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Radiotherapy induced dermatitis is a strong predictor for late fibrosis in head and neck cancer. The development of a predictive model for late fibrosis

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ABSTRACT

Purpose: To determine if the severity of radiodermatitis at the end of radio(chemo)therapy (R(C)T) for head and neck cancer (HNC) is a predictive factor for late fibrosis of the neck and to find a model to predict neck fibrosis grade $\geqslant 2$ (fibrosis $RTOG_{2\text{-}4}$) at 6 months following R(C)T for HNC.

Material/methods: 161 patients were prospectively included. We correlated radiodermatitis at the end of RCT, age, sex, T/N stage, tumor site, concomitant chemotherapy, upfront neck dissection, neo-adjuvant chemotherapy, accelerated RT, smoking, alcohol consumption, HPV status and the dose prescribed to the elective neck with fibrosis $RTOG_{2\text{-}4}$ 6 months after the end of treatment.

Results: Radiodermatitis at the end of R(C)T $\geqslant$grade 3 proved to be associated with the incidence of fibrosis $RTOG_{2\text{-}4}$ at 6 months ($p < 0.01$). Furthermore, upfront neck dissection ($p < 0.01$), increasing N stage ($p < 0.01$) and tumor site ($p = 0.02$) are significantly associated in univariate analysis with fibrosis $RTOG_{2\text{-}4}$ at 6 months of follow-up.

Upfront neck dissection and radiodermatitis grade $\geqslant 3$ at the end of R(C)T were identified by our multivariate model. Additionally, increasing N stage was selected as an independent predictor variable. The AUC for this model was 0.92.

Conclusion: A model for the prediction of fibrosis $RTOG_{2\text{-}4}$ following R(C)T for head and neck cancer is presented with an AUC of 0.92. Interestingly, radiodermatitis grade $\geqslant 3$ at the end of R(C)T is associated with $RTOG_{2\text{-}4}$ fibrosis at 6 months.

Radiotherapy (RT) for head and neck cancer (HNC) has significantly changed over the past decades. Treatment intensification improved clinical outcome, but also increased both early and late toxicity, heavily compromising Quality of Life (QoL) of the surviving HNC patients [1–5]. Neck fibrosis by example is an important late complication following radio(chemo-)therapy (R(C)T) for HNC [6–8].

Several techniques have been used to treat fibrosis within the head and neck region, including lycopene, pentoxifylline, pirfenidone, vitamin E, aloe vera, corticosteroid injections, interferon gamma, hyperbaric oxygen, stretching exercises, prophylactic swallowing exercises, hyperthermia, impedance controlled microcurrent therapy and acupuncture [9]. However, none of these techniques have shown a clear benefit up to now [9]. Since the treatment options for fibrosis following RT for HNC are limited, we must currently focus on prevention. Therefore it is important to identify which patient and treatment related parameters are associated with late fibrosis to select patients at risk for fibrosis in order to apply prophylactic interventions. Furthermore, using these parameters, we might be able to select patients for studies that further investigate potential treatments for fibrosis following RT for HNC in the future.

The purpose of this study was therefore to identify these parameters and to build a multivariate model to predict neck fibrosis grade $\geqslant 2$ (fibrosis $RTOG_{2\text{-}4}$) at 6 months following R(C)T for HNC.

Material/methods

Patient and treatment characteristics

The current paper is a second analysis of a prospective randomized controlled trial on dose de-escalation to the elective nodal volume in head and neck cancer. We collected prospectively gathered data from all 193 patients from this initial trial [10]. Inclusion criteria from the original trial were previously untreated, histologically proven squamous cell carcinoma of the oral cavity,

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oropharynx, hypopharynx, larynx or cervical lymph node metastases of unknown primary cancer (CUP). Patient work-up was done according to institutional guidelines. T1–T2N0 were allowed, if prophylactic neck irradiation was performed. Patients were older than 18 years with a Karnofsky performance status $\geqslant$70%. The decision for primary R(C)T with curative intent had to be made after a multidisciplinary meeting at each participating center. Concurrent chemotherapy was allowed, as well as pretreatment lymph node dissection. Local ethics committee approval was obtained before start of the study and all patients gave written informed consent. Patients were randomized to two treatment arms (experimental arm A and standard arm B). A total of 200 patients were included in the study (100 for each arm). To minimize the influence of center-specific parameters randomization was performed per center.

All macroscopically affected tumor sites were treated up to an equivalent dose at fractionation of 2 Gy (EQD2Gy) of 70 Gy. Fractionation schedule and total dose delivered to the primary tumor and affected lymph nodes were left to the discretion of each individual center. An overview of the different fractionation schedules and CTV–PTV margins can be found in the preliminary analysis of this study [10]. For the elective nodal volumes, patients randomized in arm A (experimental arm) were treated up to a EQD2Gy of 40 Gy. For arm B (control arm) the elective nodal volumes were treated up to a EQD2Gy of 50 Gy [10].

The endpoint of the current study is fibrosis $RTOG_{2-4}$ at 6 months of follow up. Patients from the original trial lacking toxicity scores at 6 months following the end of RT (32 patients) were excluded from the current analysis. A cohort of 161 patients (of the original 193 patients) remained available for further analysis.

All patients were treated with intensity modulated radiotherapy (IMRT). For target volume definition, a planning CT scan was used. The Planning Target Volume (PTV) was cropped for the outer contours of the patient (body). Chemotherapy consisted of cisplatin 100 mg/m^2 three weekly or cisplatin 40 mg/m^2 weekly.

Toxicity scoring and statistical analysis

Early toxicity was scored prospectively using the CTCAE criteria (version 3.0), late toxicity was scored prospectively by the physician using the RTOG-EORTC late radiation morbidity scoring.

We tested age, sex, T/N stage, tumor site, concomitant chemotherapy, upfront neck dissection, neo-adjuvant chemotherapy, accelerated RT, HPV status, smoking (never-former-current), pack years, alcohol consumption (never-former-current), drinks/week the dose prescribed to the elective neck, HPV status and radiodermatitis (grade 0–2 versus grade 3–4) at the end of treatment for their potential to predict neck fibrosis $RTOG_{2-4}$ 6 months after the end of treatment. No patients underwent adjuvant surgery, besides the patients who underwent an upfront neck dissection. Since only 4 patients never smoked, we made a group of patients who never smoked or smoked in the past to use for the further statistical analysis.

Fisher's exact test and Mann–Whitney *U* test were used for testing the association between fibrosis (grade 0–1 versus grade 2–4) with categorical or continuous variables, respectively. A stepwise selection procedure was followed to determine the best combination of predictor variables for fibrosis $RTOG_{2-4}$ at 6 months. The Area under the ROC curve (AUC) was determined for the final model. Additionally a bootstrap-corrected AUC value was calculated. This AUC value corrects for over optimism resulting from the fact that model construction and model validation were performed on the same data set. All tests are two-sided, a 5% significance level is considered for all tests. Analyses have been performed using SAS software (version 9.4 of the SAS System for Windows).

Results

The pre-treatment characteristics of these 161 patients are listed in Table 1. Different RT schedules were applied according to the policies of the individual treatment centers (Supplementary

Table 1
Pre-treatment characteristics of the patients cohort.

Patients and treatment characteristics	
Upfront neck dissection (ND)	
No ND	127/161 (78.9%)
ND	34/161 (21.1%)
Concomitant chemotherapy	
No chemotherapy	48/161 (29.8%)
Cisplatinum	113/161 (70.2%)
Neo-adjuvant chemotherapy	
No neo-adjuvant chemotherapy	155/161 (96.3%)
Neo-adjuvant chemotherapy	6/161 (3.7%)
Smoking	
Never/former	88/160[x] (55.0%)
Current	72/160[x] (45.0%)
Alcohol use of more than 3 units a day	
Never	13/160[x] (8.1%)
Former	36/160[x] (22.5%)
Current	111/160[x] (69.4%)
T-stage	
1	3/161 (1.9%)
2	59/161 (36.7%)
3	55/161 (34.2%)
4	36/161 (22.4%)
0	8/161 (5.0%)
N-stage	
0	40/161 (24.8%)
1	23/161 (14.3%)
2a	6/161 (3.7%)
2b	55/161 (34.2%)
2c	34/161 (21.1%)
3	3/161 (1.9%)
Primary tumor site	
Oral cavity	17/161 (10.6%)
Oropharynx	72/161 (44.7%) HPV + 15/72 HPV − 51/72 Unknown HPV status 6/72
Hypopharynx	36/161 (22.4%)
Larynx	28/161 (17.4%)
CUP	8/161 (5.0%)
Sex	
Male	132/161 (82.0%)
Female	29/161 (18.0%)
Age at diagnosis	
Mean	59.5
Median	58.0
Range	(39.0; 81.0)
Drinks/week	
Mean	26.0
Median	15.0
Range	(0.0; 300.0)
Pack years	
Mean	34.3
Median	35.0
Range	(0.0; 104.0)
UICC anatomical stage groups	
I	0 (0%)
II	18 (11.2%)
III	37 (23.0%)
IV	105 (65.8%)

ND = neck dissection, CUP = cancer of unknown primary, HPV = human papilloma virus.
[x] For one patient, no information regarding smoking and alcohol use.

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