Radiotherapy and Oncology 134 (2019) 10–16

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Validation of distant metastases risk-groups in oral cavity squamous cell carcinoma patients treated with postoperative intensity-modulated radiotherapy

Ali Hosni [a,*], Shao Hui Huang [a], Kevin Chiu [a], Wei Xu [b], Jie Su [b], Lin Lu [a], Andrew Bayley [a], Scott V. Bratman [a], John Cho [a], Meredith Giuliani [a], John Kim [a], Brian O'Sullivan [a], Jolie Ringash [a], John Waldron [a], Anna Spreafico [c], John R. de Almeida [d], Douglas B. Chepeha [d], Jonathan C. Irish [d], David P. Goldstein [d], Andrew Hope [a,*]

[a] Department of Radiation Oncology, Princess Margaret Cancer Centre/University of Toronto; [b] Department of Biostatistics, Princess Margaret Cancer Centre/University of Toronto; [c] Department of Medical Oncology, Princess Margaret Cancer Centre/University of Toronto; and [d] Department of Otolaryngology-Head & Neck Surgery/Surgical Oncology, Princess Margaret Cancer Centre/University of Toronto, Canada

ARTICLE INFO

Article history:
Received 7 June 2018
Received in revised form 6 December 2018
Accepted 13 January 2019
Available online 31 January 2019

Keywords:
Oral cavity cancer
Postoperative intensity modulated radiotherapy
Distant metastases
Prognostic factors
Risk groups

ABSTRACT

Background: This study aimed to derive distant metastases (DM) risk-groups in oral cavity squamous cell carcinoma (OSCC) patients treated with postoperative intensity-modulated radiation therapy (PO-IMRT).
Methods: OSCC patients treated with PO-IMRT were divided into discovery (2005–2012) and validation (2013–2014) cohorts. DM predictors were identified from multivariable analysis (MVA) to derive low- and high-risk groups in the discovery-cohort. The result was subsequently evaluated in validation-cohort.
Results: Overall 447 patients were included (discovery-cohort: $n = 300$, and validation-cohort: $n = 147$). Between the two cohorts, there were no significant differences in DM ($p = 0.16$) or OS ($p = 0.26$). MVA identified pN2-3 and histological grade 2–3 (G2-3) as DM predictors. High-risk group included patients who had both poor predictors (pN2-3 and G2-3), while low-risk group included patients with no or only one poor predictor. In discovery-cohort, 3-year distant control (DC) was 78% and 97% in high- and low-risk groups respectively ($p < 0.001$, concordance index = 0.72). In validation-cohort, risk-group classification performed similarly (concordance index = 0.73). The 3-year OS for high- versus low-risk group was 85% versus 95% in discovery-cohort ($p < 0.001$), and 74% versus 93% in validation-cohort ($p < 0.001$).
Conclusion: A model (G2-3/pN2-3) which identifies high DM risk was validated internally. This model might be used to design future prospective studies investigating treatment intensification and/or DM surveillance.

A total of more than 300,000 new cases of oral cavity cancer were reported in 2012 worldwide [1]. Over the last decades, the introduction of a multidisciplinary team approach and the technical advancements in both surgery and radiotherapy, together with the implementation of concurrent chemotherapy in the adjuvant setting for oral cavity squamous cell carcinoma (OSCC) patients, have resulted in improving the locoregional control [2–6]. Conversely, rates of distant metastases (DM) in OSCC patients have increased [6,7], potentially due to this improved locoregional control allowing patients to survive to have distant failure.

Patients with OSCC who have DM are generally not considered curable and often receive palliative treatment alone. Therefore, identification of patients who are at high risk of DM could have important implications on designing a screening schedule and/or avoiding unnecessary or inappropriate treatment [8,9].

We have previously reported the characteristics of DM following postoperative intensity-modulated radiation therapy (IMRT) for OSCC patients [10]. The objective of this study was to define DM risk group classification and to validate the prognostic value of this risk-group in an independent population.

* Corresponding authors at: Princess Margaret Cancer Centre, 610 University Ave., Toronto, Ontario M5G 2M9, Canada.
E-mail addresses: Ali.Hosni@rmp.uhn.on.ca (A. Hosni), Andrew.Hope@rmp.uhn.on.ca (A. Hope).

https://doi.org/10.1016/j.radonc.2019.01.014
0167-8140/

Methods

Study design and patients cohorts

Following institutional research ethics board approval, a retrospective review was conducted of newly diagnosed (≥18 years old) OSCC patients, who were treated at our institution with postoperative IMRT with or without concurrent chemotherapy. Patients with metastatic disease prior to initiation of postoperative IMRT were excluded from this analysis. Two sequential cohorts of OSCC patients compromised the discovery (2005–2012) and validation (2013–2014) cohorts. The discovery cohort, aimed at defining the variables to be included in the risk groups, and a validation cohort, aimed at confirming the prognostic value of the risk grouping in an independent population. The details of surgery and postoperative IMRT +/− concurrent chemotherapy have been previously described [11,12]. For patients with microscopic extranodal extension and/or positive resection margin, a 66 Gy in 33 fractions to the site of preoperative (primary or nodal) gross disease was prescribed whenever feasible. The operative bed (including dissected nodal regions) received 60 Gy in 30–33 fractions, while undissected at risk nodal levels were treated with 54–56 Gy in 30–33 fractions.

Data collection

Prospectively collected clinical and outcomes data were retrieved from the Head and Neck Anthology of Outcomes [13]. All patients were staged according to the UICC/AJCC 7th edition. PET-CT was not routinely used during the study period, however pre-treatment CT scan of the chest was generally performed in all patients except those with early stage disease with no smoking history where chest X-ray was deemed sufficient. Diagnosis of DM following postoperative radiotherapy was based on follow-up images which were performed on the basis of new indicative symptoms or following the diagnosis of local and/or regional failure, while pathologic confirmation of DM was obtained in patients with lung metastasis with difficult radiological differentiation between primary lung cancer and lung metastasis. The details of our institutional guidelines for surgical management, postoperative IMRT, concurrent chemotherapy and follow-up schedule for OSCC patients have been previously described [10].

Risk-group classification

In the discovery cohort, a set of variables was evaluated by multivariable analysis (MVA) as potential predictors of DM, including: pT-category, pN-category, resection margin status, extranodal extension, maximum primary tumor size, primary tumor thickness, histological grade, lymphovascular invasion and perineural invasion. The variables which were associated with DM in the MVA model were used to derive risk groups, and then we compared distant control (DC) and overall survival (OS) according to the derived risk groups in the discovery cohort and subsequently in the validation cohort.

Statistical analysis

Descriptive statistics were used to describe patient and treatment characteristics. Fisher's exact test was used for comparison of categorical variables. Student's *t*-test and Kruskal–Wallis test were used for comparison of continuous variables for normally distributed and non-normally distributed data respectively. Distant control (DC) rate was estimated by the cumulative incidence function. Kaplan–Meier method was used to analyze OS. For this study, we applied complete-case analysis. The univariable analysis was conducted on each of the potential predictors including categorical or continuous variables. The Fine-Gray competing risk regression model was used for both univariable and multivariable analyses. The model selection procedure is based on backward selection algorithm with significance level less than 0.1 to enter the model and significance level less than 0.05 to stay in the model. The concordance index (C-index) of the competing risk model was used to assess the predictive ability, and was calculated using R package PEC with Bootstrap cross validation.

Results

Patient and treatment characteristics

A total of 447 eligible patients were included; 300 in the discovery cohort (median follow-up: 4.2 years [range, 0.3–9.6]) and 147 in the validation cohort (median follow-up: three years [range, 0.5–4.2]). Between the two cohorts, there were no significant differences in the clinico-pathological features, except for more frequent pT3-4 category (55% vs. 40%, $p < 0.01$) and larger maximum primary tumor size (mean [sd]): 3.5 [1.4] cm vs. 3.3 [1.6] cm, $p = 0.045$) in the validation cohort. The details of patient and treatment characteristics in the entire study, discovery and validation cohorts are summarized in Table 1.

Distant metastases characteristics

With a median follow-up of 3.5 years (range, 0.3–9.6) of all identified patients, the estimated 3-year DC was 87% (95% CI: 83–90%). A total of 63 patients developed DM at a median (range) time of nine (3–49) months following the surgery; 39 in the discovery cohort and 24 in the validation cohort. In comparison of the discovery versus the validation cohort, there was no significant difference in the 3-year DC (88% [95% CI: 84–91%] versus 84% [95% CI: 77–89%], $p = 0.16$), Fig. 1. The characteristics and treatment of DM are summarized in Tables 2 and 3.

Development of risk-group classification (discovery cohort)

The final MVA model identified only two predictors of DM: pN2-3 ($p < 0.001$) and histological grade 2–3 (G2-3, $p < 0.001$), Table 4. A high risk group consisted of patients who had both adverse predictors (pN2-3 and G2-3) together, while low risk group consisted of patients who had one or no poor predictors. In the discovery cohort, the 3-year DC rate was 78% (95% CI: 70–84%) and 97% (95% CI: 92–99%) in high- and low-risk groups respectively ($p < 0.001$), Fig. 2, and the C-index value was 0.72.

Confirmation of risk-group classification (validation cohort)

In the validation cohort, the risk-group classification performed similarly. The 3-year DC in high risk group (patients who had pN2-3 and G2-3) was 69% [95% CI: 54–79%] compared to 95% [95% CI: 87–98%] in low risk group ($p < 0.001$), Fig. 2. The estimated C-index value was 0.73. Among the whole identified patients ($n = 447$), the effect of risk stratification (high risk versus low risk group) was not different in the subgroup of patients who received concurrent chemotherapy ($n = 115$; [the 3-year DC was 66% {95% CI: 54–75%} versus 97% {95% CI: 78–100%}, $p < 0.001$]) and those who did not receive concurrent chemotherapy ($n = 332$; [the 3-year DC was 81% {95% CI: 73–87%} versus 96% {95% CI: 92–98%}, $p < 0.001$]).

Survival outcome

A total of 136 patients died; 90 in the discovery cohort and 46 in the validation cohort. The 3-year OS in the entire study cohort was

Table 1
Clinico-pathological characteristics in the entire study, discovery and validation cohorts.

Characteristic	Entire study cohort (n = 447)	Discovery cohort (n = 300)	Validation cohort (n = 147)	p-Value[1]
Age[2]				
Median (range), years	61 (20–87)	60 (20–87)	62 (26–87)	0.35
Gender				
Female	156 (35%)	108 (36%)	48 (33%)	0.53
Male	291 (65%)	192 (64%)	99 (67%)	
Smoking history at the time of diagnosis				
Current	191 (45%)	127 (46%)	64 (44%)	0.24
Ex-smoker	79 (19%)	45 (16%)	34 (23%)	
Non-smoker	152 (36%)	103 (37%)	49 (33%)	
Missing	25	25	0	
pT-category				
pT1-2	245 (55%)	179 (60)	66 (45%)	**<0.01**
pT3-4	202 (45%)	121 (40)	81 (55%)	
pN-category				
pN0-1	242 (54%)	159 (53%)	83 (56%)	0.48
pN2-3	205 (46%)	141 (47%)	64 (44%)	
UICC/AJCC pathologic stage grouping				
I	24 (5%)	14 (5%)	10 (7%)	0.44
II	58 (13%)	43 (14%)	15 (10%)	
III	74 (17%)	53 (18%)	21 (14%)	
IVA	282 (63%)	183 (61%)	99 (67%)	
IVB	9 (2%)	7 (2%)	2 (1%)	
Pathologic margin status				
Negative	355 (79%)	236 (79%)	119 (81%)	0.38
Positive	89 (20)	64 (21%)	25 (17%)	
Undetermined	3 (1%)	0	3 (2%)	
Extranodal extension				
No	315 (70%)	211 (70%)	104 (71%)	1
Yes	132 (30%)	89 (30%)	43 (29%)	
Subsite				
Tongue	197 (44%)	135 (45%)	62 (42%)	0.61
Other subsites	250 (56%)	165 (55%)	85 (58%)	
Maximum primary tumor size[2]				
Mean (SD), cm	3.3 (1.5)	3.3 (1.6)	3.5 (1.4)	0.045
Primary tumor thickness[2]				
Mean (SD), cm	1.5 (1)	1.6 (1.1)	1.5 (0.9)	0.97
Histological grade				
1	22 (5%)	13 (4%)	9 (6%)	
2	307 (69%)	214 (72%)	93 (63%)	0.17
3	116 (26%)	71 (24%)	45 (31%)	
Missing	2	2	0	
Lymphovascular invasion				
No	390 (88%)	259 (88%)	131 (89%)	0.76
Yes	53 (12%)	37 (12%)	16 (11%)	
Missing	4	4	0	
Perineural invasion				
No	173 (39%)	115 (39%)	58 (39%)	1
Yes	269 (61%)	180 (61%)	89 (61%)	
Missing	5	5	0	
Concurrent chemotherapy				
No	332 (74%)	227 (76%)	105 (71%)	0.36
Yes	115 (26%)	73 (24%)	42 (29%)	

[1] Discovery versus validation cohort.
[2] Normality test was applied and it was significant for "age", but not significant for "maximum tumor size" and "tumor thickness". Student's t-test was conducted for age, while Kruskal–Wallis test was used for maximum primary tumor size and primary tumor thickness.

71% (95% CI: 67–75%), with no significant difference between discovery and validation cohort (72% [95% CI: 67–77%] versus 69% [95% CI: 61–77%], p = 0.26), Fig. 1. The median survival after detection of DM was 1.5 months (range, 0–44). Among patients with oligo-metastases in the entire study cohort (n = 18), the median OS from the date of DM was 17 months (range, 5–24) for patients treated with metastatectomy or stereotactic body radiotherapy (n = 5), 11 months (range, 5–13) for those who received palliative chemotherapy (n = 3), and three months (range, 0–5) for patients who were managed with best supportive measures. The 3-year OS for high- versus low-risk group was 85% (95% CI: 79–91%) versus 95% (95% CI: 91–98%) in the discovery cohort (p < 0.001), and 74% (95% CI: 63–86%) versus 93% (95% CI: 87–99%) in the validation cohort (p < 0.001), Fig. 2.

Discussion

This study validated a high DM risk-group in OSCC patients treated with postoperative IMRT with or without concurrent

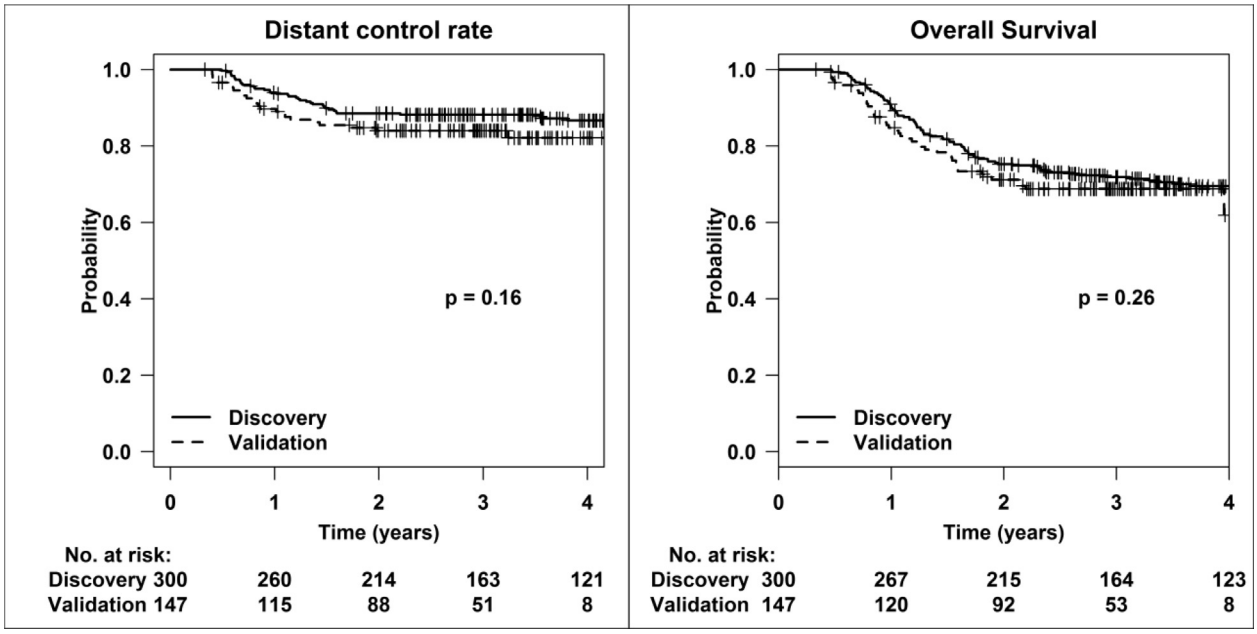

Fig. 1. Distant control and overall survival in the discovery and validation cohorts.

Table 2
Characteristics and treatment of distant metastases.

Characteristics	Patients with DM in the entire study cohort $n = 63$	Patients with DM in the discovery cohort $n = 39$	Patients with DM in the validation cohort $n = 24$	p-value
Time to DM from the date of surgery				
Median (range), months	9 (3–49)	12 (3–49)	8 (3–27)	–
Metastatic pattern				
DOF vs. DM subsequent to LRF	33 (52%) vs. 30 (48%)	20 (51%) vs 19 (49%)	13 (54%) vs 11 (46%)	
Oligo-[1] vs. disseminated- metastasis	18 (29%) vs. 45 (71%)	12 (31%) vs. 27 (69%)	6 (25%) vs. 18 (75%)	-
Metastatic sites				
Single site				
Lung	31/63 (49%)	21/39 (54%)	10/24 (42%)	
Bone	9/63 (14%)	7/39 (18%)	2/24 (8%)	
Others	4/63 (6%)	1/39 (3%)	3/24 (12.5%)	
Multiple sites				
Including lung metastasis	16/63 (25%)	10/39 (26%)	6/24 (25%)	
Not including lung metastasis	3/63 (5%)	0	3/24 (12.5%)	–
Treatment for DM				
Metastatectomy	3 (5%)	1/39 (3%)	2/24 (8.3%)	
SBRT	2 (3%)	0	2/24 (8.3%)	
Chemotherapy	6 (9.5%)	4/39 (10%)	2/24 (8.3%)	
Best supportive care/palliative RT	52 (82.5%)	34/39 (87%)	18 (75%)	–
Tumor characteristics				
pT3-4 category	32 (51%)	16 (53%)	16 (48%)	0.8
pN2-3 category	53 (84%)	26 (87%)	27 (82%)	0.74
Positive resection margin(s)	14 (23%)	6 (20%)	8 (25%)	0.76
Extranodal extension	39 (62%)	19 (63%)	20 (61%)	1
Maximum primary tumor size (cm), mean (sd)	3.5 (1.65)	3.3 (1.5)	3.6 (1.7)	0.63
Primary tumor thickness (cm), mean (sd)	1.6 (1)	1.8 (1.2)	1.5 (0.8)	0.69
Histological grade 1	0 (0)	0 (0)	0 (0)	1
Lymphovascular invasion	13 (21%)	6 (20%)	7 (21%)	1
Perineural invasion	44 (70%)	19 (63%)	25 (76%)	0.41
Treatment characteristics				
Median (range) interval between surgery and start of PORT, weeks	8 (4–23)	8 (4–23)	8 (4–23)	0.18
Median (range) interval between surgery and end of PORT, weeks	14 (10–29)	14 (10–29)	14 (10–29)	0.76

DM, distant metastasis; DOF, distant-only failure; LRF; locoregional failure; SBRT, stereotactic body radiotherapy; RT, radiotherapy, PORT, postoperative radiation therapy.
[1] Oligometastasis: ≤5 metastatic lesions in single organ.

chemotherapy. Patients with G2-3/pN2-3 were shown to be at high risk of DM and poor survival in the subsequent validation cohort. Identifying this high risk group may allow alternate treatment strategies to be explored to improve the outcomes.

Several studies identified the histological grade, pN-category and extranodal extension as independent risk factors of DM in OSCC [7,14–16]. In the current analysis, pathologic nodal category (pN2-3) and histological grade (G2-3) were associated with DM,

Table 3
Stage distribution for patients with distant metastases.

Discovery cohort						
Category	N0 $n = 103$	N1 $n = 55$	N2a $n = 6$	N2b $n = 104$	N2c $n = 30$	N3 $n = 1$
T1	–	1	2	5	–	–
T2	–	2	–	9	4	–
T3	–	–	–	3	–	–
T4	–	3	–	6	4	–
Total	–	6	2	23	8	–
Validation cohort						
Category	N0 $n = 62$	N1 $n = 21$	N2a $n = 3$	N2b $n = 43$	N2c $n = 17$	N3 $n = 1$
T1	–	–	1	2	–	–
T2	–	–	–	3	2	–
T3	1	1	–	1	3	–
T4	2	1	–	5	2	–
Total	3	2	1	11	7	–

Table 4
Univariable and multivariable analyses to identify predictors of distant metastases in the discovery cohort.

Variable	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
pT3-4 category	1.06 (0.56–2.01)	0.86	–	–
pN2-3 category	8.74 (3.46–22.08)	**<<0.001**	5.98 (2.31–15.49)	**<0.001**
Positive resection margin(s)	1.19 (0.46–3.06)	0.91	–	–
Extranodal extension	3.89 (2.07–7.33)	**<<0.001**	1.82 (0.93–3.57)	0.08
Maximum primary tumor size	1.03 (0.85–1.25)	0.77	–	–
Primary tumor thickness	1.03 (0.78–1.37)	0.83	–	–
Histological grade one[1]	$7.7 * 10^{-7}$ ($4.1 * 10^{-7}$–$1.4 * 10^{-6}$)	**<0.001**	$1.4 * 10^{-6}$ ($5.6 * 10^{-7}$–$13.8 * 10^{-6}$)	**<0.001**
Lymphovascular invasion	1.56 (0.7–3.49)	0.28	–	–
Perineural invasion	1.35 (0.7–2.6)	0.37	–	–
Time interval between surgery and start of PORT (days)[2]	0.99 (0.98–1.01)	0.39	–	–
Time interval between surgery and end of PORT (days), overall treatment time[3]	0.99 (0.98–1.01)	0.29	–	–

PORT, postoperative radiation therapy.
[1] Due to no events in histological grade 1 subgroup, the HR estimation for histological grade is very close to 0 ($7.7 * 10^{-7}$). However, the Fine-Gray competing risk regression model still can estimate the standard error of the HR and its corresponding test statistic, that is why the *p*-value can be calculated based on the test statistic (Wald Test Statistic = 1923.6) which is very small and less than 0.001.
[2] Fine-Gray competing risk regression was also used to evaluate the association between time interval between surgery and start of postoperative radiation therapy (days) and risk of locoregional failure (HR: 1.01, 95%CI: 1–1.01, $p = 0.23$), while Cox proportional-hazards model was used to evaluate the association between time interval between surgery and start of postoperative radiation therapy (days) and overall survival (HR: 1.95%CI: 0.99–1.01, $p = 1$).
[3] Fine-Gray competing risk regression was also used to evaluate the association between time interval between surgery and end of postoperative radiation therapy (days) and risk of locoregional failure (HR: 1.01, 95%CI: 1–1.02, $p = 0.07$), while Cox proportional-hazards model was used to evaluate the association between time interval between surgery and end of postoperative radiation therapy (days) and overall survival (HR: 1.95%CI: 0.99–1.01, $p = 0.69$).

while the association between extranodal extension and DM was not statistically significant on MVA ($p = 0.08$). This could be due to treatment intensification for patients with extranodal extension ($n = 89$ in the discovery cohort) using higher radiation dose (>60 Gy) in 63 out of 89 (71%) and concurrent (cisplatin) chemotherapy in 42 out of 89 (47%), which resulted in improving the regional control and decreased the DM subsequent to regional failure. However, with a larger sample and more events, extranodal extension may also be identified as an independent factor which could be incorporated into a more detailed future risk classification system. While there were no significant differences in the clinicopathological features between the discovery and validation cohorts, except for more frequent pT3-4 category and larger primary tumor in the validation cohort, locally advanced disease (i.e. pT3-4) was not associated with higher risk of DM in the discovery cohort on univariable or multivariable analyses.

Advances in imaging, such as PET-CT scan, could enable early identification of small clinically silent DM through a designed surveillance schedule for patients with high risk of DM [8,9]. Moreover, detection of limited extent DM (i.e. oligometastasis) could allow for local ablative therapy with metastatecomy and/or stereotactic body radiotherapy [17,18]. Interestingly, in the entire study cohort, five patients with oligometastasis were treated with such local therapy for DM with a median OS of 17 months following the diagnosis of DM. However, a prospective evaluation is warranted to determine whether a screening approach would result in improving the outcomes for patients with high risk of DM.

Neoadjuvant chemotherapy using cisplatin and fluorouracil for advanced resectable OSCC patients was evaluated in a phase III randomized controlled trial. With a median follow-up of 11.5 year, the 5-year cumulative incidence for DM was 4.1% for patients who received preoperative chemotherapy versus 9.3% for patients managed with up-front surgery ($p = 0.15$) [19]. Furthermore, addition of docetaxel to cisplatin and fluorouracil as a neoadjuvant treatment for OSCC was examined in a phase III randomized controlled trial and showed a trend toward a lower incidence of DM compared to patients treated with up-front surgery (5.5% versus 8.7%), however there was no statistically significant difference in distant metastasis free survival (HR = 0.9, 95% CI: 0.6 to 1.4, $p = 0.7$) [20].

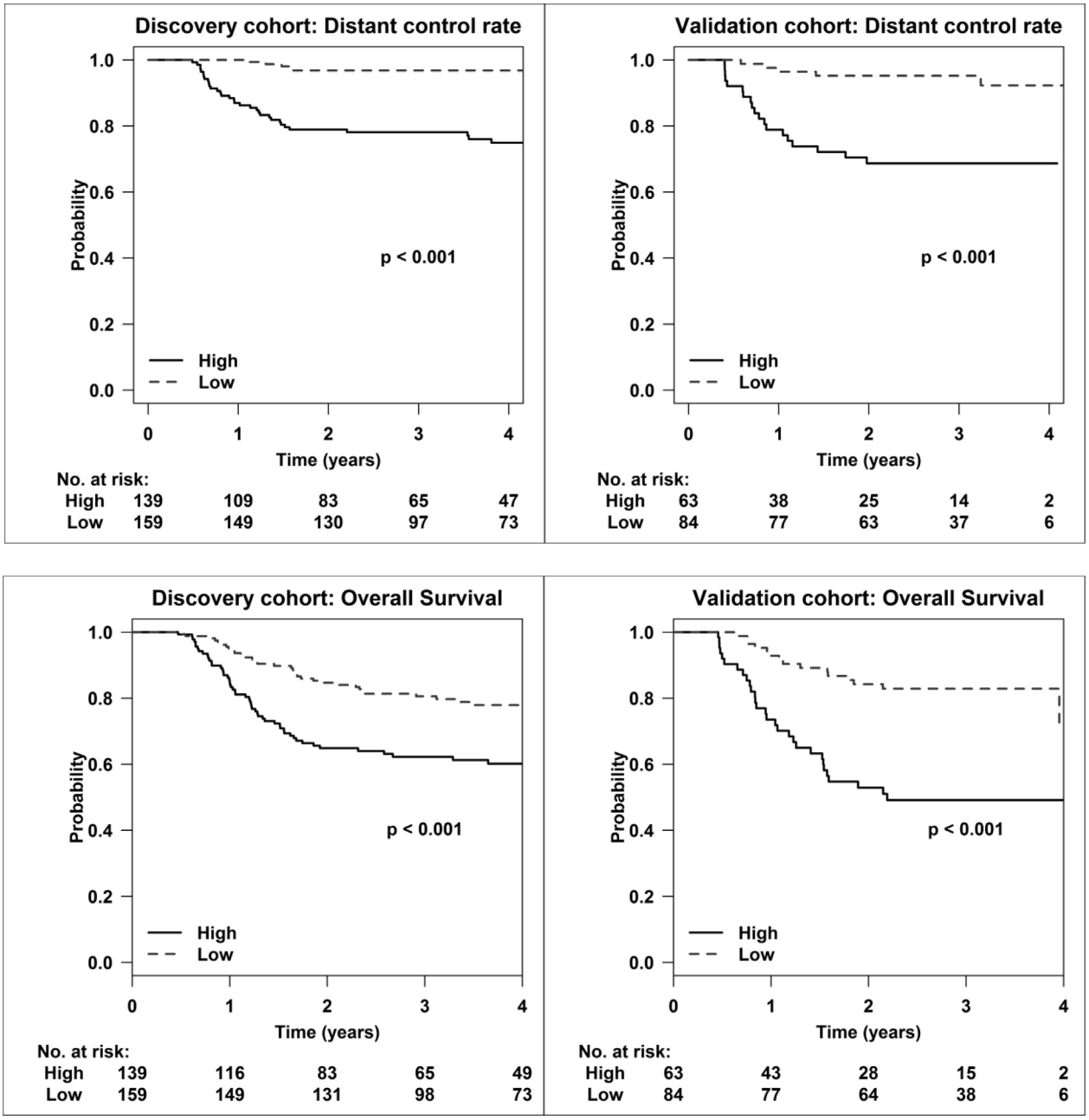

Fig. 2. Distant control and overall survival according to risk-group classification in the discovery and validation cohort.

The use of concurrent docetaxel-cetuximab regimen in the adjuvant setting showed improvement of DC with a derived-benefit in disease-free survival in a phase II randomized controlled trial [21], and the ongoing phase III RTOG 1216 study (NCT01810913) may provide a better understanding of the outcomes and pattern of failure following postoperative concurrent chemoradiation using taxane-based regimen.

This study should be interpreted within the context of its limitations. First, the study is retrospective; however the outcome data were prospectively collected. Second, the validation was performed in a subsequent cohort of patients with a shorter follow up duration, though the median time to metastasis in the discovery cohort was similar to the validation cohort. Third, all patients were treated at the same institution, and external validation is warranted before prospective evaluation. Finally, the analysis did not include any biologic, genomic, or molecular marker in the risk-group classification, though it is unclear that HPV or other molecular markers are of significant relevance within OSCC [22,23]. Nonetheless, the study has contributed toward predicting DM and OS outcomes following postoperative radiotherapy for OSCC. From a practical viewpoint, this simple validated model can be used as a "road map" with respect to predicting DM which is helpful for physician's best estimate and patient's best knowledge in terms of the DM probability. It can be used to measure the accuracy and success of future DM risk-stratification models which are built based on non-clinicopathologic features (e.g. radiomics and/or molecular genomics biomarkers). The logical next step is to use this validated model (G2-3/pN2-3) to identify OSCC patients who may benefit from: 1) more aggressive screening for DM (before initiating the treatment) in order to avoid unnecessary or inappropriate management, 2) experimental systemic treatment intensification to impact development of DM, and 3) a more

aggressive post-treatment surveillance schedule for early detection of DM and consideration of experimental ablative treatments for oligometastatic or early systemic treatment for non-oligometastatic disease.

Conclusion

The validated DM high risk group has poor survival, which could be used for the design of future prospective studies investigating treatment intensification and/or surveillance of DM in OSCC. Additional external validation should be attempted in prospective trials.

Funding sources of the work

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest notification

None declared.

Presented

Presented in part as an abstract (oral presentation) at the ESTRO annual meeting, Barcelona, 2018, and CARO annual meeting, Toronto, September 2017.

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. New Engl J Med 2004;350:1945–52.
[3] Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. New Engl J Med 2004;350:1937–44.
[4] Cooper JS, Zhang Q, Pajak TF, Forastiere AA, Jacobs J, Saxman SB, et al. Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2012;84:1198–205.
[5] Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 2005;27:843–50.
[6] Amit M, Yen TC, Liao CT, Chaturvedi P, Agarwal JP, Kowalski LP, et al. Improvement in survival of patients with oral cavity squamous cell carcinoma: An international collaborative study. Cancer 2013;119:4242–8.
[7] Sumioka S, Sawai NY, Kishino M, Ishihama K, Minami M, Okura M. Risk factors for distant metastasis in squamous cell carcinoma of the oral cavity. J Oral Maxillofac Surg 2013;71:1291–7.
[8] Senft A, de Bree R, Hoekstra OS, Kuik DJ, Golding RP, Oyen WJ, et al. Screening for distant metastases in head and neck cancer patients by chest CT or whole body FDG-PET: a prospective multicenter trial. Radiotherapy Oncol 2008;87:221–9.
[9] Senft A, Hoekstra OS, Witte BI, Leemans CR, de Bree R. Screening for distant metastases in head and neck cancer patients using FDG-PET and chest CT: validation of an algorithm. Eur Archiv Oto-rhino-laryngol 2016;273:2643–50.
[10] Hosni A, Huang SH, Xu W, Su J, Bayley A, Bratman SV, et al. Metastases following postoperative intensity-modulated radiotherapy for oral cavity squamous cell carcinoma. JAMA Otolaryngol 2016.
[11] Hosni A, Huang SH, Xu W, Su J, Bayley A, Bratman SV, et al. Metastases following postoperative intensity-modulated radiotherapy for oral cavity squamous cell carcinoma. JAMA Otolaryngol 2017;143:368–75.
[12] Hosni A, McMullen C, Huang SH, Xu W, Su J, Bayley A, et al. Lymph node ratio relationship to regional failure and distant metastases in oral cavity cancer. Radiotherapy Oncol 2017;124:225–31.
[13] Wong K, Huang SH, O'Sullivan B, Lockwood G, Dale D, Michaelson T, et al. Point-of-care outcome assessment in the cancer clinic: audit of data quality. Radiotherapy Oncol 2010;95:339–43.
[14] Sakamoto Y, Matsushita Y, Yamada S, Yanamoto S, Shiraishi T, Asahina I, et al. Risk factors of distant metastasis in patients with squamous cell carcinoma of the oral cavity. Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:474–80.
[15] Hasegawa T, Tanakura M, Takeda D, Sakakibara A, Akashi M, Minamikawa T, et al. Risk factors associated with distant metastasis in patients with oral squamous cell carcinoma. Otolaryngol Head Neck Surg 2015;152:1053–60.
[16] Liao CT, Wang HM, Chang JT, Ng SH, Hsueh C, Lee LY, et al. Analysis of risk factors for distant metastases in squamous cell carcinoma of the oral cavity. Cancer 2007;110:1501–8.
[17] Florescu C, Thariat J. Local ablative treatments of oligometastases from head and neck carcinomas. Critic Rev Oncol Hematol 2014;91:47–63.
[18] Young ER, Diakos E, Khalid-Raja M, Mehanna H. Resection of subsequent pulmonary metastases from treated head and neck squamous cell carcinoma: systematic review and meta-analysis. Clin Otolaryngol 2015;40:208–18.
[19] Bossi P, Lo Vullo S, Guzzo M, Mariani L, Granata R, Orlandi E, et al. Preoperative chemotherapy in advanced resectable OCSCC: long-term results of a randomized phase III trial. Ann Oncol 2014;25:462–6.
[20] Zhong LP, Zhang CP, Ren GX, Guo W, William Jr WN, Sun J, et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. J Clin Oncol 2013;31:744–51.
[21] Harari PM, Harris J, Kies MS, Myers JN, Jordan RC, Gillison ML, et al. Postoperative chemoradiotherapy and cetuximab for high-risk squamous cell carcinoma of the head and neck: Radiation Therapy Oncology Group RTOG-0234. J Clin Oncol 2014;32:2486–95.
[22] Zafereo ME, Xu L, Dahlstrom KR, Viamonte CA, El-Naggar AK, Wei Q, et al. Squamous cell carcinoma of the oral cavity often overexpresses p16 but is rarely driven by human papillomavirus. Oral Oncol 2016;56:47–53.
[23] Lopes V, Murray P, Williams H, Woodman C, Watkinson J, Robinson M. Squamous cell carcinoma of the oral cavity rarely harbours oncogenic human papillomavirus. Oral Oncol 2011;47:698–701.