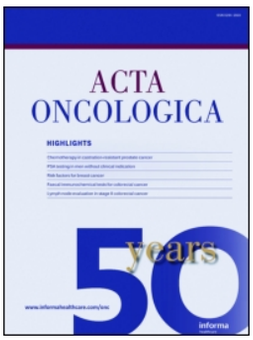

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ORIGINAL ARTICLE

Post radiation mucosal ulcer risk after a hypofractionated stereotactic boost and conventional fractionated radiotherapy for oropharyngeal carcinoma

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ABSTRACT

Background/purpose: Post radiation mucosal ulcers (PRMU) after treatment for oropharyngeal squamous cell carcinoma (OPSCC) can have a huge negative impact on patients' quality of life, but little is known concerning risk factors and the impact of fraction size. Therefore, the goal of this study was to determine the pattern of PRMU development and to identify risk factors after a hypofractionated stereotactic body radiotherapy boost (SBRT) compared to conventionally fractionated radiotherapy for OPSCC.

Material and methods: We performed a retrospective cohort study ($N = 332$) of OPSCC patients with $\geq$ 1-year disease-free survival, treated with 46 Gy Intensity Modulated Radiotherapy (IMRT) (2 Gy fractions) followed by either an SBRT boost of 16.5 Gy (5.5 Gy fractions) ($N = 180$), or 24 Gy IMRT (2 Gy fractions) ($N = 152$). PRMU (grade $\geq$ 2) was scored when observed $>$ three months after the last radiotherapy (RT) fraction (CTCAE v5.0). Potential risk factors were analyzed with Cox regression models using death as competing risk. Dose at the PRMU site was calculated by projecting delineated PRMU on the planning CT.

Results: All cases of PRMU ($N = 64$) occurred within 24 months; all were grade 2. The cumulative incidence at 2 years in the SBRT boost group was 26% ($N = 46$) vs. 12% ($N = 18$) for conventional fractionation ($p = 0.003$). Most PRMU developed within nine months ($N = 48$). PRMU occurring $>$ nine months ($N = 16$) were mainly observed in the SBRT boost group ($N = 15$). Sex ($p = 0.048$), acute tube feeding ($p = < 0.001$), tumor subsite tonsil ($p = 0.001$), and N stage ($p = 0.017$) were associated with PRMU risk at multivariable regression in the hypofractionated SBRT boost group. All 25 delineated PRMU were located within the high dose regions.

Conclusion: The risk of PRMU should be included in the cost benefit analysis when considering future research using a hypofractionated SBRT boost for OPSCC patients.

ARTICLE HISTORY
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KEYWORDS
Post radiation mucosal ulcers (PRMU); oropharyngeal squamous cell carcinoma (OPSCC); radiotherapy; hypofractionation; stereotactic body radiotherapy (SBRT)

Introduction

Radiotherapy (RT) is an important treatment strategy for patients with oropharyngeal squamous cell carcinoma (OPSCC). A frequently reported side effect after RT for OPSCC is a post radiation mucosal ulcer (PRMU) which is defined as an ulcer of the mucosa and the underlying tissue of the pharynx. It typically occurs months to years after RT. Radiotherapy causes endothelial damage and fibrosis. Tissues can become hypoxic, hypocellular, and hypovascular, which can result in necrosis and ulceration [1–4]. A PRMU can cause significant pain, dysfunction, and susceptibility to infections and therefore can have a significant impact on quality of life or can result in life threatening bleeding. In general, PRMU is considered as a late side effect (late PRMU), however, there are also reports showing that it can occur directly after treatment at the site of the primary tumor where it progresses from malignant tissue to a PRMU without evidence of remaining tumor tissue (direct PRMU) [5].

Little is known concerning the incidence, risk factors, and dose effect relations of PRMU, compared to other side effects, such as dysphagia and xerostomia. Because of the rising incidence of OPSCC due to human papilloma virus (HPV) infection, the incidence and risk factors of PRMU are of rising importance. Furthermore, there is a renewed interest in hypofractionation for head and neck tumors [6–8], which potentially could cause more PRMU [9,10].

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The aim of this study was to evaluate the development of PRMU over time in a large cohort of OPSCC patients treated with either conventional fractionation or a hypofractionated SBRT boost. Amongst others, the effect of acceleration and boost type were assessed for the risk of PRMU. Moreover, dose volume parameters in the PRMU were determined for a subgroup of patients, for which imaging at the time of PRMU was available.

Material and methods

Patients

The protocol for this retrospective cohort study was reviewed by the Medical Ethical Committee of Erasmus Medical Center (MEC2017-0404). All patients with OPSCC treated at the Department of Radiotherapy at Erasmus MC between January 2009 and May 2016 were retrospectively reviewed. Eligibility criteria were OPSCC patients treated with curative (chemo-)radiation with one of our two fractionation schemes (see below). Only patients with at least 1-year disease-free survival were included as information concerning possible PRMU during follow up in patients with disease recurrence was not or poorly recorded. Exclusion criteria included diagnosis with another primary malignancy within six months, non-SCC histology, previous oropharyngeal cancer, or previous head and neck RT. Tumor stage classification was determined according to the 7th AJCC/UICC TNM staging. Data on patient demographics, tumor characteristics, and treatment information were analyzed. A subgroup of this patient cohort was earlier published by Baker et al. with a focus on overall toxicity after a hypofractionated SBRT boost [11].

Treatment and follow up

For RT, two different fractionation schemes were used. Treatment selection was done at the discretion of the multidisciplinary tumor board for every patient. All patients were treated with IMRT with 46 Gy in 2 Gy fractions to the macroscopic tumor and elective lymphnodes with six or five fractions per week based on the condition and age of the patient and at the discretion of the treating physician. In general, patients below 70 years or 70 years and above that were medically fit, were treated with 6 fractions per week. Medically unfit patients of 70 years or older received five fractions per week. Patients with cT1-smallT3N0-2cM0 tumors were in our institute until 2016 and additionally treated with a hypofractionated SBRT boost to the primary tumor of 16.5 Gy in 5.5 Gy daily fractions with the Cyberknife system (Accuray Inc., Sunnyvale, CA, USA), with a total treatment time of five weeks. After the SBRT boost a neck dissection was performed in case of an initially N + neck (SBRT boost group) [12,13]. Patients with a largeT3-T4N0-2M0, anyT1-4N3M0, or cT1-smallT3N0-2cM0 tumors not qualifying for the hypofractionated SBRT boost, continued treatment with IMRT up to 70 Gy in 2 Gy fractions to the macroscopic tumor and pathological lymph nodes with a total treatment time of six to seven weeks. For patients with an age below 70 years and a cT1-4N + M0 or cT3-4N0M0 tumor that were medically fit, cisplatin (100 mg/m2 on days 1, 22, and 43) or cetuximab (400 mg/m2 initial dose, followed by a weekly dose of 250 mg/m2) was added to the treatment, irrespective of the type of boost (SBRT or IMRT). All patients were immobilized with a thermoplastic mask. CT based dose planning was performed with the target coverage objective being PTV V95 > 98% for the IMRT treatment and a maximum dose < 107% (i.e. 49.2 Gy). For the SBRT boost, the dose of 16.5 Gy was prescribed to the 80% isodoseline which led to a maximum physical boost dose of 20.6 Gy. Based on an $\alpha/\beta = 3$ Gy for late toxicity, the EQD2 of the combined plan in terms of prescribed dose was 74.05 Gy. Note that due to the inhomogeneous target dose of the SBRT boost, the maximum EQD2 dose of the combined plan was considerably higher, namely up to 91 Gy which would occur if the maximum dose of the IMRT plan would be at the exact same location as of the SBRT boost plan.

For both fractionation regimens, the dose constraints for the total plan (EQD2 with $\alpha/\beta = 3$ Gy) were: spinal cord Dmax < 50 Gy, brain stem Dmax < 60 Gy (both hard planning constraints), parotid glands Dmean < 26 Gy, submandibular glands Dmean < 39 Gy, oral cavity Dmean < 50 Gy, and constrictor muscles Dmean < 55 Gy (when achievable).

Patients were followed by the head and neck multidisciplinary team according to national guidelines. Follow-up visits were planned every 2 months for the first year following RT. Starting from the second year, the frequency gradually reduced to every six months for a minimum of five years. In case there was a suspicion of PRMU, tumor recurrence was excluded with MRI or CT scan and/or pathology confirmation if needed. A PRMU was defined as local tissue loss at the mucosal lining, surrounded by increased enhancement after contrast material injection on CT and MRI. On T2w MRI also an increased signal was visible surrounding the tissue defect in case of PRMU. Treatment of PRMU consisted of conservative treatment, pain medication, and/or hyperbaric oxygen treatment at the discretion of the treating physician.

Toxicity scoring

A PRMU was identified as a mucosal defect causing pain and/or dysfunction that developed more than three months after RT or already developed during or directly after RT and still existed three months after RT without proof of residual or recurrent tumor located in the high dose area. PRMU were graded according to the CTCAE v5.0 (Table S1; Supplementary material). When a mechanical cause for an ulcer was present, such as a sharp tooth edge, or the ulcer was present in the close vicinity of osteoradionecrosis, no PRMU was scored. Furthermore, PRMU was scored as direct PRMU (appearing at the site of the primary tumor where it progresses from malignant tissue to a PRMU) or late PRMU (arising more than three months after RT), and the duration of PRMU was determined.

Dosimetric assessment

If CT or MR imaging at time of PRMU was available, which was mainly the case when there was a suspicion of tumor

recurrence, the region of PRMU was visually projected and manually delineated on the planning CT scan by an experienced head and neck radiologist and an experienced head and neck radiation oncologist. Only the region that was clearly affected was delineated. Subsequently, dose volume histograms of the PRMU regions were calculated where all dose distributions were converted into the equivalent uniform dose in 2 Gy fractions with an $\alpha/\beta = 3$ Gy.

Statistical analyses

Statistical analyses were performed using STATA software (Release 16, College Station, TX: StataCorp LLC). *p*-Values $<$ 0.05 were considered statistically significant. Follow up time was calculated from the last day of RT. Patients without PRMU were censored at date of last toxicity assessment and death was used as competing risk. Risk factors were evaluated in univariable Cox regression models and multivariable models using the backward selection method, where variables with an univariable *p*-value $<$ 0.2 in the total group or one of the boost groups were included in the backward selection. Possible risk factors included: age, sex, WHO performance score, HN-CCI (Head and Neck-Charlson Comorbidity Index; Table S2; Supplementary material), alcohol, smoking, BMI pre-RT, weight loss (between end acute period at three months and start RT), acute tube feeding, Hb pre-RT (low: male $<$ 8.5 mmol/l, female $<$ 7.5 mmol/l; according to national guidelines), T stage, N stage, tumor subsite (tonsil vs. other), concurrent systemic therapy, RT treatment scheme, accelerated RT (six vs. five fractions per week), and volume CTV tumor (per 10 cc). All variables were analyzed for the total group as well as for the hypofractionated SBRT and conventional IMRT boost group separately.

Results

Patient and treatment characteristics

In total 479 patients with OPSCC were treated in our hospital of which 424 patients met the inclusion criteria. Three hundred thirty-two patients had at least 1-year disease-free survival (see for details Figure S1; Supplementary material). Patient and tumor characteristics are shown in Table 1. One hundred eighteen patients (54%) were treated with the hypofractionated SBRT boost and 152 patients (46%) were treated with 70 Gy IMRT. One hundred forty-three (79%) in the SBRT boost group had a WHO 0 compared to 49 patients (32%) in the IMRT boost group. Eighty-six percent and 30% had a T1–2 tumor, concurrent chemotherapy was added in 10% and 70%, and acceleration was applied in 99% and 53% in the SBRT boost and IMRT boost group, respectively.

Incidence PRMU

The median follow-up for PRMU evaluation was 3.7 years; 83% had a follow-up $\geq$ two years, 68% $\geq$ three years, and 31% $\geq$ five years. Despite the presence of $\geq$ 1 year disease-free survival in all patients, ten patients had a follow-up of $<$ ten months because they missed follow-up visits. A total of 64 patients out of 332 patients (19.3%) developed PRMU grade $\geq$ 2; 46 (25.5%) in the hypofractionated SBRT boost group, and 18 (11.8%) in the conventional IMRT boost group. In two patients (both in the IMRT boost group) we were not able to fully discriminate between a PRMU or tumor recurrence due to insufficient follow up. However, as these two ulcers, based on clinical aspects, were most likely PRMU, they were included in the PRMU group for further analyses. The onset of all PRMU was within two years with 53 out of 64 (83%) occurring within twelve months (Figure 1). The estimated cumulative incidence in the total group at one year was 16.9% (2.1% 1SE) and at two years 19.8% (2.2% 1SE). Median time to PRMU was 6.4 months (range 1–23 months). In the hypofractionated SBRT boost group, the 2-year cumulative incidence of PRMU grade $\geq$ 2 was 26%, compared to 12% in the conventional fractionation group. The PRMU characteristics of the SBRT boost group and the IMRT boost group separately, are presented in Table 2. PRMU developed later in the hypofractionated SBRT group (Chisquare

Table 1. Patients and treatment characteristics.

Patient and treatment characteristics	Total	SBRT boost	IMRT boost
Patients	332	180	152
Age (mean; sd)	61; 8.6	61; 8.5	62; 8.7
Sex			
Male	219 (66)	111 (62)	108 (71)
Female	113 (34)	69 (38)	44 (29)
WHO			
0	192 (58)	143 (79)	49 (32)
1–2	140 (42)	37 (21)	103 (68)
HN-CCI			
0	184 (55)	92 (51)	92 (61)
$\geq$1	148 (45)	88 (49)	60 (39)
Alcohol			
No/previous	90 (27)	41 (23)	49 (32)
Current	242 (73)	139 (77)	103 (68)
Smoking			
No/previous	155 (47)	83 (46)	72 (47)
Current	177 (53)	97 (54)	80 (53)
BMI pre-RT			
$\leq$22	83 (25)	37 (21)	46 (30)
$>$22	249 (75)	143 (79)	106 (70)
% Weight loss (mean; SD)	−9.0; 6.9	−9.5; 7.4	−7.9; 5.4
Acute tube feeding			
No	170 (51)	121 (67)	49 (32)
Yes	162 (49)	59 (33)	103 (68)
Hb pre-RT			
Low	84 (25)	27 (15)	57 (38)
Normal	248 (75)	153 (85)	95 (63)
T stage			
T1–T2	199 (60)	154 (86)	45 (30)
T3–T4	133 (40)	26 (14)	107 (70)
N stage			
N0	129 (39)	83 (46)	46 (30)
N1–3	203 (61)	97 (54)	106 (70)
Tumor subsite			
Tonsil	163 (49)	104 (58)	59 (39)
Other	169 (51)	76 (42)	93 (61)
Concurrent systemic therapy			
No	208 (63)	162 (90)	46 (30)
Yes	124 (37)	18 (10)	106 (70)
Fractions per week			
5	73 (22)	2 (1)	71 (47)
6	259 (78)	178 (99)	81 (53)
Volume CTV tumor (cc, mean; SD)	78.9; 59.5	54.9; 31.4	108; 71.5

Percentages are shown in brackets. SBRT: Stereotactic body radiotherapy; IMRT: intensity modulated radiotherapy; WHO: World Health Organization performance score; HN-CCI: Head and Neck-Charlson Comorbidity Index; BMI: body mass index; Hb: hemoglobin; CTV: clinical target volume; SD: standard deviation.

$p < 0.027$) (Figure 1) and 91% of PRMU resolved within two years. In the conventional IMRT boost group the persistence was shorter (though not statistically significant) with 78% vs. 61% of PRMU resolving within six months, 11% vs. 20% between six to 12, and 11% vs. 20% persisted longer than 12 months.

In 11 (3%) patients, PRMU evolved directly after tumor regression and was still present more than three months post-RT (direct PRMU). Seven (64%) direct PRMU were in the SBRT boost group and four (36%) were in the IMRT boost group. Because of the small number of events within each subgroup, we refrained from univariable and multivariable analysis per type of PRMU. However, different characteristics appeared to be present. In the direct PRMU group, 36% were current smokers compared to 66% in the late PRMU group, a HN-CCI $\geq$ 1 was present in 73% and 53%, and HBOT and opioids were prescribed in 73% and 27%, and in 45% and 11%, respectively. The tumor volume between the two groups differed; with a median of 72 cc (SD = 81.3) (direct PRMU), and 52 cc (SD = 64.3) (late PRMU), respectively.

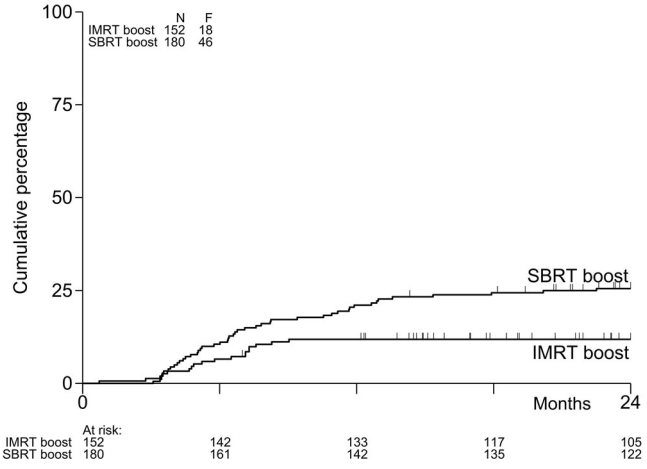

Figure 1. Cumulative incidence of PRMU per boost group. The onset of all PRMU was within 2 years. PRMU: Post radiation mucosal ulcer.

Table 2. PRMU grade $\geq$ 2 characteristics SBRT boost and IMRT boost.

PRMU characteristics	SBRT boost	IMRT boost
PRMU incidence at 2 yr	46 (26)	18 (12)
Median time to PRMU (m)	6.5	5.5
PRMU onset < 9 m	31 (67)	17 (94)
PRMU resolving < 6 m	28 (61)	14 (78)
PRMU resolving < 12 m	9 (20)	2 (11)
PRMU resolving > 12 m	9 (20)	2 (11)
Direct PRMU ($n = 11$)	7 (64)	4 (36)

The onset of all PRMU was within 2 years. Percentages are shown in brackets. PRMU: Post radiation mucosal ulcers; SBRT: stereotactic body radiotherapy; IMRT: intensity modulated radiotherapy; yr: years; m: months.

Risk factors PRMU

Table 3 shows the results of the univariable and multivariable analysis of the total patient group. Sex (SHR = 1.92), HN-CCI $\geq$ 1 (SHR = 1.68), N stage (SHR = 0.54), tumor subsite tonsil (SHR = 1.83), systemic therapy (SHR = 0.54), SBRT boost (SHR = 2.27), and accelerated radiotherapy (SHR = 2.43) were significantly associated with PRMU. Sex (SHR = 1.72), age at start RT (SHR = 1.03), acute tube feeding (SHR = 1.96), tumor subsite tonsil (SHR = 1.87), and SBRT boost (SHR = 2.74) remained significance in the multivariable model.

In the hypofractionated SBRT boost group, presented in Table 4, sex (SHR = 2.07), acute tube feeding (SHR = 2.38), N stage (SHR = 0.46), and tumor subsite tonsil (SHR = 2.09) were strongly associated with PRMU in univariable analysis. Sex (SHR = 1.84), acute tube feeding (SHR = 2.9), tumor subsite tonsil (SHR = 2.93), and N stage (SHR = 0.47) remained significance in the multivariable model. In the conventional IMRT boost group, no variable reached significance both in the univariable and multivariable model (Table 4).

Imaging and dosimetric analysis PRMU

In 27 (43%) patients imaging was performed at time of PRMU; an MRI scan in 25 patients and a CT scan in two patients. The location of the PRMU was visible and

Table 3. Risk factors for grade $\geq$ 2 PRMU according to CTCAE v5.0.

Total group	Univariable			Multivariable		
Patient and treatment characteristics	SHR	95% CI	*p*	SHR	95% CI	*p*
Age	1.03	1.00–1.05	0.051	1.03	1.00–1.06	0.048
Sex female vs. male	1.92	1.18–3.13	0.009	1.72	1.06–2.79	0.027
WHO 1–2 vs. 0	0.88	0.53–1.45	0.616			
HN-CCI $\geq$ 1 vs. 0	1.68	1.03–2.76	0.038			
Alcohol current vs. no/prev	1.53	0.84–2.81	0.167			
Smoking current vs. no/prev	1.35	0.82–2.25	0.242			
BMI pre-RT > 22 vs. $\leq$ 22	0.72	0.43–1.22	0.223			
Weight loss (%)	0.98	0.95–1.02	0.426			
Acute tube feeding yes vs. no	1.23	0.75–2.01	0.407	1.96	1.11–3.46	0.020
Hb pre–RT low vs. normal	0.53	0.27–1.05	0.068			
T stage T3–4 vs. T1–2	0.72	0.43–1.22	0.227			
N stage N1–3 vs. N0	0.54	0.33–0.89	0.015			
Tumor subsite tonsil vs. other	1.83	1.11–3.04	0.019	1.87	1.13–3.10	0.015
Systemic therapy yes vs. no	0.54	0.31–0.96	0.036			
RT boost SBRT vs. IMRT	2.27	1.31–3.94	0.003	2.74	1.44–5.19	0.002
Accelerated RT yes vs. no	2.43	1.10–5.36	0.028			
Volume CTV tumor (per 10 cc)	1.00	0.95–1.05	0.921			

PRMU: Post radiation mucosal ulcer; WHO: World Health Organization performance score; HN-CCI: Head and Neck–Charlson Comorbidity Index; BMI: body mass index; Hb: hemoglobin; SBRT: stereotactic body radiotherapy; IMRT: intensity modulated radiotherapy; CTV: clinical target volume; SHR: subhazard ratio; CI: confidence interval.

Table 4. Risk factors for grade $\geq$ 2 PRMU according to CTCAE v5.0 for SBRT boost and IMRT boost, respectively.

	SBRT boost						IMRT boost		
	Univariable			Multivariable			Univariable		
Patient and treatment characteristics	SHR	95% CI	p	SHR	95% CI	p	SHR	95% CI	p
Age	1.03	0.99–1.06	0.109				1.04	0.99–1.09	0.170
Sex female vs male	2.07	1.16–3.70	0.014	1.84	1.00–3.39	0.048	1.26	0.47–3.35	0.648
WHO 1–2 vs. 0	1.43	0.74–2.74	0.284				1.27	0.46–3.51	0.648
HN-CCI $\geq$ 1 vs. 0	1.73	0.96–3.13	0.068				1.28	0.50–3.23	0.608
Alcohol current vs. no/prev	1.09	0.54–2.18	0.811				2.49	0.72–8.60	0.150
Smoking current vs. no/prev	1.63	0.88–3.01	0.121				0.87	0.35–2.18	0.764
BMI pre-RT $>$ 22 vs. $\leq$ 22	0.63	0.34–1.19	0.154				0.68	0.27–1.74	0.419
Weight loss	1.00	0.95–1.05	0.994				0.98	0.91–1.04	0.495
Acute tube feeding yes vs. no	2.38	1.33–4.23	0.003	2.97	1.62–5.45	<0.001	0.73	0.28–1.88	0.514
Hb pre–RT low vs. normal	0.89	0.36–2.20	0.805				0.45	0.15–1.35	0.154
T stage T3–4 vs. T1–2	1.33	0.61–2.87	0.471				1.10	0.39–3.06	0.857
N stage N1–3 vs. N0	0.46	0.25–0.85	0.012	0.47	0.25–0.87	0.017	1.16	0.42–3.21	0.776
Tumor subsite tonsil vs. other	2.09	1.11–3.93	0.023	2.94	1.53–5.66	0.001	0.99	0.39–2.55	0.991
Systemic therapy yes vs. no	1.20	0.45–3.18	0.719				0.66	0.26–1.70	0.392
Accelerated RT yes vs. no	**						1.41	0.55–3.63	0.472
Volume CTV tumor (per 10 cc)	1.05	0.97–1.13	0.235				1.03	0.97–1.10	0.334

In the IMRT boost group, no variable reached significance both in the univariable as well as the multivariable model. **In only 2 out of 180 patients RT was not accelerated; therefore univariable regression was not performed. PRMU: Post radiation mucosal ulcers; SBRT: stereotactic body radiotherapy; IMRT: intensity modulated radiotherapy; WHO: World Health Organization performance score; HN-CCI: Head and Neck–Charlson Comorbidity Index; BMI: body mass index; Hb: hemoglobin; CTV: clinical target volume; SHR: subhazard ratio; CI: confidence interval.

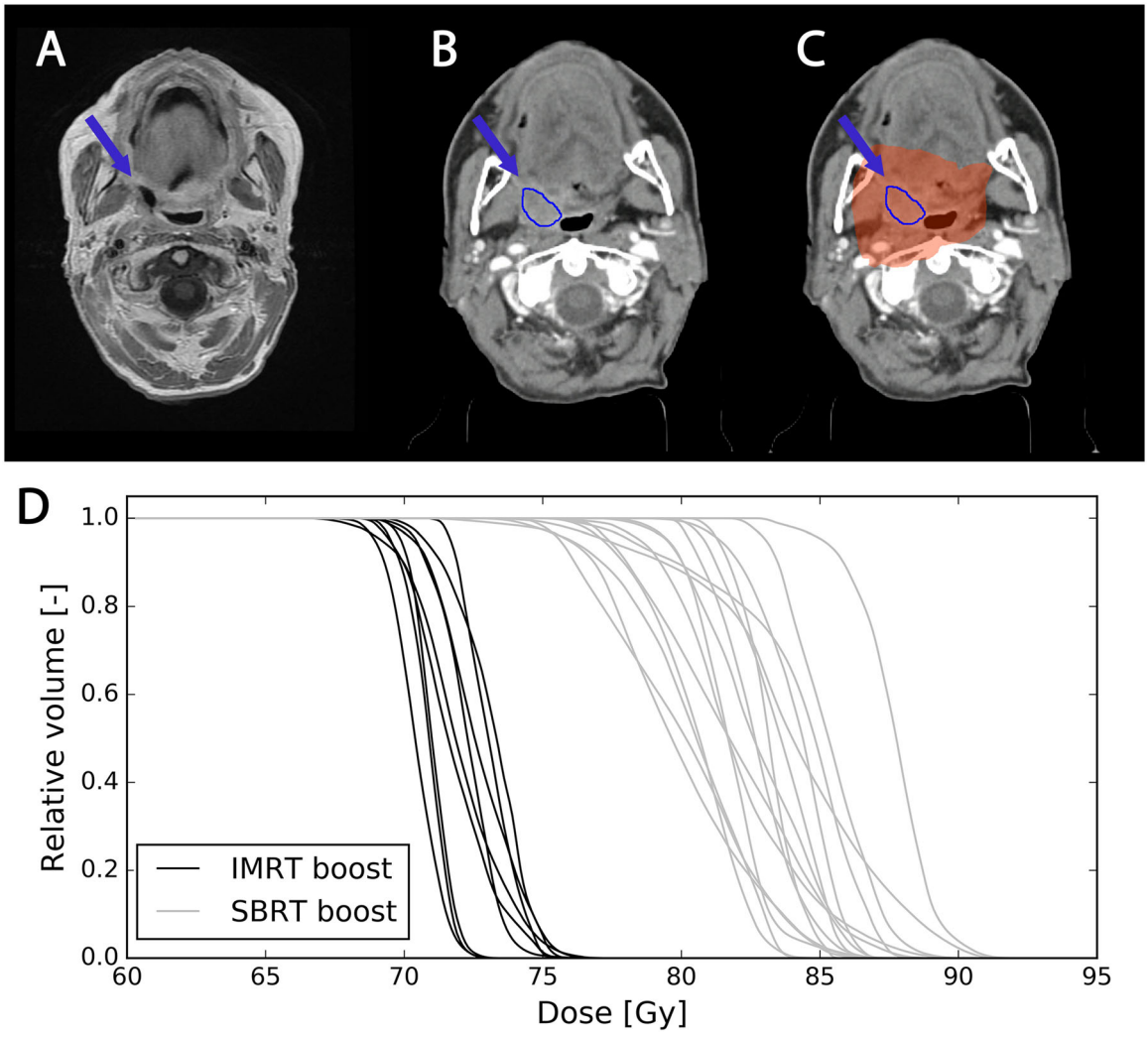

Figure 2. Patient with a cT4bN1M0 right tonsillar fossa carcinoma treated with 70 Gy IMRT. She developed a PRMU 7.5 months after radiotherapie. (A) PRMU visible in the right tonsillar fossa on axial gadolinium enhanced T1-weighted image (see arrow). (B) Delineation of the PRMU projected on the planning CT (see arrow). (C) Dose distribution (95% dose level in orange) at the level of the PRMU (see arrow). (D) Dose volume histogram of 26 delineated PRMU treated with conventional IMRT (dark grey) or a SBRT boost (light grey). PRMU = Post radiation mucosal ulcer.

delineated in 26 out of the 27 patients (17 hypofractionated SBRT boost group and nine IMRT boost group). In 25 of the 26 delineated PRMU, the 3 D dose distribution could be retrieved. As shown in Figure 2, all PRMU were situated within the high dose regions. The Dmean ($\alpha/\beta = 3$) was higher in the PRMU in the hypofractionated SBRT boost group (median Dmean = 82.7 Gy; SD = 2.0) compared to the IMRT group (median Dmean = 71.9 Gy; SD = 0.9), as expected.

Discussion

We have demonstrated in a group of 332 OPSCC patients an increase in 2-year cumulative incidence of PRMU grade $\geq$ 2 of 26% versus 12% for those treated with conventional IMRT plus a hypofractionated SBRT boost versus conventional IMRT alone. This difference was remarkable since patients in the IMRT boost group were on average older, had more advanced disease stages, and were treated more often with concurrent chemotherapy compared to the hypofractionated SBRT boost group. Female sex, acute tube feeding, tumor subsite tonsil, and an N0 stage, were risk factors for PRMU in the hypofractionated SBRT boost group.

The incidence of 12% after conventional fractionation for OPSCC in our study is higher compared to incidences of 3–8% reported previously [11,14–16]. This could be explained by several reasons. First, patients included in our study that were treated more recently (from 2013 and onwards) had a somewhat lower incidence of 10% compared to 16% for the earlier treated patients (before 2013). Second, in the papers of Ang et al. and Nguyen et al. [14,15], all head and neck subsites were included, where larynx and hypopharynx carcinoma lead to lower PRMU incidences compared to oral cavity and oropharyngeal carcinoma due to more favorable anatomical location of the former [17]. Third, in the study of Selek et al. [16], 49% received a lower median dose of 66 Gy compared to at least 70 Gy in our group. This difference in total RT dose might have resulted in a lower percentage of mucosal ulcers. Furthermore, based on the lower prevalence of HPV in the Dutch OPSCC population [15] compared to the US population, it is expected that the studies of Ang and Nguyen included relatively more HPV positive patients compared to our study. HPV positive patients, in general, are in better condition and experience fewer side effects than HPV negative patients.

Although late responding tissues are more sensitive to a higher dose per fraction [18], data on hypofractionation treatments and the risk of PRMU in the primary setting are scarce. Several papers described the risk of hypofractionation and the risk of PRMU [9,19]. Lee et al. published in a cohort of 26 HNC patients treated with an SBRT boost with a median cumulative BED_{10} of 94.9 Gy (which is higher than in the current study) a 35% late grade $\geq$ 3 soft tissue necrosis [20]. They concluded that a high fraction dose in combination with a large volume is associated with late complications. Vargo et al. published a 25% late grade 2 mucosal ulceration risk in a cohort of 12 stage III and IV HNC patients treated with 44 Gy SBRT in five fractions [10]. Furthermore, Shuryak et al. postulated that doses per fraction above 3.0 Gy will result in unacceptable rates of late toxicity [7].

The higher incidence of PRMU after the hypofractionated SBRT boost could be due to a higher dose to the tumor compared to the conventional fractionated IMRT boost group. Indeed, for the 25 PRMU for which dosimetric data were available, the median Dmean to the PRMU was higher (82.7 Gy) than in the IMRT boost group (71.9 Gy). This is consisted with the findings in several dose-painting escalation trials where higher doses also resulted in a higher incidence of PRMU [21,22].

Although there is no clear evidence that a shorter overall treatment time has an influence on late toxicity [18], and no effect was found in the IMRT alone group when comparing five and six fractions per week, it cannot be ruled out that the shorter overall treatment time of the SBRT boost group compared to the IMRT boost group (five weeks vs. six to seven weeks) could have affected the increased incidence of PRMU in the SBRT boost group. This may explain possibly as well the longer PRMU duration in the hypofractionated SBRT boost group compared to the IMRT boost group (PRMU duration $>$ 12 months: 19.5 vs 11.2%) [23].

The risk factors in the total group (age, female sex, tumor subsite tonsil, and acute tube feeding) were equivalent to those for the hypofractionated SBRT boost group; apart from age that lost its significance in the hypofractionated SBRT boost group, and N0 stage that became significant. Tumor subsite tonsil possibly may have been relevant due to the close proximity of the tumor to the pharyngeal wall. Acute tube feeding is hypothesized not to be the cause of PRMU, but a surrogate for acute mucositis and/or malnutrition leading to weight loss, which are the most common indications for tube feeding. Acute mucositis can lead to the development of consequential late tissue reactions, such as ulcers [9,17], and malnutrition may result in hypoxia, necrosis, and delayed tissue healing which can facilitate the development of PRMU [5,24–26].

Surprisingly, an initially positive N stage resulted in a lower risk for developing PRMU in the hypofractionated SBRT boost group. In that group, tumors were on average smaller than in the IMRT group. HPV positive patients are often characterized by a small tumor and N positive disease. So, potentially N positive disease in the hypofractionated SBRT boost group may have been a surrogate for HPV positive patients, which are in better health and suffer from less toxicity in general.

Smoking has been reported as a risk factor for late side effects after RT [11,22,27,28], and about half of head and neck cancer patients continue to smoke during radiation [29–31], which was the case in our cohort as well. However, it did not reach significance in our cohort.

We made a distinction between direct and late PRMU, which appeared to have different characteristics. Although patients groups were small, patients with direct PRMU were less frequent smokers and had more often an HN-CCI $\geq$ 1. A possible explanation might be a lower intrinsic inability for an adequate wound healing due to comorbidities. Although there are some reports concerning different types of PRMU

in nasopharyngeal carcinoma [5,32], to the best of our knowledge, there is no detailed information concerning different types of PRMU after RT for OPSCC.

For all of the 25 patients for which the dose to the PRMU could be determined, the PRMU was situated within the high dose area, which was expected since imaging was performed for these patients specifically to discriminate between a recurrence and a PRMU. Other studies also observed PRMU often in high-dose regions [22,33]. Li et al. found for 25 radiation induced nasopharyngeal ulcer (RINU) patients the RINU was located at the site of the primary tumor location in the high-dose regions. In a dose-escalated adaptive dose-painting study by Olteanu et al. in a group of 39 HNC patients, nine patients developed a grade 4 mucosal ulcer. Seven out of these nine patients had a $D_{1.75\,cc}$ above 84 Gy.

Besides the retrospective nature, this study has some additional limitations that need to be mentioned. The group for which the imaging of PRMU was available, was biased in terms of PRMU location toward the site of the tumor since imaging was primarily performed to discriminate PRMU from recurrent tumor. Furthermore, our hypofractionated SBRT boost protocol may not be representative of hypofractionated treatments in general, as the effect may depend on the fraction dose, overall treatment time, and total prescribed dose as described earlier.

To the best of our knowledge, this is the largest cohort of OPSCC patients for which the incidence and risk factors of PRMU are described thoroughly, including the effect of a hypofractionated SBRT boost.

Conclusion

More information concerning incidence and risk factors of PRMU is urgently needed. In our analyses, a hypofractionated SBRT boost (EQD2 74.05 Gy prescribed at the 80% isodose) was associated with a higher total dose to the mucosal wall in the high dose area and an increased risk of PRMU (26% vs. 12%) compared to conventional fractionation (EQD2 70 Gy) for OPSCC patients. Even though the patients in the IMRT boost group were on average older, had more advanced disease stages, and were treated more often with concurrent chemotherapy compared to the hypofractionated SBRT boost group. Although almost all PRMU (91%) resolved within two years, the risk of PRMU should be included in the cost benefit analysis when considering future research using a hypofractionated SBRT boost for OPSCC patients.

Disclosure statement

The department of radiotherapy has research collaborations with Elekta AB, Stockholm, Sweden, and Accuray, Sunnyvale, California.

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Data availability statement

Research data are stored in an institutional repository and a request for data sharing can be send to the corresponding author.

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