.14–0.96)	0.04	0.49 (0.21–1.16)	0.10	0.57 (0.23–1.40)	0.22

Table 2 (continued)

Variable	Overall survival				Disease-free survival				Distant metastasis-free survival				Locoregional-free survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
cCR at 3 months (yes vs no)	0.31 (0.15–0.66)	< 0.01	0.45 (0.20–1.00)	0.05	0.23 (0.11–0.47)	< 0.01	0.21 (0.99–4.52)	< 0.01	0.27 (0.13–0.57)	< 0.01	0.30 (0.13–0.67)	< 0.01	0.26 (0.12–0.54)	< 0.01	0.33 (0.15–0.75)	< 0.01

HR hazard ratio, *95%CI* 95% confidence interval, *vs* versus, *T* tumor, *BoT* base of tongue, *N* nodes, *SIB-IMRT* simultaneously integrated boost intensity modulated radiotherapy, *S-IMRT* sequential intensity modulated radiotherapy, *cCR* clinical complete response

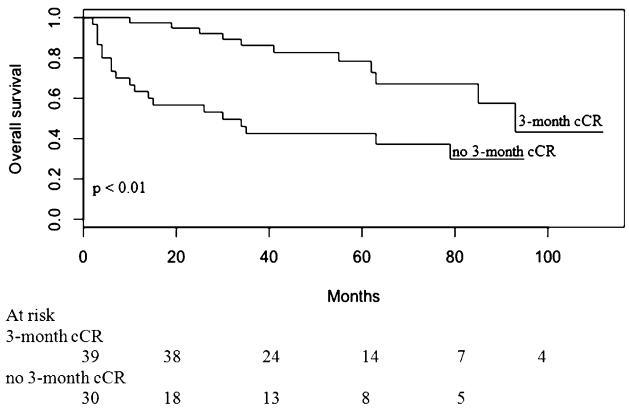

Fig. 1 Overall survival according to clinical complete response (cCR) at 3 months after treatment

the question of whether intensification of standard-dose CRT (70 Gy, 2 Gy/fr and cisplatin 100 mg/m^2) in HPV-negative OPSCC results in high cure rates is less clear and not definitively answered by clinical trials. At least two scenarios can be depicted: (1) radiation dose intensification to the macroscopic tumor; and (22) concomitant chemotherapy intensification by multidrug regimen (Bourhis et al. 2006; Blanchard et al. 2011). Yet, there are no data from randomized clinical trials to define optimal intensification strategies in HPV-negative OPSCC, suggesting that retrospective series describing alternatives to standard CRT in this setting of patients may yield research interest.

By increasing daily fraction dose to primary tumor volume, we intensify the standard cisplatin-based CRT with the short-term goal of assessing the clinical response. It might be reasonable to consider our CRT schedule—slightly hypofractionated dose per fraction to macroscopic disease of 2.25 Gy/fraction up to 67.5 Gy (5 days a week for 6 weeks) with concurrent three-weekly high-dose cisplatin-based chemotherapy—safe and effective. This SIB-IMRT resulted in increased fraction size and shorter treatment time when compared to the traditional S-IMRT 70 Gy in 2 Gy per fraction, 5 days a week, for 7 weeks. We recorded a higher cCR rate (69%) compared to S-IMRT (47.5%). Probably because of the small SIB-IMRT sample size, no significant difference was found in the statistical analysis for this endpoint. But a potential correlation between increased daily RT dose with high-dose cisplatin and improved cCR rates would require further evaluation, as well as its impact on the cost-effectiveness.

At present, IMRT is the standard of care for OPSCC management (National Comprehensive Cancer Network 2019). It may be applied using either the sequential boost (S-IMRT) or simultaneous integrated boost (SIB-IMRT) techniques. To our knowledge, no clinical studies have specifically and directly compared clinical outcomes and toxicity rates

Table 3 Severe toxicity frequencies during and after treatment

Toxicity	During CRT			3 months after CRT			1 year after CRT		
	S-IMRT (%)	SIB-IMRT (%)	*p* value	S-IMRT (%)	SIB-IMRT (%)	*p* value	S-IMRT (%)	SIB-IMRT (%)	*p* value
Mucositis ≥ G3	17 (42.5)	7 (24.1)	0.13	.	.		.	.	
Dermatitis ≥ G3	2 (5)	2 (6.9)	1.00	.	.		.	.	
Dysphagia ≥ G3	7 (17.5)	5 (17.2)	1.00	.	1 (3.4)	0.42	.	.	
Xerostomia ≥ G3	.	.		.	.		.	.	
Feeding tube	10 (25)	11 (37.9)	0.29	3 (7.5)	2 (6.9)	1.00	.	.	

S-IMRT sequential intensity modulated radiotherapy, *SIB-IMRT* simultaneously integrated boost intensity modulated radiotherapy, *G* grade

among HPV-negative OPSCC patients treated with S-IMRT and SIB-IMRT. In the head and neck cancer literature, several groups have reported their experience in using S-IMRT and SIB-IMRT (Lertbutsayanukul et al. 2018; Vlacich et al. 2017; Spiotto and Weichselbaum 2014). Results are often contrasting and inconclusive regarding OPSCC cases. Direct comparisons are not suitable mainly due to differences in patient population. Retrospective series, including all head and neck primary sites, confirmed equivalent treatment outcomes in S-IMRT and SIB-IMRT cohorts but reported more severe acute skin and pharyngeal toxicity profiles in the SIB-IMRT patients (Vlacich et al. 2017). By contrast, a recent randomized phase III study examined toxicity differences between S-IMRT and SIB-IMRT in nasopharyngeal carcinoma (Lertbutsayanukul et al. 2018). Final results showed no statistically significant differences in terms of survival outcomes and incidence of grade ≥ 3 acute and late toxicities between the two techniques. This is consistent with the outcomes in our series, even though our study was specific to HPV-negative OPSCC patients. However, we found a positive trend in terms of 3-year OS (81.6% versus 57.5%, $p = 0.06$) and 3-year DMFS (79.0% versus 55.0%, $p = 0.06$) in the SIB-IMRT group. Based on these latter data and merging the higher SIB-IMRT cCR rate, one could speculate that SIB-IMRT might lead to better outcomes than S-IMRT. Surely, this assumption should be interpreted with caution and the benefit of SIB-IMRT in improving HPV-negative OPSCC survival still remains to be proven. Studies with a larger patient population are needed.

The main limitation of this study is its retrospective nature. The two cohorts of patients have been treated at distinct time periods and therefore, results are limited by the lack of a prospective comparison of the two RT techniques. Moreover, we did not collect the patient-reported outcomes which might detect differences in quality of life. However, we analyzed consecutive patients, with equal chemotherapy regimen, same dose–volume constraints in treatment planning and prospective toxicity grading by a single experienced radiation oncologist.

Although not practice-changing, our study does draw attention to the paucity of data on this topic. We hope to improve the quality of future research to allow personalization of therapy in HPV-negative OPSCC.

To conclude, relapse remains the major issue in the management of HPV-negative OPSCC patients. Our study defined cCR and confirmed alcohol abuse and advanced disease stage as potential prognostic factors. The use of SIB-IMRT might be a way to improve the rate of cCR at 3 months after CRT, while preserving tolerable toxicity profile. Our assumptions await validation in future randomized control trials.

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Compliance with ethical standards

Conflict of interest None.

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