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Evaluation of the Impact of Smoking and Alcohol Consumption on Toxicity and Outcomes of Chemoradiation for Head and Neck Cancer

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Abstract. *Background/Aim: Smoking and alcohol abuse may impair outcomes of chemoradiation for squamous cell head and neck cancer (SCCHN). Potential associations with toxicity, loco-regional control (LRC), and overall survival (OS) were investigated. Patients and Methods: Ninety-six patients were retrospectively analyzed for impacts of pre-radiotherapy (pre-RT) smoking history, smoking during radiotherapy, and pre-RT alcohol abuse on toxicity, LRC, and OS. Results: A trend was found for associations between pre-RT smoking history and grade ≥2 dermatitis. Smoking during radiotherapy was significantly associated with grade ≥3 mucositis and showed trends regarding grade ≥2 mucositis and dermatitis. On univariate analyses, smoking during radiotherapy was negatively associated with LRC and OS, pre-RT alcohol abuse with OS, and >40 pack years with LRC and OS. In multivariate analyses, smoking during radiotherapy remained significant for decreased OS, and pack years showed a trend. Conclusion: Smoking during radiotherapy was an independent predictor of OS and associated with increased toxicity. Thus, it is important to stop smoking prior to the start of radiotherapy.*

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Many patients treated with chemoradiation for squamous cell head and neck cancer (SCCHN) have a history of smoking and alcohol use (1-3). A pre-radiotherapy (pre-RT) history of smoking, namely the number of pack years, was reported by several authors to be associated with worse outcomes including decreased local control (LC) and overall survival (OS) (4-8). Moreover, a negative impact of a greater number of pack years on treatment outcomes were also reported for patients irradiated for lung cancer or carcinoma of the urinary bladder (9-11). However, in a population-based study of 316 patients with larynx cancer, no significant associations were found between pre-RT history of smoking and outcomes in terms of disease-free survival (DFS) and OS (12). The results of available studies in patients irradiated for SCCHN regarding the impact of smoking during a course of radiotherapy and treatment outcomes were more heterogeneous. A few studies showed significant associations between smoking during the radiotherapy course and treatment outcomes (5, 13, 14), whereas other studies did not find such correlations (8, 12, 15). The results of previous studies in patients irradiated for SCCHN were heterogeneous also with respect to the impact of smoking on treatment-related toxicity. Several studies found significant associations between smoking history or smoking during radiotherapy and increased acute toxicities (16-19), whereas other studies and a systematic review did not show such associations (8, 13, 14, 20).

Thus, additional studies are required to better define the impact of smoking prior to and during a course of radiotherapy on toxicity and other treatment outcomes in patients with SCCHN. The present study was performed to help answer this important question. In addition, the potential role of a history of alcohol abuse was investigated. The study focused particularly on patients treated with concurrent cisplatin-based chemoradiation, who are at a higher risk of

experiencing treatment-related toxicities than patients receiving radiotherapy alone (21, 22).

Patients and Methods

This retrospective study (Ethics Committee of the University of Lübeck, 21-034) included data of 96 patients with SCCHN, who were treated with concurrent chemoradiation between 2010 and 2020. Sixty-six of these patients were included in a previous study (23). Median total dose of conventionally fractionated external beam radiotherapy (EBRT), mostly performed as volumetric modulated arc therapy, was 66 Gy (range=60-70 Gy). Nine patients received a brachytherapy boost in addition to EBRT, ranging between 7.5 and 16 Gy in 3 to 5 fractions. Concurrent chemotherapy was planned to include two courses of cisplatin alone, each course consisting of 20 mg/m^2 on days 1-5 or 25 mg/m^2 on days 1-4. Thus, the planned cumulative cisplatin dose was 200 mg/m^2.

The major goal of this study was to evaluate potential associations between pre-RT history of smoking (no *vs.* yes), smoking during the radiotherapy course (no *vs.* yes), and pre-RT history of alcohol abuse (no *vs.* yes) and outcomes in terms of toxicity, loco-regional control (LRC), and OS. Alcohol consumption during the radiotherapy course was not properly documented in many patient files and, therefore, could not be studied. Investigated grade ≥2 and ≥3 toxicities included oral mucositis, radiation dermatitis, xerostomia, subcutaneous fibrosis, and cervical lymph edema. Oral mucositis was graded according to the Radiation Therapy Oncology Group (RTOG) criteria, other toxicities according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) (24, 25).

Regarding LRC and OS, 11 patient-, tumor- or treatment-related characteristics were evaluated in addition to smoking and alcohol consumption. These characteristics included age (≤60 *vs.* >60 years), sex (female *vs.* male), Karnofsky performance score (KPS ≤80 *vs.* 90-100), cancer site (oropharynx *vs.* hypopharynx *vs.* larynx *vs.* oral cavity/floor of mouth *vs.* more than one site), primary tumor stage (T1-3 *vs.* T4), nodal stage (N0-2a *vs.* N2b-3), histologic grading (G1-2 *vs.* G3), human papilloma virus (HPV) status (negative *vs.* positive), upfront surgical resection (no *vs.* yes), radiotherapy breaks >1 week (no *vs.* yes), and cumulative cisplatin dose (≤180 mg/m^2 *vs.* >180 mg/m^2). The distribution of these characteristics is shown in Table I. Moreover, in 48 patients with pre-RT history of smoking, the number of pack years was available and analyzed.

Statistical analyses regarding toxicities were performed with the Fisher's exact test. *p*-Values <0.05 were considered indicating significance, *p*-values <0.20 a trend. Univariate analyses of LRC and OS rates were performed with the Kaplan-Meier method and the log-rank test. LRC and OS were calculated from the day of the last radiation fraction. Again, *p*-values <0.05 were considered indicating significance, *p*-values <0.20 a trend. Characteristics significantly associated with LRC or OS were subsequently analyzed for independence using a Cox proportional hazards model (multivariate analyses). Additional multivariate analyses were performed limited to characteristics that were available for at least 90 patients. The same criteria regarding significance and trends were applied as for the univariate analyses.

Table I. *Patient characteristics.*

Characteristic		N patients (%)
Smoking prior to radiotherapy	No	19 (20)
	Yes	77 (80)
Smoking during radiotherapy	No	60 (63)
	Yes	36 (38)
History of alcohol abuse	No	53 (55)
	Yes	43 (45)
Age	≤60 Years	46 (48)
	>60 Years	50 (52)
Sex	Female	16 (17)
	Male	80 (83)
KPS	≤80	38 (40)
	90-100	58 (60)
Cancer site	Oropharynx	45 (47)
	Hypopharynx	9 (9)
	Larynx	10 (10)
	Oral cavity/FoM	18 (19)
	More than one site	14 (15)
T-stage	T1-3	54 (56)
	T4	42 (44)
N-stage	N0-2a	33 (34)
	N2b-3	59 (61)
	Unclear	4 (4)
Histologic grade	G1-2	54 (56)
	G3	34 (35)
	Unclear	8 (8)
HPV-status	Negative	43 (45)
	Positive	31 (32)
	Unknown	22 (23)
Upfront resection	No	38 (40)
	Yes	58 (60)
Radiotherapy break >1 week	No	82 (85)
	Yes	14 (15)
Cumulative cisplatin dose	≤180 mg/m^2	22 (23)
	>180 mg/m^2	74 (77)

KPS: Karnofsky performance score; FoM: floor of mouth; HPV: human papilloma virus.

Results

The comparison of patients with a pre-RT history of smoking and those patients without such a history revealed no significant differences with respect to the rates of the investigated toxicities (Table II). A trend was found for an association between pre-RT history of smoking and grade ≥2 radiation dermatitis (86% *vs.* 72%, p=0.16). Moreover, smoking during the radiotherapy course was significantly associated with grade ≥3 oral mucositis (37% *vs.* 14%, p=0.012) and showed trends for associations with grade ≥2 oral mucositis (80% *vs.* 64%, p=0.11) and grade ≥2 radiation dermatitis (91% *vs.* 79%, p=0.15) (Table III). No significant associations were found between pre-RT history of alcohol abuse and treatment-related toxicity (Table IV).

On univariate analyses of LRC, smoking during the radiotherapy course was significantly associated with worse outcomes (p=0.020) (Table V). No such associations were found for pre-RT history of smoking (p=0.90) and pre-RT history of alcohol abuse (p=0.26). In contrast, improved LRC

Table II. *Comparison (Fisher's exact test) of patients with pre-radiotherapy (pre-RT) smoking history (n=77) and patients without pre-RT smoking history (n=19) for toxicities.*

Toxicity	Pre-RT smoking history n/N patients (%)	No pre-RT smoking history n/N patients (%)	*p*-Value
Grade ≥2 oral mucositis	52/74 (70)	13/19 (68)	>0.99
Grade ≥3 oral mucositis	17/74 (23)	4/19 (21)	>0.99
Grade ≥2 radiation dermatitis	64/74 (86)	13/18 (72)	0.16
Grade ≥3 radiation dermatitis	25/74 (34)	6/18 (33)	>0.99
Grade ≥2 xerostomia	23/77 (30)	5/19 (26)	>0.99
Grade ≥3 xerostomia	5/77 (6)	1/19 (5)	>0.99
Grade ≥2 subcutaneous fibrosis	6/75 (8)	3/19 (16)	0.38
Grade ≥3 subcutaneous fibrosis	0/75 (0)	1/19 (5)	0.20
Grade ≥2 cervical lymph edema	6/76 (8)	1/19 (5)	>0.99
Grade ≥3 cervical lymph edema	0/76 (0)	0/19 (0)	>0.99

was significantly associated with favorable cancer site (oropharynx or larynx, $p=0.013$), T1-3 stage ($p<0.001$), N0-2a stage ($p=0.046$), HPV-positive tumors ($p=0.026$), and upfront resection ($p<0.001$). In addition, trends were found for KPS 90-100 ($p=0.17$) and cumulative cisplatin doses >180 mg/m^2 ($p=0.19$). In the subsequent multivariate analysis, upfront surgery [hazard ratio (HR)=0.21, 95% confidence interval (CI)=0.04-1.13, $p=0.069$] and T-stage (HR=3.37, 95%CI=0.62-18.23, $p=0.16$) showed trends for associations with LRC. N-stage (HR=1.49, 95%=CI 0.69-3.23, $p=0.31$), smoking during radiotherapy (HR=1.94, 95%CI=0.65-5.81, $p=0.23$), cancer site (HR=1.03, 95%CI=0.80-1.32, $p=0.82$), and HPV-status (HR=0.33, 95%CI=0.03-3.12, $p=0.33$) were not significant in the multivariate analyses of LRC.

In an additional univariate analysis in those 48 patients with pre-RT history of smoking and available number of pack years, >40 pack years were significantly associated with worse LRC ($p=0.049$). In the corresponding additional multivariate analysis, pack years were not significant (HR=1.33, 95%CI=0.13-13.18, $p=0.81$).

On univariate analyses of OS, smoking during the radiotherapy course ($p<0.001$) and pre-RT history of alcohol abuse ($p=0.025$) were significantly associated with worse outcomes (Table VI). No association was observed for pre-RT history of smoking ($p=0.31$). Moreover, OS was positively associated with KPS 90-100 ($p=0.020$), HPV-positivity ($p=0.009$), and cumulative cisplatin doses >180 mg/m^2 ($p=0.041$). In the multivariate analyses, smoking during the RT course was significant (HR=4.80, 95%CI=1.38-16.67, $p=0.013$), and a trend was found for HPV-status (HR=0.30, 95%CI=0.05-1.68, $p=0.17$). Cumulative cisplatin dose (HR=0.52, 95%CI=0.19-1.45, $p=0.21$). KPS (HR=0.64, 95%CI=0.21-1.97, $p=0.44$), and pre-RT history of alcohol abuse (HR=1.37, 95%CI=0.44-4.25, $p=0.59$) did not achieve significance in the multivariate analysis. In the additional analysis of the 48 patients with pre-RT history of smoking and available number of pack years, >40 pack years were significantly associated with decreased OS ($p=0.027$) on univariate analysis and showed a trend in the multivariate analysis (HR=8.72, 95%CI=0.76-100.55, $p=0.083$).

Discussion

Despite the contribution of many studies performed during recent years, the outcomes of patients receiving radiotherapy or chemoradiation for SCCHN need to be improved (26-31). The prognosis may be impaired by several lifestyle factors including smoking and alcohol consumption (1-3). Available studies had produced conflicting results regarding the impact of cigarette smoking and alcohol on treatment-related toxicities and outcomes in terms of LC, LRC, and OS (4-8, 12-20). Several studies found that a greater number of pack years prior to the start of radiotherapy was associated with worse outcomes (4-8). In the study of Oliva *et al*., the number of pack years was negatively associated with OS (HR=1.14, $p=0.01$) but not with cancer-specific survival (4). In two other studies, a greater number of pack years was associated with significantly decreased OS and recurrence-free survival (RFS) or with significantly decreased OS and progression-free survival (PFS), respectively (6, 7). However, in the population-based study of Sjögren *et al*. that included 316 consecutive patients irradiated for T1-stage glottic cancer, smoking history showed no significant impact on LC, DFS, and OS (12). Five-year LC rates were 89% in

Table III. *Comparison (Fisher's exact test) of patients smoking during the radiotherapy (RT) course (n=36) and patients not smoking during the RT course (n=60) for toxicities.*

Toxicity	Smoking during RT n/N patients (%)	Not smoking during RT n/N patients (%)	*p*-Value
Grade ≥2 oral mucositis	28/35 (80)	37/58 (64)	0.11
Grade ≥3 oral mucositis	13/35 (37)	8/58 (14)	**0.012**
Grade ≥2 radiation dermatitis	32/35 (91)	45/57 (79)	0.15
Grade ≥3 radiation dermatitis	11/35 (31)	20/57 (35)	0.82
Grade ≥2 xerostomia	10/36 (28)	18/60 (30)	>0.99
Grade ≥3 xerostomia	3/36 (8)	3/60 (5)	0.67
Grade ≥2 subcutaneous fibrosis	5/35 (14)	4/59 (7)	0.29
Grade ≥3 subcutaneous fibrosis	0/35 (0)	1/59 (2)	>0.99
Grade ≥2 cervical lymph edema	2/35 (6)	5/60 (8)	>0.99
Grade ≥3 cervical lymph edema	0/35 (0)	0/60 (0)	>0.99

Bold *p*-values represent significant results.

Table IV. *Comparison (Fisher's exact test) of patients with pre-radiotherapy (pre-RT) alcohol abuse (n=43) and patients without pre-RT alcohol abuse (n=53) for toxicities.*

Toxicity	Pre-RT alcohol abuse n/N patients (%)	No pre-RT alcohol abuse n/N patients (%)	*p*-Value
Grade ≥2 oral mucositis	26/40 (65)	39/53 (74)	0.49
Grade ≥3 oral mucositis	11/40 (28)	10/53 (19)	0.45
Grade ≥2 radiation dermatitis	33/40 (83)	44/52 (85)	0.78
Grade ≥3 radiation dermatitis	13/40 (33)	18/52 (35)	>0.99
Grade ≥2 xerostomia	10/43 (23)	18/53 (34)	0.27
Grade ≥3 xerostomia	2/43 (5)	4/53 (8)	0.69
Grade ≥2 subcutaneous fibrosis	5/43 (12)	4/51 (8)	0.73
Grade ≥3 subcutaneous fibrosis	1/43 (2)	0/51 (0)	0.46
Grade ≥2 cervical lymph edema	3/43 (7)	4/52 (8)	>0.99
Grade ≥3 cervical lymph edema	0/43 (0)	0/52 (0)	>0.99

non-smokers, 94% in ex-smokers, and 84% in smokers, respectively (p=0.27). Data were even more conflicting regarding associations between smoking during the radiotherapy course and subsequent outcomes. In the study of Vawda *et al*., patients smoking during the radiotherapy course had significantly worse 5-year OS rates than former smokers and never smokers (62% *vs*. 87% and 76%, respectively; p<0.001) (5). Five-year RFS rates were also significantly worse in that study (72% *vs*. 86% and 83%, respectively; p=0.03). In another study and in a systematic review, smoking during the radiotherapy course resulted in significantly worse OS and response and in worse LRC and OS, respectively (13, 14). In contrast to these studies, three other studies did not find significant associations between smoking during the radiotherapy course and treatment outcomes including LC and OS (8, 12, 15). When considering these conflicting results, it becomes obvious that additional studies are needed to clarify the potential impact of smoking prior to and during radiotherapy for SCCHN.

This need is further supported by examining the available data regarding the impact of smoking on treatment-related toxicities. In several studies, smoking prior to or during a course of radiotherapy was associated with increased rates of acute toxicities and complications including oral mucositis, skin

Table V. *Univariate analyses of loco-regional control. p-Values were obtained from the log-rank test.*

Characteristic		1 Year (%)	3 Years (%)	4 Years (%)	*p*-Value
Smoking prior to radiotherapy	No	89	83	83	0.90
	Yes	89	84	80	
Smoking during radiotherapy	No	93	89	89	**0.020**
	Yes	81	74	66	
History of alcohol abuse	No	94	85	85	0.26
	Yes	82	82	75	
Age	≤60 Years	91	86	79	0.90
	>60 Years	87	81	81	
Sex	Female	100	78	78	0.70
	Male	87	84	81	
KPS	≤80	86	79	71	0.17
	90-100	91	86	86	
Cancer site	Oropharynx	95	93	88	**0.013**
	Hypopharynx	67	56	56	
	Larynx	100	100	100	
	Oral cavity/FoM	88	81	81	
	More than one site	76	63	63	
T-stage	T1-3	96	96	96	**<0.001**
	T4	80	68	61	
N-stage	N0-2a	97	97	89	**0.046**
	N2b-3	84	75	75	
Histologic grade	G1-2	88	78	78	0.40
	G3	91	91	83	
HPV-status	Negative	87	81	75	**0.026**
	Positive	97	97	97	
Upfront resection	No	78	64	58	**<0.001**
	Yes	96	96	96	
Radiotherapy break >1 week	No	88	85	81	0.55
	Yes	92	75	75	
Cumulative cisplatin dose	≤180 mg/m^2	80	74	74	0.19
	>180 mg/m^2	91	86	82	

KPS: Karnofsky performance score; FoM: floor of mouth; HPV: human papilloma virus; significant *p*-values are given in bold.

reactions, need for enteral feeding, and hospitalization (16-19). Moreover, one study and a systematic review reported higher rates of late toxicities (13, 19). However, the systematic review and three previous studies did not find significant associations between smoking and acute toxicities (8, 13, 14, 20).

The current study was conducted to contribute to further clarification of the prognostic role of smoking on toxicity, LRC and OS. In order to reduce the risk of a treatment-related selection bias, only patients who were scheduled for concurrent chemoradiation with two courses of 20 mg/m^2/d1-5 or 25 mg/m^2/d1-4 of cisplatin were included. According to the results of this study, a greater number of pack years and smoking during radiotherapy were negatively associated with LRC and OS. Moreover, smoking during radiotherapy was significantly associated with grade ≥3 mucositis and trends were found for associations between pre-RT smoking history and grade ≥2 dermatitis and for smoking during radiotherapy and grade ≥2 mucositis and grade ≥2 dermatitis. These results agree with the findings of some previous studies and support the idea that it is important to stop smoking prior to the start of radiotherapy to improve LRC and OS and reduce acute toxicities (4-8, 13, 14, 16-19). Reduction of acute toxicities is particularly important, since adverse effects may lead to interruption of the radiation treatment. Such interruptions were shown to impair patient prognoses in terms of decreased LRC and OS (32). Furthermore, continuation of smoking during a course of radiotherapy was shown to have a negative impact on the patients' quality of life (33, 34).

The fact that smoking during radiotherapy has a negative impact on treatment outcomes can be explained to a certain extent by the fact that smoking increases the levels of carboxy-hemoglobin, which is known to impair the delivery of oxygen to the tumor cells (35-37). Hemoglobin binds to carbon monoxide significantly stronger (approximately by factor 200) than to oxygen. Thus, hemoglobin cannot take sufficient oxygen to the tumor cells. Oxygenation of tumor cells is very important for radiotherapy-induced tumor-cell

Table VI. *Univariate analyses of survival. p-Values were obtained from the log-rank test.*

Characteristic		1 Year (%)	3 Years (%)	4 Years (%)	*p*-Value
Smoking prior to radiotherapy	No	89	89	89	0.31
	Yes	90	79	79	
Smoking during radiotherapy	No	95	93	93	**<0.001**
	Yes	81	61	61	
History of alcohol abuse	No	94	87	87	**0.025**
	Yes	84	75	75	
Age	≤60 Years	93	82	82	0.62
	>60 Years	86	81	81	
Sex	Female	94	76	76	0.86
	Male	89	82	82	
KPS	≤80	84	72	72	**0.020**
	90-100	93	88	88	
Cancer site	Oropharynx	91	88	88	0.56
	Hypopharynx	100	71	71	
	Larynx	90	90	90	
	Oral cavity/FoM	83	74	74	
	More than one site	86	69	69	
T-stage	T1-3	89	87	87	0.38
	T4	90	74	74	
N-stage	N0-2a	91	87	87	0.54
	N2b-3	90	80	80	
Histologic grade	G1-2	91	83	83	0.98
	G3	85	81	81	
HPV-status	Negative	79	70	70	**0.009**
	Positive	100	96	96	
Upfront resection	No	89	75	75	0.43
	Yes	90	85	85	
Radiotherapy break >1 week	No	90	84	84	0.32
	Yes	86	67	67	
Cumulative cisplatin dose	≤180 mg/m^2	86	70	70	**0.041**
	>180 mg/m^2	91	85	85	

KPS: Karnofsky performance score; FoM: floor of mouth; HPV: human papilloma virus; significant *p*-values are given in bold.

killing, which is mediated through cytotoxic free oxygen-radicals (38). Associations between biomarkers of poor oxygenation and poor prognoses were previously described in patients with head and neck cancer (39). These explanations are supported by the results of the present study. Moreover, an enhanced impact of smoking and alcohol abuse on the immunological balance of monocyte subsets and CD4/CD8 T-cells in the peripheral blood of head and neck cancer patients was previously observed (40). When interpreting the results of the current study, the retrospective design bearing the risk of hidden selection biases needs to be considered. Furthermore, since all patients received concurrent chemoradiation, it is not clear whether these results are applicable to patients treated with radiotherapy alone or sequential chemoradiation.

In addition to smoking, the potential impact of a history of alcohol abuse was investigated in the current study. Pre-treatment alcohol consumption was associated with significantly worse OS on univariate analysis but not in the multivariate analysis. This may be explained by a correlation between alcohol abuse and HPV-status. Significantly more patients with HPV-negative tumors had a history of alcohol abuse than patients with HPV-positive tumors (70% *vs*. 16%, $p<0.001$; Fisher's exact test). The studies available so far produced conflicting results regarding the prognostic role of alcohol consumption. In the study of Zanoni *et al*., a history of alcohol consumption was significantly associated with worse disease-specific survival in patients with cancer of the oral cavity (41). Moreover, Sawabe *et al*. reported a negative impact of alcohol consumption in the subgroup of head and neck cancer patients irradiated for cancer of the oropharynx, hypopharynx, or larynx (42). In contrast, in the study of Colasanto *et al*., OS and local recurrence-free survival were not associated with history of alcohol consumption or alcohol abuse during treatment of 190 patients receiving definitive radiotherapy for T1 or T2 larynx cancer (15). In another study of 168 patients with oropharynx cancer, the unit years of alcohol consumption were not associated with OS ($p=0.55$) but

showed a trend for reduced PFS (p=0.057) (7). Since the results of the available studies regarding the prognostic role of alcohol consumption are conflicting, additional (prospective) studies are required for further clarification.

In conclusion, smoking during radiotherapy was an independent predictor of OS and associated with increased toxicity. Thus, it is important to stop smoking prior to the start of radiotherapy. Moreover, this factor should be considered when designing future prospective trials in patients receiving chemoradiation for SCCHN.

Conflicts of Interest

The Authors report no conflicts of interest related to this study.

Authors' Contributions

The study was designed and supported by all Authors. Data were collected by I.Z., and subsequently analyzed by D.R., N.Y.Y. and S.E.S. The article drafted by D.R. was reviewed and finally approved by all Authors.

References

1 Rettig EM and D'Souza G: Epidemiology of head and neck cancer. Surg Oncol Clin N Am *24(3)*: 379-396, 2015. PMID: 25979389. DOI: 10.1016/j.soc.2015.03.001

2 Cohen N, Fedewa S and Chen AY: Epidemiology and demographics of the head and neck cancer population. Oral Maxillofac Surg Clin North Am *30(4)*: 381-395, 2018. PMID: 30078696. DOI: 10.1016/j.coms.2018.06.001

3 Miranda-Galvis M, Loveless R, Kowalski LP and Teng Y: Impacts of environmental factors on head and neck cancer pathogenesis and progression. Cells *10(2)*: 389, 2021. PMID: 33668576. DOI: 10.3390/cells10020389

4 Oliva M, Huang SH, Xu W, Su J, Hansen AR, Bratman SV, Ringash J, Jang R, Cho J, Bayley A, Hope AJ, Chen E, Giuliani M, Waldron J, Weinreb I, Perez-Ordonez B, Chepeha D, Kim J, O Sullivan B, Siu LL and Spreafico A: Impact of cisplatin dose and smoking pack-years in human papillomavirus-positive oropharyngeal squamous cell carcinoma treated with chemoradiotherapy. Eur J Cancer *118*: 112-120, 2019. PMID: 31330486. DOI: 10.1016/j.ejca.2019.06.019

5 Vawda N, Banerjee RN and Debenham BJ: Impact of smoking on outcomes of HPV-related oropharyngeal cancer treated with primary radiation or surgery. Int J Radiat Oncol Biol Phys *103(5)*: 1125-1131, 2019. PMID: 30513378. DOI: 10.1016/j.ijrobp.2018.11.046

6 Chen C, Shen LJ, Li BF, Gao J and Xia YF: Smoking is a poor prognostic factor for male nasopharyngeal carcinoma treated with radiotherapy. Radiother Oncol *110(3)*: 409-415, 2014. PMID: 24021341. DOI: 10.1016/j.radonc.2013.08.003

7 Rios Velazquez E, Hoebers F, Aerts HJ, Rietbergen MM, Brakenhoff RH, Leemans RC, Speel EJ, Straetmans J, Kremer B and Lambin P: Externally validated HPV-based prognostic nomogram for oropharyngeal carcinoma patients yields more accurate predictions than TNM staging. Radiother Oncol *113(3)*: 324-330, 2014. PMID: 25443497. DOI: 10.1016/j.radonc.2014.09.005

8 Browman GP, Mohide EA, Willan A, Hodson I, Wong G, Grimard L, MacKenzie RG, El-Sayed S, Dunn E and Farrell S: Association between smoking during radiotherapy and prognosis in head and neck cancer: a follow-up study. Head Neck *24(12)*: 1031-1037, 2002. PMID: 12454940. DOI: 10.1002/hed.10168

9 Werner EM, Glatzel E, Bohnet S, Schild SE and Rades D: Prognostic factors of survival after radiotherapy for lung cancer-the impact of smoking pack years. In Vivo *36(3)*: 1297-1301, 2022. PMID: 35478154. DOI: 10.21873/invivo.12830

10 Manig L, Janssen S, Schild SE and Rades D: A new prognostic tool for patients undergoing radiotherapy plus upfront transurethral resection for bladder cancer. In Vivo *31(4)*: 745-748, 2017. PMID: 28652451. DOI: 10.21873/invivo.11125

11 Rades D, Manig L, Janssen S and Schild SE: Factors impacting the overall survival of patients irradiated for invasive carcinoma of the urinary bladder. In Vivo *31(4)*: 741-744, 2017. PMID: 28652450. DOI: 10.21873/invivo.11124

12 Sjögren EV, Wiggenraad RG, Le Cessie S, Snijder S, Pomp J and Baatenburg de Jong RJ: Outcome of radiotherapy in T1 glottic carcinoma: a population-based study. Eur Arch Otorhinolaryngol *266(5)*: 735-744, 2009. PMID: 18839197. DOI: 10.1007/s00405-008-0803-9

13 Smith J, Nastasi D, Tso R, Vangaveti V, Renison B and Chilkuri M: The effects of continued smoking in head and neck cancer patients treated with radiotherapy: A systematic review and meta-analysis. Radiother Oncol *135*: 51-57, 2019. PMID: 31015170. DOI: 10.1016/j.radonc.2019.02.021

14 Browman GP, Wong G, Hodson I, Sathya J, Russell R, McAlpine L, Skingley P and Levine MN: Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med *328(3)*: 159-163, 1993. PMID: 8417381. DOI: 10.1056/NEJM199301213280302

15 Colasanto JM, Haffty BG and Wilson LD: Evaluation of local recurrence and second malignancy in patients with T1 and T2 squamous cell carcinoma of the larynx. Cancer J *10(1)*: 61-66, 2004. PMID: 15000497. DOI: 10.1097/00130404-200401000-00012

16 Rugg T, Saunders MI and Dische S: Smoking and mucosal reactions to radiotherapy. Br J Radiol *63(751)*: 554-556, 1990. PMID: 2390690. DOI: 10.1259/0007-1285-63-751-554

17 Porock D, Nikoletti S and Cameron F: The relationship between factors that impair wound healing and the severity of acute radiation skin and mucosal toxicities in head and neck cancer. Cancer Nurs *27(1)*: 71-78, 2004. PMID: 15108954. DOI: 10.1097/00002820-200401000-00009

18 Mangar S, Slevin N, Mais K and Sykes A: Evaluating predictive factors for determining enteral nutrition in patients receiving radical radiotherapy for head and neck cancer: a retrospective review. Radiother Oncol *78(2)*: 152-158, 2006. PMID: 16466819. DOI: 10.1016/j.radonc.2005.12.014

19 Zevallos JP, Mallen MJ, Lam CY, Karam-Hage M, Blalock J, Wetter DW, Garden AS, Sturgis EM and Cinciripini PM: Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer *115(19)*: 4636-4644, 2009. PMID: 19569250. DOI: 10.1002/cncr.24499

20 Szeszko B, Osowiecka K, Rucińska M, Wasilewska-Teśluk E, Gliński K and Kępka L: Smoking during radiotherapy for head and neck cancer and acute mucosal reaction. Rep Pract Oncol Radiother *20(4)*: 299-304, 2015. PMID: 26109918. DOI: 10.1016/j.rpor.2015.04.001

21 Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A, van Glabbeke M and European Organization for Research and Treatment of Cancer Trial 22931: Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med *350(19)*: 1945-1952, 2004. PMID: 15128894. DOI: 10.1056/NEJMoa032641

22 Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N, Fu KK and Radiation Therapy Oncology Group 9501/Intergroup: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med *350(19)*: 1937-1944, 2004. PMID: 15128893. DOI: 10.1056/NEJMoa032646

23 Zwaan I, Soror T, Bruchhage KL, Hakim SG, Schild SE and Rades D: Comparison of two cisplatin regimens for chemoradiation in patients with squamous-cell carcinoma of the head and neck. Anticancer Res *43(2)*: 795-800, 2023. DOI: 10.21873/anticanres.16220.

24 RTOG. Available at: http://www.rtog.org/ [Last accessed on December 30, 2022]

25 National Institutes of Health/National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. National Institutes of Health/National Cancer Institute, 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf [Last accessed on December 30, 2022]

26 Warwas B, Cremers F, Gerull K, Leichtle A, Bruchhage KL, Hakim SG, Schild SE and Rades D: Risk factors for xerostomia following radiotherapy of head-and-neck cancers. Anticancer Res *42(5)*: 2657-2663, 2022. PMID: 35489760. DOI: 10.21873/anticanres.15743

27 Mayo ZS, Ilori EO, Matia B, Smile TD, Fleming CW, Reddy CA, Scharpf J, Lamarre ED, Prendes BL, Ku J, Burkey BB, Joshi NP, Woody NM, Koyfman SA and Campbell SR: Limited toxicity of hypofractionated intensity modulated radiation therapy for head and neck cancer. Anticancer Res *42(4)*: 1845-1849, 2022. PMID: 35347002. DOI: 10.21873/anticanres.15660

28 Rades D, Warwas B, Gerull K, Pries R, Leichtle A, Bruchhage KL, Hakim SG, Schild SE and Cremers F: Prognostic factors for complete recovery from xerostomia after radiotherapy of head-and-neck cancers. In Vivo *36(4)*: 1795-1800, 2022. PMID: 35738613. DOI: 10.21873/invivo.12894

29 DE Felice F, Musio D, Serpone M, Vavalle G, Marchetti C and Tombolini V: Simultaneously integrated boost affects survival in locally advanced p16-negative oropharyngeal squamous cell carcinoma. Anticancer Res *42(12)*: 5909-5915, 2022. PMID: 36456162. DOI: 10.21873/anticanres.16100

30 Nassif S, Wichmann J, Strube D, Vassis S, Christiansen H and Steinmann D: Cisplatin versus carboplatin and paclitaxel in radiochemotherapy for patients with locally advanced head and neck squamous cell carcinoma. In Vivo *36(2)*: 821-832, 2022. PMID: 35241538. DOI: 10.21873/invivo.12769

31 Narvaez C, Schild SE and Rades D: Comparison of conventional fractionation and accelerated fractionation with concomitant boost for radiotherapy of non-metastatic stage IV head-and-neck cancer. In Vivo *35(1)*: 411-415, 2021. PMID: 33402490. DOI: 10.21873/invivo.12272

32 Rades D, Stoehr M, Kazic N, Hakim SG, Walz A, Schild SE and Dunst J: Locally advanced stage IV squamous cell carcinoma of the head and neck: impact of pre-radiotherapy hemoglobin level and interruptions during radiotherapy. Int J Radiat Oncol Biol Phys *70(4)*: 1108-1114, 2008. PMID: 17905528. DOI: 10.1016/j.ijrobp.2007.07.2380

33 Egestad H and Emaus N: Changes in health related quality of life in women and men undergoing radiation treatment for head and neck cancer and the impact of smoking status in the radiation treatment period. Eur J Oncol Nurs *18(4)*: 339-346, 2014. PMID: 24877857. DOI: 10.1016/j.ejon.2014.04.003

34 Silveira MH, Dedivitis RA, Queija DS and Nascimento PC: Quality of life in swallowing disorders after nonsurgical treatment for head and neck cancer. Int Arch Otorhinolaryngol *19(1)*: 46-54, 2015. PMID: 25992151. DOI: 10.1055/s-0034-1395790

35 Rades D, Setter C, Schild SE and Dunst J: Effect of smoking during radiotherapy, respiratory insufficiency, and hemoglobin levels on outcome in patients irradiated for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys *71(4)*: 1134-1142, 2008. PMID: 18258387. DOI: 10.1016/j.ijrobp.2007.11.006

36 Deller A, Stenz R, Forstner K, Schreiber MN, Konrad F and Fösel T: Carbomonoxyhemoglobin and methemoglobin in patients with and without a smoking history during ambulatory anesthesia. Consequences for the use of pulse oximetry. Anasthesiol Intensivmed Notfallmed Schmerzther *26(4)*: 186-190, 1991. PMID: 1892968. DOI: 10.1055/s-2007-1000561

37 Whincup P, Papacosta O, Lennon L and Haines A: Carboxyhaemoglobin levels and their determinants in older British men. BMC Public Health *6*: 189, 2006. PMID: 16848898. DOI: 10.1186/1471-2458-6-189

38 Vaupel P, Thews O and Hoeckel M: Treatment resistance of solid tumors: role of hypoxia and anemia. Med Oncol *18(4)*: 243-259, 2001. PMID: 11918451. DOI: 10.1385/MO:18:4:243

39 Bredell MG, Ernst J, El-Kochairi I, Dahlem Y, Ikenberg K and Schumann DM: Current relevance of hypoxia in head and neck cancer. Oncotarget *7(31)*: 50781-50804, 2016. PMID: 27434126. DOI: 10.18632/oncotarget.9549

40 Idel C, Loyal K, Rades D, Hakim SG, Schumacher U, Bruchhage KL and Pries R: Smoking-, alcohol-, and age-related alterations of blood monocyte subsets and circulating CD4/CD8 T cells in head and neck cancer. Biology (Basel) *11(5)*: 658, 2022. PMID: 35625386. DOI: 10.3390/biology11050658

41 Zanoni DK, Montero PH, Migliacci JC, Shah JP, Wong RJ, Ganly I and Patel SG: Survival outcomes after treatment of cancer of the oral cavity (1985-2015). Oral Oncol *90*: 115-121, 2019. PMID: 30846169. DOI: 10.1016/j.oraloncology.2019.02.001

42 Sawabe M, Ito H, Oze I, Hosono S, Kawakita D, Tanaka H, Hasegawa Y, Murakami S and Matsuo K: Heterogeneous impact of alcohol consumption according to treatment method on survival in head and neck cancer: A prospective study. Cancer Sci *108(1)*: 91-100, 2017. PMID: 27801961. DOI: 10.1111/cas.13115

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