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Original Article

Disease outcome and associated factors after definitive platinum based chemoradiotherapy for advanced stage HPV-negative head and neck cancer

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ABSTRACT

Background: Definitive concomitant cisplatin-based chemoradiotherapy (CRT) is the current gold standard for most patients with advanced stage head and neck squamous cell carcinoma (HNSCC) of the pharynx and larynx. Since previous meta-analysis on CRT outcomes in HNSCC have been reported, advances have been made in radiotherapy techniques and clinical management, while HPV-status has been identified as a strong confounding prognostic factor in oropharyngeal cancer. Here, we present real-world outcome data from a large multicenter cohort of HPV-negative advanced stage HNSCC treated with CRT using contemporary IMRT-based techniques.

Method: Retrospective data were collected from a multicenter cohort of 513 patients treated with definitive concurrent platinum-based CRT with curative intent between January 2009 and August 2017. Only patients with HPV-negative advanced stage (III-IV) HNSCC were included. A prognostic model for outcome was developed based on clinical parameters and compared to TNM.

Results: Nearly half of the 513 patients (49%) had an oropharyngeal tumor, often locally advanced (73.3% T3-T4b) and with involvement of the regional lymph nodes (84%). Most patients (84%) received cisplatin as single agent. In total 66% received the planned number of cycles and 75% reached a cumulative cisplatin dose of $\geq$200 mg/m^2. Locoregional control was achieved in 324 (63%) patients during follow-up, and no association with tumor sites was observed (p = 0.48). Overall survival at 5 year follow-up was 47%, with a better survival for laryngeal cancer (p = 0.02) compared to other sites. A model with clinical variables (gender, high pre-treatment weight loss, N2c/N3-stage and <200 mg/m^2 dose of cisplatin) provided a noticeably stronger association with overall survival than TNM-staging (C- index 0.68 vs 0.55). Simultaneous Integrated Boosting (SIB) significantly outperformed Sequential Boosting (SEQ) to reduce the development of distant metastasis (SEQ vs SIB: OR 1.91 (1.11–3.26; p = 0.02).

Conclusion: Despite advances in clinical management, more than a third of patients with HPV-negative HNSCC do not complete CRT treatment protocols due to cisplatin toxicity. A model that consists of clinical

Abbreviations: ACE-27, Adult comorbidity evaluation – 27; CRT, Chemoradiotherapy; DHNOCG, Dutch Head and Neck Oncology Cooperative Group; DM, Distant metastasis; HNSCC, Head and neck squamous cell carcinoma; HPSCC, Hypopharyngeal squamous cell carcinoma; HPV, Human papilloma virus; IMRT, Intensity-Modulated Radiation Therapy; IQR, Interquartile range; KM, Kaplan Meier; LSCC, Laryngeal squamous cell carcinoma; LRR, Locoregional recurrence; MI, Multiple imputation; MV, Multi variable; OPSCC, Oropharyngeal squamous cell carcinoma; OS, Overall survival; OTT, Overall treatment time; SEQ, Sequential boost; SIB, Simultaneous integrated boost; SCC, Squamous Cell Carcinoma; SPT, Second primary tumor.

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variables and treatment parameters including cisplatin dose provided the strongest association with overall survival. Since cisplatin toxicity is a major obstacle in completing definitive CRT, the development of alternative and less toxic radiosensitizers is therefore warranted to improve treatment results. The association of RT-boost technique with distant metastasis is an important finding and requires further study.

Head and neck squamous cell carcinomas (HNSCCs) arise in the mucosal lining of the upper aerodigestive tract. Classical risk factors for HNSCC are exposure to exogenous carcinogens (i.e. tobacco and/or alcohol) as well as infection with the human papillomavirus (HPV), especially in oropharyngeal carcinoma (OPSCC) [1,2]. HPV-positive OPSCC is nowadays considered as a separate disease entity with distinctive clinical and molecular characteristics and treatment outcome, and a separate staging in the 8th edition of the TNM system [3,4]. The larger proportion of HNSCC patients are HPV-negative [5]. Most patients (~60%) present with locoregionally advanced disease.

Current treatment protocols aim at achieving locoregional disease control with good quality of life, and consist of surgery, radiotherapy, chemoradiotherapy (CRT) and immunotherapy. Definitive cisplatin-based CRT has become the treatment of choice in advanced stage HNSCC that arise outside the oral cavity and larynx. This organ-preserving protocol has become the preferred treatment with salvage surgery for residual or relapsed cancers [6].

The cornerstone of CRT is radiotherapy, focused on delivering the appropriate dose to the gross disease and the elective nodal areas. The introduction of Intensity-Modulated Radiation therapy (IMRT) and VMAT has greatly reduced toxicity and improved quality of life [7], without hampering survival [8–10]. Boosting techniques are employed to increase the dose on the gross tumor volume. Contemporary RT boosting techniques include sequential (SEQ) or simultaneous integrated boost (SIB) [10].

Systemic platinum is considered the preferred concomitant treatment regimen for definitive CRT for patients younger than 70 years and consists of high-dose cisplatin (3 cycles of 100 mg/m^2) administered in week 1 and repeated every-three weeks concurrently with radiotherapy [11]. This regimen resulted in 6.5% survival benefit at five years and a reduction of locoregional recurrence (9.3%) and distant metastases (0.3%) [12,13]. Also alternative systemic regimens have been applied, with at least a platinum-based component. They consistently improved overall survival compared to radiotherapy alone [12,13]. Patients with HPV-negative HNSCC unfit to receive cisplatin may be treated with cetuximab, an anti-EGFR antibody [14].

Most of our knowledge about treatment failure after CRT and its associated factors is based on heterogeneous patient cohorts with respect to HPV-status, applied chemotherapy protocols or radiotherapy techniques [12,13,15,16]. Recent clinical trials confirmed the key role of cisplatin treatment in HPV-positive disease [17,18], substantiating the combination treatment for these tumors. There is however much less recent information on HPV-negative disease. Here, we present the outcome results of a recent multicenter retrospective cohort of HPV-negative advanced stage HNSCC treated with definitive concurrent platinum-based CRT and contemporary IMRT/VMAT-based radiotherapy techniques.

Methods

Patient selection and data collection

We analyzed a multicenter retrospective cohort of patients included in the DESIGN study (KWF-A6C7072). This cohort consisted of patients treated with definitive platinum-based concomitant CRT with curative intent at Amsterdam UMC (location VUmc), Netherlands Cancer Institute (Amsterdam, the Netherlands), UMC Utrecht or Maastro clinic/Maastricht University Medical Center (Maastricht, the Netherlands) for advanced-stage HPV-negative oropharyngeal, hypopharyngeal or laryngeal SCC between January 2009 and August 2017. HPV status of the OPSCC cases was determined by p16 immunohistochemical staining followed by HPV DNA PCR on the p16-immunopositive cases [19]. Patients with a history of previous malignancy that could impact prognosis or if they were previously treated with radiotherapy in the head and neck region, were excluded. Diagnostic work-up consisted of physical examination, (nuclear) imaging and examination under general anesthesia, according to the guidelines of the Dutch Head and Neck Oncology Cooperative Group (DHNOCG) guidelines [20]. Clinical staging in that period was according to the 7th edition of the American Joint Committee on Cancer staging manual. Clinical data were collected from patient files and recorded in OpenClinica open source software, version 3.14 (Copyright © OpenClinica LLC and collaborators, Waltham, MA, USA, https://www.OpenClinica.com). Comorbidity was classified according to the Adult Comorbidity Evaluation – 27 (ACE-27) [21]. This study was carried out in accordance to the Declaration of Helsinki and performed following the guidelines of the Code of Conduct for Human Tissue and Medical Research (https://www.federa.org/-codes-conduct) for informed consent, and the General Data Protection Regulation of the EU commission.

Treatment

Locoregional treatment was according to the DHNOCG-guidelines. In short, patients were diagnosed and reviewed in a multidisciplinary tumor board at each individual center. All patients planned for CRT were treated with IMRT to receive a minimal total dose of 70 Gy in 35 fractions over a period of 6–7 weeks on the gross tumor volumes (GTVs) including the primary tumor and the involved neck-nodes using either conventional fractionation or accelerated fractionation. The elective nodal volumes were treated with a dose-equivalent to 46–50 Gy. In conventional fractionation protocols, patients received daily 2 Gy fractions 5 times a week; in the accelerated-fractionation protocol patients received the same dose but in a schedule of 6 fractions per week, resulting in a reduced overall treatment time (OTT). Different boosting methods were applied, either simultaneous integrated boost (SIB) techniques or with sequential (SEQ) boosting protocols, depending on the preference of the institution. In 76% of patients chemotherapy was administered in a three-weekly high-dose cisplatin (100 mg/m^2) regimen, and most patients (84%) received cisplatin as single agent. Alternative treatment (weekly or daily) strategies were applied in cases where the three-weekly schedule was deemed to be too toxic.

Clinical outcome

The clinical endpoints evaluated in this study were overall survival (OS), locoregional recurrence (LRR), and distant metastasis

(DM). Overall survival time was defined as the time between histological confirmation of the primary tumor and date of death or the last follow-up date. Criteria for local recurrence were residual or recurrent tumor within 2 cm from and within 3 years after the index-tumor as confirmed by histological analysis [22] or in few cases by radiological imaging. LRRs not fulfilling these criteria were considered as second primary tumors (SPT), and these patients were censored at the date of SPT diagnosis except for overall survival. DM were diagnosed during follow-up by routine imaging.

Missing data handling and multivariable regression analysis

Both missing data handling and multivariable regression analysis (MV) are extensively described in the Supplementary methods. In short, we chose to split the data based on primary diagnosis date into two cohorts, one for exploration and one for validation (Supplementary methods; first paragraph). Both cohorts were compared to assess structural differences. Missing values were handled using Multivariate Imputation by Chained Equations procedure using the MICE R package (version 3.7.0) [23].

MV regression analysis with backward-selection included all variables with a $p < 0.20$ in univariate analysis on the source data (Supplementary Table 2). MV analysis and selection was based on the obtained pooled p-values according to Rubin's Rules [24] using a critical p-value of 0.05 using the psfmi R-package (version 0.7.1). For OS a Cox regression model was generated, and a logistic regression analysis was performed for both LRR and DM. All analyses were performed in R: a language and environment for statistical computing (version 3.6.1).

Results

Between January 2009 and August 2017, a total of 513 patients with advanced stage III-IV HPV-negative oropharyngeal, hypopharyngeal or laryngeal HNSCC were treated with definitive concomitant platinum-based CRT and fulfilled the inclusion criteria for this study. Baseline characteristics are listed in Table 1. Median age of the patient group was 61 (IQR: 56–65) years. The majority was male (68%) and most patients had been exposed to the classical risk factors: almost all (96%) were former or current tobacco smokers with a median tobacco exposure of 40 (IQR: 26–48) pack-years. Nearly half of the patients (49.3%) had oropharyngeal cancer, most tumors were locally advanced (73% T3-T4b) and regional lymph nodes were involved in 85%. Most patient, tumor and treatment-characteristics were comparable between tumor-sites. The proportion of never-alcohol users was highest amongst patients with LSCC (OPSCC vs HPSCC vs LSCC; 7% vs 10% vs 20%; $p < 0.01$). There were significant differences in baseline weight-loss values for the different tumor sites, with more weight loss for patients with OPSCC or HPSCC compared to patients with LSCC. The median follow-up time was 57.7 months (95% CI: 46.9–65.1).

Most patients received conventional fractionation radiotherapy and in 12.5% of the patients accelerated-fractionation radiotherapy was given. The boosting method was different at different centers according to local preferences resulting in approximately half (54%) to have received SIB and half (46%) SEQ. This resulted in a different physical radiation total dose to the elective neck: patients treated with SIB received on average 54.7 Gy (SD = 1.43 Gy), while patients treated with SEQ received 46.0 Gy (SD = 0.54 Gy).

Most patients were to receive a total of 300 mg/m^2 cisplatin divided over a three-weekly regimen. Ten percent received cisplatin weekly (dose 40 mg/m^2) and 11% received daily low-dose cisplatin (dose 6 mg/m^2). In total 34.5% of patients did not complete their planned chemotherapy scheme. The most frequent (86 of 177 patients) reason to discontinue further cisplatin treatment was the occurrence of nephrotoxicity (Table 2). Nevertheless, 35% of these patients were still eligible to a subsequent alternative concomitant systemic regimen, mostly carboplatin. Consequently, patients who switched to a carboplatin regimen received a lower cumulative dose (mean = 140, SD = 64.6) of cisplatin compared to patients who did not switch (mean = 178, SD = 54.4) ($p \leq 0.001$). A quarter (25%) of patients (n = 126) did not reach a cumulative dose of 200 mg/m^2 cisplatin, due to the use of alternative systemic therapy or dose schedule regimen (n = 47) or in the majority due to toxicity (n = 79).

Of the 513 patients, 324 (63.2%) remained relapse-free. A total of 127 (24.7%) patients developed a LRR of whom 27 also developed DM simultaneously or within a 3 month period. In 14 patients a DM occurred more than 3 months from date of LRR. DM were diagnosed in 103 (20.1%) patients and in 62 cases (12.1%) this was the sole event. (Fig. 1**A**). The total incidence of treatment failure (developing LRR or DM) did not differ significantly between sites (OPSCC = 38.4% vs HPSCC = 35.9% vs LSCC = 31.9%; p = 0.48).

The estimated OS for this cohort was 46.6% (95% CI 41.6–52.3%) at 5-year (Supplementary Fig. 2) with a significant different (p = 0.02) survival distribution for sites; OPSCC: 43.5% (95% CI 36.5–51.8%), HPSCC 45.5% (95% CI 37.5–55.2%) and LSCC 58.2% (95% CI 46.2–73.3%). As expected, patients who developed a LRR had worse OS compared to those who did not and remained DM-free with median OS of 20.3 months (95% CI 15.6–25.3) and 70.6 months ($p < 0.001$), respectively. Patients who developed DM had a median OS of 21.5 months (95% CI 16.6–24.7) compared to 70.6 months (95% CI 65.1–NA) for patients without DM ($p < 0.001$). For both LRR and DM patients there was no significant difference in survival between sites (LRR: $\chi^2(2) = 3.9$, p = 0.1 vs DM: $\chi^2(2) = 0.8$, p = 0.7).

To determine factors associated with outcome, we created an exploration (patients diagnosed between 2009 and 2014; n = 379) and a validation cohort (patients diagnosed between 2015 and August 2017; n = 134). The split in time was chosen to have unbiased data with a long follow-up time for the exploration cohort. No significant differences were observed between both cohorts in patient or tumor characteristics except for applied treatment protocols reflecting development in treatment protocols within the guidelines and related to chemotherapy scheme (validation cohort less distinctive schemes), radiotherapy fractionation (less accelerated schemes in validation cohort) and boosting method (SIB in test-cohort vs validation-cohort: 47% vs 73%, all $p < 0.05$) (Supplementary Table 1). Univariate analysis was carried out on the training cohort on the following covariates: age, gender, WHO performance score, ACE-27, history of previous malignancies, tobacco/alcohol usage and pack/unit years, weight loss, hemoglobin levels, tumor site and lateralization, overall disease stage, T- and N-stage, pathological features (perineural- or vaso-invasive growth), chemotherapy type, cumulative cisplatin dose, radiotherapy boosting method and scheme and overall treatment time. Participating center was added as a covariate to test center-specific effects. Covariates with an assumed association ($p \leq 0.20$) on univariate analysis on the exploration data (Supplementary Table 2) were processed in multivariable analysis with backward selection across the multiple imputed datasets. Since we considered tumor site as a critical parameter in these analyses [25], this covariate was forced into the final model, despite it only met our criteria for variable selection in OS (p = 0.09).

Multivariable analysis and backward selection revealed 4 outcome parameters: a less favorable OS was significantly associated with male gender, high weight loss, N2c/N3-stage and <200 mg/m^2 cumulative dose of cisplatin (Table 3). A model based on these clinical variables achieved a pooled C-index for OS of 0.65 (95% CI

Table 1
Descriptive characteristics of patients treated with concomitant platinum based chemoradiotherapy from 2009- August 2017.

Patient characteristics	Total (n = 513) No. (%)	HPV-OPSCC (n = 253) No. (%)	HPSCC (n = 167) No. (%)	LSCC (n = 93) No. (%)	p-value*
Participating center					0.391
Center A	156 (0.30)	75 (0.30)	49 (0.29)	32 (0.34)	
Center B	179 (0.35)	87 (0.34)	63 (0.38)	29 (0.31)	
Center C	122 (0.24)	69 (0.27)	34 (0.20)	19 (0.20)	
Center D	56 (0.11	22 (0.09)	21 (0.13)	13 (0.14)	
Age (Median (IQR))	61.0 (56.0–65.0)	61.0 (56.0–65.0)	61.0 (58.0–65.0)	61.0 (55.0–64.0)	0.408
Gender					0.184
Male	347 (0.68)	165 (0.65)	122 (0.73)	60 (0.65)	
Female	163 (0.32)	88 (0.35)	44 (0.26)	31 (0.33)	
Unknown	3 (0.01)	0 (0.00)	1 (0.01)	2 (0.02)	
WHO					0.501
1	154 (0.37)	72 (0.36)	60 (0.36)	22 (0.24)	
2	240 (0.58)	113 (0.56)	75 (0.45)	52 (0.56)	
3	19 (0.05)	16 (0.08)	2 (0.01)	1 (0.01)	
Unknown	100 (0.20)	52 (0.21)	30 (0.18)	18 (0.19)	
Comorbidity					0.326
None	169 (0.39)	86 (0.42)	53 (0.32)	30 (0.32)	
Mild	204 (0.47)	95 (0.46)	73 (0.44)	36 (0.39)	
Moderate	54 (0.13)	25 (0.12)	15 (0.09)	14 (0.15)	
Severe	3 (0.01)	1 (0.00)	2 (0.01)	0 (0.00)	
Unknown	83 (0.16)	46 (0.18)	24 (0.14)	13 (0.14)	
Previous malignancies					0.126
No	458 (0.90)	223 (0.89)	146 (0.88)	89 (0.96)	
Yes	51 (0.10)	28 (0.11)	19 (0.12)	4 (0.04)	
Unknown	4 (0.01)	2 (0.01)	2 (0.01)	0 (0.00)	
Tobacco user					0.553
Never	14 (0.03)	6 (0.02)	7 (0.04)	1 (0.01)	
Former	371 (0.72)	189 (0.75)	111 (0.66)	71 (0.76)	
Current	125 (0.25)	56 (0.22)	49 (0.29)	20 (0.22)	
Unknown	3 (0.01)	2 (0.01)	0 (0.00)	1 (0.01)	
Packyears (Median (IQR))	39.8 (25.8–48.0)	40.0 (30.0–48.0)	34.0 (21.0–45.0)	40.0 (27.3–50.0)	0.073
Low (0–31.5)	168 (0.36)	74 (0.32)	66 (0.45)	28 (0.32)	0.068
Medium (31.5–46.0)	171 (0.37)	94 (0.40)	47 (0.32)	30 (0.34)	
High (>46.0)	128 (0.27)	65 (0.28)	34 (0.23)	29 (0.33)	
Unknown	46 (0.09)	20 (0.08)	20 (0.12)	6 (0.06)	
Alcohol user					**0.002**
Never	53 (0.10)	17 (0.07)	17 (0.10)	19 (0.21)	
Former	361 (0.71)	181 (0.73)	119 (0.71)	61 (0.69)	
Current	91 (0.18)	51 (0.20)	31 (0.19)	9 (0.10)	
Unknown	8 (0.02)	4 (0.02)	0 (0.00)	4 (0.04)	
Alcohol years (Median (IQR))	120 (27.5–206)	150 (76.2–240)	120 (40.5–200)	25.0 (0.00–144)	**<0.001**
Low (0–84)	88 (0.37)	31 (0.28)	31 (0.39)	26 (0.58)	**0.004**
Medium (84–185)	72 (0.31)	34 (0.31)	25 (0.31)	13 (0.29)	
High (>185)	75 (0.32)	45 (0.41)	24 (0.30)	6 (0.13)	
Unknown	278 (0.54)	143 (0.57)	87 (0.52)	48 (0.52)	
Haemoglobin level					0.193
Low	107 (0.24)	58 (0.26)	36 (0.26)	13 (0.16)	
Normal-high	332 (0.76)	166 (0.74)	100 (0.74)	66 (0.84)	
Unknown	74 (0.14)	29 (0.12)	31 (0.19)	14 (0.15)	
Weightloss per month (%/month)					**<0.001**
No (0)	196 (0.49)	78 (0.40)	66 (0.53)	52 (0.70)	
Low (<1.4)	75 (0.19)	37 (0.19)	29 (0.23)	9 (0.12)	
High (>1.4)	125 (0.32)	82 (0.42)	30 (0.24)	13 (0.18)	
Unknown	117 (0.23)	56 (0.22)	42 (0.25)	19 (0.20)	
Tumor characteristics					
Tumor lateralisation					0.177
Left	221 (0.44)	113 (0.46)	72 (0.43)	36 (0.41)	
Right	223 (0.45)	103 (0.42)	83 (0.50)	37 (0.43)	
Midline	56 (0.11)	30 (0.12)	12 (0.07)	14 (0.16)	
Unknown	13 (0.03)	7 (0.03)	0 (0.00)	6 (0.06)	
T-classification					**0.047**
T1-T2	137 (0.27)	61 (0.24)	56 (0.34)	20 (0.22)	
T3-T4b	376 (0.73)	192 (0.76)	111 (0.66)	73 (0.78)	
N-classification					**<0.001**
N0	78 (0.15)	36 (0.14)	15 (0.09)	27 (0.29)	
N1-N2b	281 (0.55)	143 (0.57)	104 (0.63)	34 (0.37)	
N2c-N3	152 (0.30)	73 (0.29)	47 (0.28)	32 (0.34)	
Unknown	2 (0.00)	1 (0.00)	1 (0.01)	0 (0.00)	
Stage					**0.017**
III	85 (0.17)	37 (0.15)	23 (0.14)	25 (0.27)	
IVA	370 (0.72)	187 (0.74)	120 (0.72)	63 (0.68)	
IVB	58 (0.11)	29 (0.11)	24 (0.14)	5 (0.05)	

(*continued on next page*)

Table 1 (*continued*)

Patient characteristics	Total (n = 513) No. (%)	HPV-OPSCC (n = 253) No. (%)	HPSCC (n = 167) No. (%)	LSCC (n = 93) No. (%)	p-value*
Growth pattern					0.118
Cohesive	218 (0.63)	110 (0.63)	65 (0.58)	43 (0.74)	
Non-Cohesive	127 (0.37)	65 (0.37)	47 (0.42)	15 (0.26)	
Unknown	168 (0.33)	78 (0.31)	55 (0.33)	35 (0.38)	
Perineural growth					0.364
No	369 (0.95)	182 (0.96)	122 (0.95)	65 (0.92)	
Yes	20 (0.05)	8 (0.04)	6 (0.05)	6 (0.08)	
Unknown	124 (0.24)	63 (0.25)	39 (0.23)	22 (0.24)	
Vaso-invasion					0.541
No	381 (0.98)	186 (0.98)	126 (0.99)	69 (0.97)	
Yes	7 (0.02)	4 (0.02)	1 (0.02)	2 (0.03)	
Unknown	125 (0.24)	63 (0.25)	40 (0.24)	22 (0.24)	
Treatment characteristics					
Chemotherapy					
Scheme					0.920
Daily	56 (0.11)	28 (0.11)	15 (0.09)	13 (0.14)	
Weekly	50 (0.10)	26 (0.10)	16 (0.10)	8 (0.09)	
3-weekly	387 (0.76)	192 (0.76)	127 (0.77)	68 (0.74)	
Alternative	16 (0.03)	7 (0.03)	6 (0.04)	3 (0.03)	
Unknown	4 (0.01)	0 (0.00)	3 (0.02)	1 (0.01)	
Chemotherapy details					0.855
Cisplatin single	429 (0.84)	207 (0.82)	143 (0.86)	79 (0.85)	
Carboplatin single	7 (0.01)	3 (0.01)	3 (0.02)	1 (0.01)	
Cisplatin + carboplatin	64 (0.12)	37 (0.15)	16 (0.10)	11 (0.12)	
Cisplatin + other	12 (0.02)	5 (0.02)	5 (0.03)	2 (0.02)	
Carboplatin + other	1 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	
Cumulative dose cisplatin					0.789
>=200 mg/m2	375 (0.73)	181 (0.72)	126 (0.75)	68 (0.73)	
<200 mg/m2	126 (0.25)	67 (0.26)	36 (0.22)	23 (0.25)	
Miscellaneous	12 (0.02)	5 (0.02)	5 (0.03)	2 (0.02)	
Radiotherapy					
Details					0.581
Conventional	445 (0.87)	218 (0.87)	149 (0.89)	78 (0.85)	
Accelerated	64 (0.12)	32 (0.13)	18 (0.11)	14 (0.15)	
Unknown	4 (0.01)	3 (0.01)	0 (0.00)	1 (0.01)	
Boost					0.845
SIB	276 (0.54)	132 (0.53)	92 (0.55)	52 (0.57)	
SEQ	231 (0.46)	116 (0.47)	75 (0.45)	40 (0.43)	
Unknown	6 (0.01)	5 (0.02)	0 (0.00)	1 (0.01)	
Overall treatment time	47.0 (47.0–47.0)	47.0 (47.0–48.0)	47.0 (47.0–47.0)	47.0 (46.0–47.0)	0.119

* Shapiro-Wilk test is performed to assess normality of the distribution, with a significance level of p = 0.05. Comparisons between groups were made by Kruskal Wallis test for non-normal distributed continuous variables, and the Spearmans' rank correlation and Chi-square test for categorical variables.

Table 2
Analysis of dose-limiting factors for cisplatin and consequences for cumulative dose and further treatment.

Dose-limiting factor	Total patients (n = 513) No. (%)	Cumulative dose cisplatin		Switch to carboplatin No. (%)
		≥200 mg/m^2 (No. (%))	<200 mg/m^2 (No. (%))	
Tumor progression during treatment	1 (0.2)	1 (100)	0 (0)	0 (0.0)
High grade nephrotoxicity	86 (16.8)	31 (36.0)	55 (64.0)	34 (39.5)
High grade ototoxicity	27 (5.3)	22 (81.5)	5 (18.5)	21 (77.8)
Infection	19 (3.7)	17 (89.5)	2 (10.5)	1 (5.3)
Other	44 (8.6)	27 (61.4)	17 (38.6)	6 (13.6)
Subtotal	177 (34.5)	98 (55.4)	79 (44.6)	62 (35.0)

0.57–0.73). Independent validation on the second cohort showed a slightly improved C-index (0.68; 95% CI 0.59–0.76). Fig. 2A shows KM (Kaplan-Meier) survival curves of the validation cohort after stratification into low- and high-risk groups based on these variables. The p-value of the log-rank test of the low–high split was <0.005. Risk stratification based on TNM-stage had a C-index of 0.55 in the exploration cohort and a C-index of 0.64 in the validation cohort. KM survival curves based on stratification by TNM-stage are displayed in Fig. 2B.

Further MV logistic regression analyses with backward selection on parameters associated with DM and LRR, showed that a more advanced disease stage and a cumulative cisplatin dose <200 mg/m^2 was significantly associated with LRR in this patient cohort. DM was significantly associated with N-stage, previous malignancies and radiotherapy boosting method (Table 3 & Supplementary Table 2). A model based on these variables had an AUC of 0.66 (95% CI 0.59–0.72) in the exploration cohort and 0.71 (95% CI 0.60–0.80) in the validation set. SIB and SEQ boosting

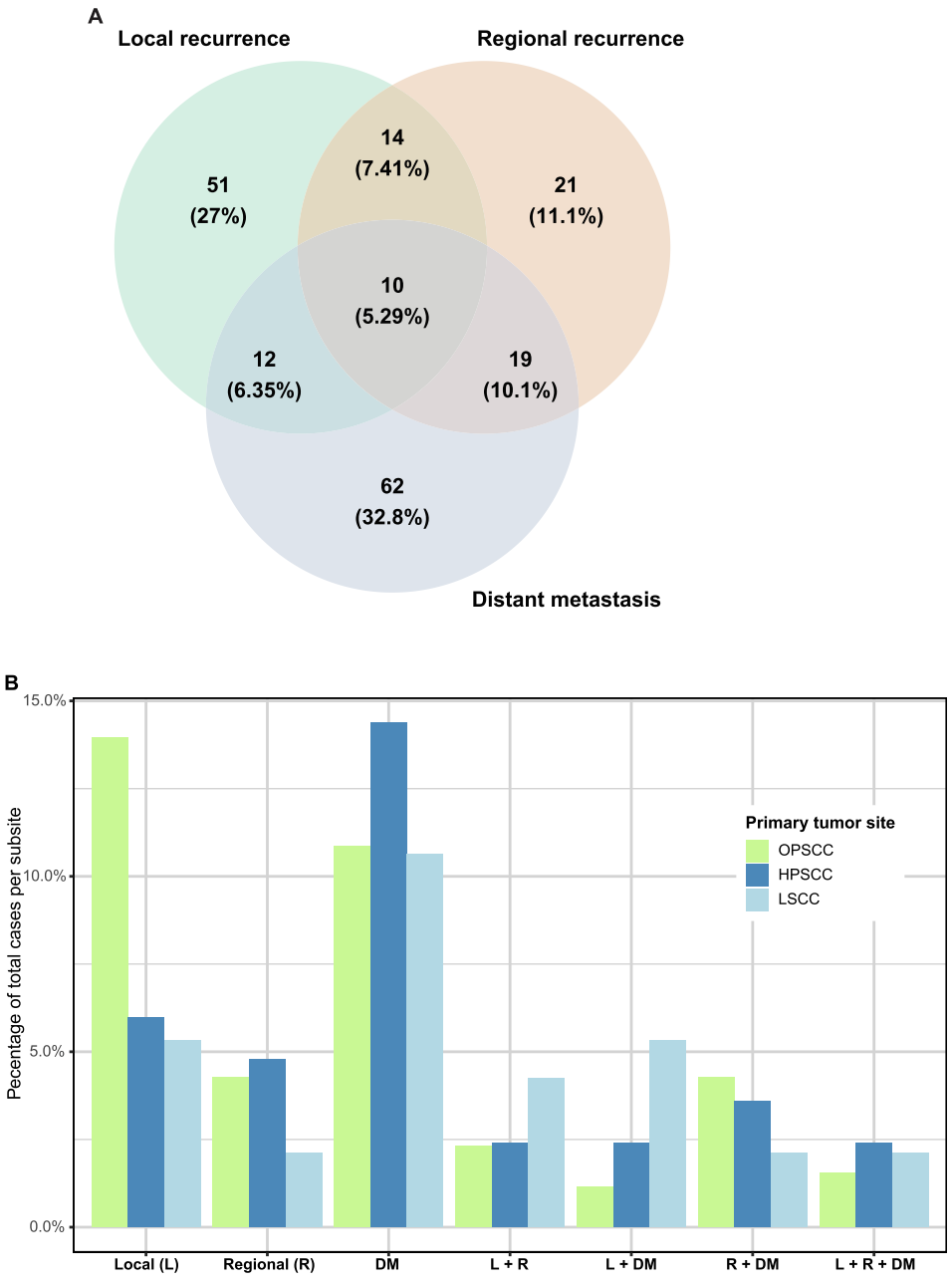

Fig. 1. Failure pattern after concomitant platinum-based CRT.

method were associated to the participating centers, but participating center was not favored in the model when SIB and SEQ were selected as the stronger predicting variables.

Discussion

This multicenter study with a large cohort of uniformly diagnosed, treated and followed patients provides insight in real-world data using modern CRT techniques in a representative group of patients with HPV-negative tumors and without trial selection. Moreover, the focus on HPV-negative disease allows us to evaluate the significant parameters of treatment failure in this more treatment-resistant disease [1].

As a consequence of the current treatment-guidelines, our cohort consists of patients without significant comorbidities, as in these patients high dose chemotherapy is omitted. The differences between sites were often non-significant with few exceptions including alcohol consumption and weight loss which occurred less frequently in the LSCC group. Weight loss is a common symptom in patients with HNC and associated with poor prognosis [26,27] as was confirmed by our data and further selection in our model for OS.

Our study confirms results of previous authors [28,29] on the importance of a cumulative cisplatin-dose ($\geq$200 mg/m^2) for LRR risk reduction and improved OS. Despite intensive patient support and exclusion of patients with high comorbidities, concomitant CRT treatment is too toxic for many patients with up to 35% of patients requiring adaptation in the cisplatin-dose schedule. This number is comparable to other studies [28,30], and the dose-limiting factors have been reported previously. [28,30–32] In our study we find that clinicians tend to switch to carboplatin if

Table 3
Uni- and multivariable analysis of factors associated with overall survival, locoregional recurrence and distant metastasis across multiply imputed datasets on the exploration set. Variables that were associated (p < 0.20) in univariable analysis on the source data were included in a multivariable regression analysis with backward selection with a critical p-value of 0.05.

	Overall survival				Locoregional recurrence				Distant metastasis			
	Univariable		Multivariable		Univariable		Multivariable		Univariable		Multivariable	
Covariate	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Clinical characteristics												
Gender												
Male	**1 (Reference)**		**1 (Reference)**		1 (Reference)		NS	NS	1 (Reference)		NS	NS
Female	**0.74 (0.54–1.02)**	**0.06**	**0.65 (0.47–0.90)**	**0.01**	0.66 (0.39–1.09)	0.11	NS	NS	0.63 (0.35–1.1)	0.11	NS	NS
Weight loss per month (%)												
No	**1 (Reference)**		**1 (Reference)**		1 (Reference)		NT	NT	1 (Reference)		NT	NT
Low	**1.15 (0.73–1.86)**	**0.51**	**1.23 (0.80–1.89)**	**0.34**	1.36 (0.68–2.68)	0.37	NT	NT	1.18 (0.53–2.53)	0.67	NT	NT
High	**2.03 (1.42–2.91)**	**< 0.01**	**1.83 (1.29–2.61)**	**< 0.01**	1.2 (0.66–2.18)	0.54	NT	NT	1.29 (0.67–2.48)	0.45	NT	NT
Previous malignancies												
No	1 (Reference)		NT	NT	1 (Reference)		NT	NT	**1 (Reference)**		**1 (Reference)**	
Yes	0.92 (0.58–1.46)	0.73	NT	NT	0.91 (0.41–1.89)	0.82	NT	NT	**2.08 (0.99–4.21)**	**0.05**	**2.19 (1.04–4.63)**	**0.04**
Tumor characteristics												
Tumor site[1]												
OPSCC	**1 (Reference)**		**1 (Reference)**		**1 (Reference)**		**1 (Reference)**		**1 (Reference)**		**1 (Reference)**	
HPSCC	**0.89 (0.66–1.21)**	**0.46**	**1.02 (0.74–1.41)**	**0.89**	**0.70 (0.41–1.17)**	**0.18**	**0.77 (0.46–1.31)**	**0.34**	**1.25 (0.71–2.17)**	**0.44**	**1.25 (0.71–2.23)**	**0.44**
LSCC	**0.61 (0.40–0.95)**	**0.03**	**0.64 (0.40–1.00)**	**0.05**	**0.78 (0.40–1.44)**	**0.44**	**0.82 (0.43–1.57)**	**0.55**	**1.34 (0.67–2.58)**	**0.4**	**1.44 (0.71–2.93)**	**0.31**
N-classification												
N0	**1 (Reference)**		**1 (Reference)**		1 (Reference)		NT	NT	**1 (Reference)**		**1 (Reference)**	
N1-N2b	**1.35 (0.83–2.18)**	**0.22**	**1.16 (0.71–1.89)**	**0.56**	1.35 (0.67–2.93)	0.42	NT	NT	**6.71 (1.97–41.99)**	**0.01**	**6.33 (1.46–27.4)**	**0.01**
N2c-N3	**2.17 (1.32–3.58)**	**< 0.01**	**1.88 (1.12–3.15)**	**0.02**	1.57 (0.73–3.53)	0.26	NT	NT	**9.68 (2.77–61.37)**	**<0.01**	**9.19 (2.07–40.7)**	**<0.01**
Stage												
III	1 (Reference)		NS	NS	**1 (Reference)**		**1 (Reference)**		1 (Reference)		NS	NS
IVA	1.46 (0.94–2.18)	0.09	NS	NS	**2.58 (1.23–6.09)**	**0.02**	**2.49 (1.12–5.56)**	**0.03**	3.12 (1.31–9.27)	0.02	NS	NS
IVB	2.26 (1.32–3.88)	<0.01	NS	NS	**2.49 (0.94–6.93)**	**0.07**	**2.56 (0.94–6.98)**	**0.07**	3.36 (1.12–11.48)	0.04	NS	NS
Treatment characteristics												
Cumulative dose cisplatin												
>=200 mg/m2	**1 (Reference)**		**1 (Reference)**		**1 (Reference)**		**1 (Reference)**		1 (Reference)		NT	NT
<200 mg/m2	**1.67 (1.23–2.26)**	**< 0.01**	**1.69 (1.23–2.33)**	**< 0.01**	**2.00 (1.21–3.3)**	**<0.01**	**1.95 (1.17–3.25)**	**0.01**	0.85 (0.46–1.51)	0.59	NT	NT
Miscellaneous	**2.34 (1.14–4.78)**	**0.02**	**2.85 (1.36–5.96)**	**< 0.01**	**1.41 (0.3–5.22)**	**0.63**	**1.37 (0.34–5.53)**	**0.66**	1.56 (0.33–5.81)	0.53	NT	NT
Boost												
SIB	1 (Reference)		NS	NS	1 (Reference)		NS	NS	**1 (Reference)**		**1 (Reference)**	
SEQ	1.41 (1.06–1.88)	0.02	NS	NS	1.40 (0.88–2.22)	0.15	NS	NS	**2.18 (1.31–3.71)**	**<0.01**	**1.91 (1.11–3.26)**	**0.02**

[1] Factors that are forced in the backward selection of the final model. NT: Not Tested in multivariable analysis (p > 0.20 in univariable analysis). NS: Not significant in multivariable analysis (p > 0.05).

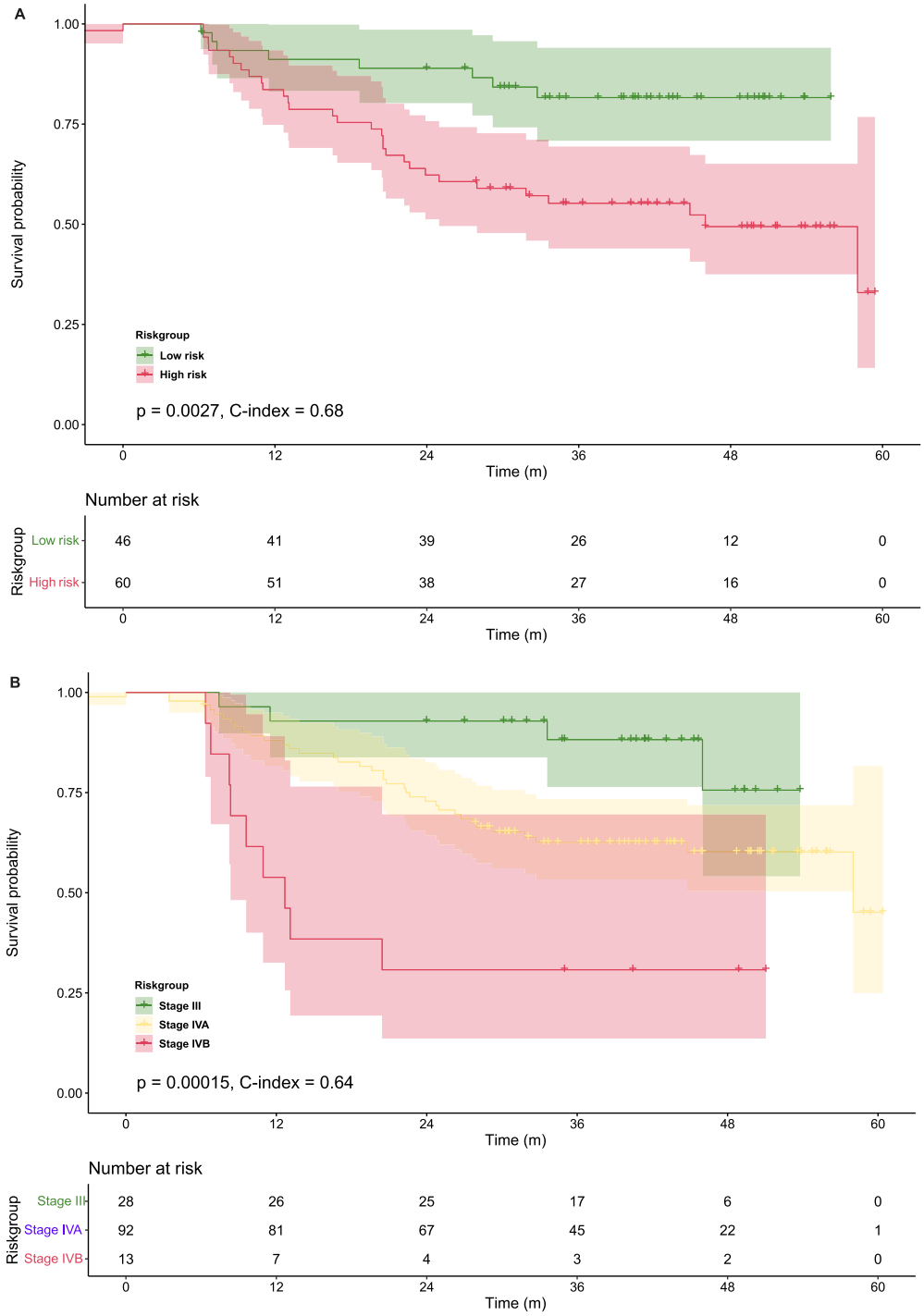

Fig. 2. A model based on four clinical parameters (gender, weight loss, N-stage and dose of cisplatin) predicts overall survival better than TNM-staging. Kaplan-Meier analysis of overall survival of different risk groups as defined by the clinical model and median predicted risk value in the validation cohort (A) and of risk groups as defined by the TNM-stage (B). All p-values are calculated by the log-rank test, the areas around the curves indicate the 95% CI.

patients have to withdraw from cisplatin due to cisplatin-specific side effects at an early phase. Nevertheless, 22.4% (n = 115) of the cases had to ultimately withdraw from any systemic agent during the course of the treatment. The effect of substituting cisplatin by carboplatin if the cumulative dose of cisplatin is below 200 mg/m^2 seems limited: patients who receive substitutional carboplatin have a non-significant increased hazard on OS analysis (HR 1.49 (95% CI 0.97–2.30), p = 0.068) which seems to be more comparable to the outcome in patients who received <200 mg/m^2 cisplatin as single agent (i.e. no substitution with carboplatin)(HR 1.59 (95% CI 1.16–2.19), p = 0.004)(Suppl Fig. 1). This suggests that patients experiencing dose-limiting toxicity due to cisplatin do not benefit from the switch to carboplatin. Even though these findings result from a large patient cohort, we only had 62 (12.1%) cases in whom this switch occurred and larger or randomized studies are needed to confirm this finding. Furthermore, given the main added value of cisplatin, biomarkers predicting response in subgroups [33,34] as well as toxicity would be very valuable, as also is the search for

alternative and effective radiosensitizers when cisplatin is not tolerated (such as olaparib [35]). As described previously, intratumor heterogeneity and crosslink repair status may play a role in cisplatin response of HNSCC [36,37].

The 5-year overall survival in our cohort was approximately 46%, and higher than previously reported in meta-analyses (with 5-year OS of 34%) [12,13] (supplementary Table 3). In our study, patients treated with curative intent still suffered from treatment failure in around 37%. The rate of LRR was much lower compared to the previous meta-analysis [12,13] with (28.4% in the present study compared to 43.0% in the previous meta-analyses; supplementary Table 3). This 28.4% of LRR can be regarded as low, especially because our study solely included HPV-negative disease. These favorable treatment results are likely explained by standardization of treatment protocols, improved image-guided radiotherapy techniques, and improved patient selection. More recent studies reported even lower incidence (∼15%) of LRR, but outcomes in these studies are highly biased by the inclusion of HPV-positive OPSCC [15,16].

In accordance to a reported rate of 12.8–17% from previous studies [15,16,38–40], DM is a frequent event after treatment in this HNSCC cohort of advanced stage tumors and occurs in about 20%. Disappointingly, while the LRR rate over the years has decreased by improved treatment modalities, the prevalence of DM has increased [41].The development of DM was strongly associated with the presence of lymph node metastasis at primary presentation (N0 vs N1-N2b or N2c-N3; OR 6.33 and 9.19, $p < 0.01$), and also with the method of boosting (SEQ vs SIB; OR 1.91, $p = 0.02$). Patients who were treated with sequential boosting method, had an increased risk of developing DM (SIB vs SEQ: OR 1.91 (1.11–3.26)). A recent study by De Felice [40] showed a favorable effect of SIB-IMRT over SEQ-IMRT on distant metastasis-free survival (79.0%, 95% CI 59.1–90.0 versus 55.0%, 95% CI 38.5–68.8), although not significant ($p = 0.06$), which was explained by the small cohort size of 69 patients. According to dosimetric analyses, both boosting methods result in comparable target coverage [42]. SIB-IMRT results in a reduced treatment time, however this was not related to outcome in our analysis.(Supplementary Table 2) Other authors did not report significant effects of boosting technique on outcome, but these studies were performed in heterogeneous patient groups, particularly lacking data on HPV-involvement. [43,44] The data presented here suggests treatment with SIB-IMRT might have a superior outcome considering development of DM compared to SEQ-IMRT in HPV-negative advanced stage HNSCC. However, this finding would need to be verified in a prospective setting.

Our clinical model based on gender, weight loss, N-stage and dose of cisplatin, predicts OS with a C-index of 0.68, and was superior to the C-index of 0.55 and 0.64 of the TNM staging in the exploration and validation cohort respectively which is likely due to selection of advanced stage disease. (Fig. 2) These results are supported by studies in the field of non-surgically treated HNSCC [45–48]. This study is limited by its retrospective nature, but on the other hand this means that no patient selection occurred, an issue in most prospective clinical trials. Hence, studied patient populations were unbiased and treatment policy as well as patient support were well standardized [20], which was supported by the finding that the participating center was neither significantly associated with OS nor with LRR and DM, other than related to the preferred boosting method.

In conclusion, our study describes the unique treatment course and outcome pattern of definitive platinum-based CRT for advanced stage HPV-negative HNSCC, including the importance of total cumulative dose of and limited tolerance to cisplatin in practice. It demonstrates on one hand the toxicity and on the other the added value of high dose cisplatin regimes and stresses the importance for adequate patient support, including adequate hydration and magnesium supplementation, next to identifying biomarkers of toxicity and the need for alternative radiosensitizers. Optimal preparation of patients to sustain the cisplatin doses seem the way to optimize definitive CRT. Furthermore, It reveals a potential influence of boosting technique on DM incidence. These findings will help to guide future research on biomarkers and patient-tailored treatment protocols.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.08.013.

References

[1] Ang KK et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:24–35.
[2] Rietbergen MM et al. Increasing prevalence rates of HPV attributable oropharyngeal squamous cell carcinomas in the Netherlands as assessed by a validated test algorithm. Int J Cancer 2013;132:1565–71.
[3] O'Sullivan B et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol 2016;17:440–51.
[4] Nauta IH et al. Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. Ann Oncol 2018;29:1273–9.
[5] Castellsague X et al. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst 2016;108:p. djv403.
[6] Iyer NG et al. Randomized trial comparing surgery and adjuvant radiotherapy versus concurrent chemoradiotherapy in patients with advanced, nonmetastatic squamous cell carcinoma of the head and neck: 10-year update and subset analysis. Cancer 2015;121:1599–607.
[7] Vergeer MR et al. Intensity-modulated radiotherapy reduces radiation-induced morbidity and improves health-related quality of life: results of a nonrandomized prospective study using a standardized follow-up program. Int J Radiat Oncol Biol Phys 2009;74:1–8.
[8] Gupta T et al. Systematic review and meta-analyses of intensity-modulated radiation therapy versus conventional two-dimensional and/or or three-dimensional radiotherapy in curative-intent management of head and neck squamous cell carcinoma. PLoS ONE 2018;13:e0200137.
[9] Klein J, Livergant J, Ringash J. Health related quality of life in head and neck cancer treated with radiation therapy with or without chemotherapy: a systematic review. Oral Oncol 2014;50:254–62.
[10] Marta GN et al. Intensity-modulated radiation therapy for head and neck cancer: systematic review and meta-analysis. Radiother Oncol 2014;110:9–15.
[11] Oosting SF, Haddad RI. Best practice in systemic therapy for head and neck squamous cell carcinoma. Front Oncol 2019;9:815.
[12] Pignon J-P et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009;92:4–14.
[13] Lacas B et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. Radiother Oncol 2021;156:281–93.
[14] Bonner JA et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006;354:567–78.
[15] Leeman JE et al. Patterns of treatment failure and postrecurrence outcomes among patients with locally advanced head and neck squamous cell carcinoma after chemoradiotherapy using modern radiation techniques. JAMA Oncol 2017;3:1487–94.
[16] Oksuz DC et al. Recurrence patterns of locally advanced head and neck squamous cell carcinoma after 3D conformal (chemo)-radiotherapy. Radiat Oncol 2011;6:54.

[17] Gillison ML et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet 2019;393:40–50.
[18] Mehanna H et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet 2019;393:51–60.
[19] Smeets SJ et al. A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen. Int J Cancer 2007;121:2465–72.
[20] NWHTT. Available from: https://www.nwhht.nl/.
[21] Piccirillo JF. Importance of comorbidity in head and neck cancer. Laryngoscope 2015;125:2242.
[22] Braakhuis BJ et al. Second primary tumors and field cancerization in oral and oropharyngeal cancer: molecular techniques provide new insights and definitions. Head Neck 2002;24:198–206.
[23] van Buuren S, Groothuis-Oudshoorn K. Mice, multivariate imputation by chained equations in R. J Statist Softw 2011;45:67.
[24] Eekhout I, van de Wiel MA, Heymans MW. Methods for significance testing of categorical covariates in logistic regression models after multiple imputation: power and applicability analysis. BMC Med Res Method 2017;17:129.
[25] Braakhuis BJ, Leemans CR, Visser O. Incidence and survival trends of head and neck squamous cell carcinoma in the Netherlands between 1989 and 2011. Oral Oncol 2014;50:670–5.
[26] Langius JA et al. Critical weight loss is a major prognostic indicator for disease-specific survival in patients with head and neck cancer receiving radiotherapy. Br J Cancer 2013;109:1093–9.
[27] Ghadjar P et al. Impact of weight loss on survival after chemoradiation for locally advanced head and neck cancer: secondary results of a randomized phase III trial (SAKK 10/94). Radiat Oncol 2015;10:21.
[28] Al-Mamgani A et al. The impact of cumulative dose of cisplatin on outcome of patients with head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol 2017;274:3757–65.
[29] Strojan P et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: a systematic review. Head Neck 2016;38:E2151–8.
[30] Hoek J et al. Nephrotoxicity as a dose-limiting factor in a high-dose cisplatin-based chemoradiotherapy regimen for head and neck carcinomas. Cancers (Basel) 2016;8.
[31] Fan KY et al. Comparison of acute toxicities in two primary chemoradiation regimens in the treatment of advanced head and neck squamous cell carcinoma. Ann Surg Oncol 2012;19:1980–7.
[32] Rades D et al. Comparison of four cisplatin-based radiochemotherapy regimens for nonmetastatic stage III/IV squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 2011;80:1037–44.
[33] van der Heijden M et al. Biological determinants of chemo-radiotherapy response in HPV-negative head and neck cancer: a multicentric external validation. Front Oncol 2019;9:1470.
[34] Budach V, Tinhofer I. Novel prognostic clinical factors and biomarkers for outcome prediction in head and neck cancer: a systematic review. Lancet Oncol 2019;20:e313–26.
[35] de Haan R et al. Study protocols of three parallel phase 1 trials combining radical radiotherapy with the PARP inhibitor olaparib. BMC Cancer 2019;19:901.
[36] de Roest RH et al. Molecular characterization of locally relapsed head and neck cancer after concomitant chemoradiotherapy. Clin Cancer Res 2019;25:7256–65.
[37] Essers PBM et al. Drug sensitivity prediction models reveal a link between DNA repair defects and poor prognosis in HNSCC. Cancer Res 2019;79:5597–611.
[38] Beckham TH et al. Platinum-based regimens versus cetuximab in definitive chemoradiation for human papillomavirus-unrelated head and neck cancer. Int J Cancer 2020;147:107–15.
[39] Duprez F et al. Distant metastases in head and neck cancer. Head Neck 2017;39:1733–43.
[40] De Felice F et al. Impact of clinical complete response on treatment outcomes in patients with locally advanced HPV-negative oropharyngeal squamous cell carcinoma. J Cancer Res Clin Oncol 2020;146:477–83.
[41] Allen CT et al. Emerging insights into head and neck cancer metastasis. Head Neck 2013;35:1669–78.
[42] Stromberger C et al. Comparative treatment planning study on sequential vs. simultaneous integrated boost in head and neck cancer patients: Differences in dose distributions and potential implications for clinical practice. Strahlenther Onkol 2016;192:17–24.
[43] Vlacich G et al. A comparative analysis between sequential boost and integrated boost intensity-modulated radiation therapy with concurrent chemotherapy for locally-advanced head and neck cancer. Radiat Oncol 2017;12:13.
[44] Spiotto MT, Weichselbaum RR. Comparison of 3D confromal radiotherapy and intensity modulated radiotherapy with or without simultaneous integrated boost during concurrent chemoradiation for locally advanced head and neck cancers. PLoS ONE 2014;9:e94456.
[45] Datema FR et al. Update and external validation of a head and neck cancer prognostic model. Head Neck 2013;35:1232–7.
[46] Egelmeer AG et al. Development and validation of a nomogram for prediction of survival and local control in laryngeal carcinoma patients treated with radiotherapy alone: a cohort study based on 994 patients. Radiother Oncol 2011;100:108–15.
[47] Rios Velazquez E et al. Externally validated HPV-based prognostic nomogram for oropharyngeal carcinoma patients yields more accurate predictions than TNM staging. Radiother Oncol 2014;113:324–30.
[48] Hakansson K et al. A failure-type specific risk prediction tool for selection of head-and-neck cancer patients for experimental treatments. Oral Oncol 2017;74:77–82.