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Original Article

Randomized phase-III-trial of concurrent chemoradiation for locally advanced head and neck cancer comparing dose reduced radiotherapy with paclitaxel/cisplatin to standard radiotherapy with fluorouracil/cisplatin: The PacCis-trial ☆

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ABSTRACT

Background and purpose: This multicenter, phase 3 trial investigates whether the incorporation of concurrent paclitaxel and cisplatin together with a reduced total dose of radiotherapy is superior to standard fluorouracil–cisplatin based CRT.

Materials and methods: Patients with SCCHN, stage III–IVB, were randomized to receive paclitaxel/cisplatin (PacCis)–CRT (arm A; paclitaxel 20 mg/m^2 on days 2, 5, 8, 11 and 25, 30, 33, 36; cisplatin 20 mg/m^2, days 1–4 and 29–32; RT to a total dose of 63.6 Gy) or fluorouracil/cisplatin (CisFU)–CRT (arm B; fluorouracil 600 mg/m^2; cisplatin 20 mg/m^2, days 1–5 and 29–33; RT: 70.6 Gy). Endpoint was 3-year-disease free survival (3y-DFS).

Results: A total of 221 patients were enrolled between 2010 and 2015. With a median follow-up of 3.7 years, 3y-DFS in the CisFU arm and PacCis arm was 58.2% and 48.4%, respectively (HR 0.82, 95% CI 0.56–1.21, p = 0.52). The 3y-OS amounted to 64.6% in the CisFU arm, and to 59.2% in the PacCis arm (HR 0.82, 95% CI 0.54–1.24, p = 0.43). In the subgroup of p16-positive oropharyngeal carcinomas, 3y-DFS and 3y-OS was 84.6% vs 83.9% (p = 0.653), and 92.3% vs. 83.5% (p = 0.76) in arm A and B, respectively. Grade 3–4 hematological toxicities were significantly reduced in arm A (anemia, p = 0.01; leukocytopenia, p = 0.003), whereas grade 3 infections were reduced in arm B (p = 0.01).

Conclusion: Paclitaxel/cisplatin–CRT with a reduced RT-dose is not superior to standard fluorouracil/cisplatin–CRT. Subgroup analyses indicate that a reduced radiation dose seems to be sufficient for p16+ oropharyngeal cancer or non-smokers.

Clinical trial information: NCT01126216; EudraCT Number 2005-003484-23.

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Patients with squamous cell carcinoma of the head and neck (SCCHN) commonly present with locoregionally advanced disease. Concurrent chemoradiotherapy (CRT) has emerged as the standard of care, as reflected by improvement of overall survival (OS) rates for the concurrent use of cisplatin and radiotherapy [1]. Overall survival, however, remains low, especially for human papilloma virus (HPV) unassociated disease [1]. Attempts to improve outcomes through administering induction chemotherapy prior to CRT [2–4] did not provide any significant benefits. However, one lesson learned from applying induction chemotherapy is the superiority of taxane-including regimens when compared with cisplatin/fluorouracil combinations [5–7]. Moreover, taxanes also demonstrated enhanced efficacy in the palliative situation [8–10], as well as in phase 2 studies concomitant to radiotherapy [11–13].

In a previous phase 2 trial, high survival rates (3-year-OS: 71%) were observed for a combination of hyperfractionated-accelerated radiotherapy (HART) with cisplatin–paclitaxel [14], similar to the cisplatin–paclitaxel-arm of the RTOG-trial by Garden et al. [12] (66.6%). Conversely, fluorouracil-combinations concomitant to radiotherapy provide 3y-OS rates equal or lower than 50% [15–18], similar to most other platinum-based CRT-regimens.

An analysis of over 6000 patients and 18 trials concluded that HART might allow for a 5–8% reduction of the total dose with similar tumor control and reduced high grade toxicities [19]. The combination of HART with concurrent chemotherapy has resulted in more frequent and severe side effects than standard fractionated CRT [20] and paclitaxel is a well-known, potent radiosensitizer [21,22]. These considerations, together with the expected improvement in 3y-DFS of at least 10% through the application of paclitaxel, led to the decision to prescribe a total dose of 63.6 Gy in the experimental arm, as previous studies had shown that a dose under 65 Gy to the pharyngeal constrictors reduces the risk of long-time dysphagia [23–25].

The main objective of the present study was to determine whether paclitaxel applied concomitantly with cisplatin-based CRT improves disease-free survival (DFS) compared with fluorouracil–cisplatin, despite a slight reduction in the total dose of radiotherapy. The PACCIS–RT (PAClitaxel–CISplatin combined with RadioTherapy) trial was a multicentre, randomized phase 3 trial for patients with locoregionally advanced SCCHN.

Patients and methods

Patients ≥18 years of age, with stage III-IVB (UICC/AJCC, seventh edition) SCCHN, ECOG-performance status <2 were eligible. Immunhistochemical staining for p16 was performed retrospectively as an unplanned investigation. The independent ethics committee of each participating site approved the trial. All patients provided written informed consent and all data were reviewed by an interdisciplinary data safety monitoring board.

Patients were randomly assigned by a central, electronic automated system (1:1 ratio) to receive HART (2 Gy daily up to 30 Gy, and then 1.4 Gy twice-daily) up to a total dose of either 63.6 Gy concomitant to paclitaxel (20 mg/m^2/d, days 2, 5, 8, 11 and 25, 30, 33, 36) and cisplatin (20 mg/m^2/d, days 1–4 and 29–32) (arm A, experimental), or 70.6 Gy concomitant to fluorouracil (600 mg/m^2/d, days 1–5 and 29–33 as continuous infusion) and cisplatin (20 mg/m^2/d, days 1–5 and 29–33) (arm B, standard). If creatinine-clearance declined to values <60 ml/min during chemotherapy, cisplatin was substituted with carboplatin (AUC 1/d, days 1–5 and 29–33). No prophylactic antibiotics or granulocyte stimulating factors were applied.

A contrast-enhanced planning CT was performed for initial treatment planning, and repeated after 49.6 Gy in order to define the boost volumes. The prescribed radiation doses included 70.6 Gy (arm B) and 63.6 Gy (arm A), respectively, to the gross primary tumor volume (PTV 1 = boost), 58 Gy to involved nodal levels (PTV 2), and 49.6 Gy (PTV 3) to neck regions at low-risk. Re-staging, including panendopscopy, was performed after 6 weeks; clinical follow up and assessment of toxicities according to CTCAE version 3.0 was performed every three months, for a total of 4 years.

The primary endpoint was disease-free survival (DFS) as defined from the time of randomization to either locoregional persistent disease at re-staging or recurrent disease during follow-up, distant metastases, or death from any cause, whichever occurred first.

The trial started in 2010, but after 4 years it became clear that the recruitment was slower than anticipated (221 of 542 planned patients). A blinded interim sample size recalculation was conducted. In the interim analysis, a sample size of 3378 patients was calculated to ensure the detection of significant differences between the two treatment arms. Based on this calculation, the study committee decided to stop recruitment in February 2015.

Analyses of the primary and secondary endpoints were performed with the "intent-to treat (ITT)" variant. Toxicity was analyzed in the safety set, according to the treatment received. Further considerations, including sample size calculation, can be found under Supplementary data.

Results

221 patients were enrolled and randomized in 14 participating institutions. Five patients who did not receive any protocol-specified treatment were excluded from analysis, the remaining 216 patients were assigned to receive paclitaxel/cisplatin–CRT (arm A, n = 111) or fluorouracil/cisplatin–CRT (arm B, n = 105, Fig. 1). The median age was 59 (range, 36–80) years, 172 patients were male (79.6%) and 44 were female. Most of the patients presented with stage IV disease and ECOG performance status of 0 or 1. The most common tumor localization was oropharynx (53.7%). Only 11.7% of the patients in arm A and 10.5% of the patients in arm B were never smokers. Of the 159 tumor specimens available for evaluation of the HPV-status, 49 (22.7%) stained p16–positive (22.5% in Arm A, 22.9% in arm B). Patient and tumor characteristics were well balanced between the treatment arms (Table 1).

A total of 94.6% of the patients in arm A and 96.2% in arm B received a prophylactic feeding tube at the start of CRT. The RT dose applied to PTV 2 and PTV 3 did not differ significantly between the two arms; however, according to the protocol, the median dose applied to PTV 1 was 63.6 Gy in arm A (range, 26.0–76.6 Gy) and 70.6 Gy in arm B (range, 4–74.6 Gy), with an overall median treatment duration of 37 and 42 days for arm A and B, respectively. The planned total dose of radiotherapy could be delivered without any interruption in 89 (80.2%) patients treated in arm A and in 85 (81%) in arm B. Ten patients in arm A (9%) and 11 patients in arm B (10.5%) required a radiotherapy interruption due to toxicity for a median time interval of 2 days in both arms. A definitive discontinuation of radiotherapy was required in 13 patients (4 due to infections, 4 due to patient wish/incompliance and 5 due to other reasons/intercurrent diseases). Of these, 6 patients were in the paclitaxel/cisplatin–CRT-arm (3 due to toxicity) and 7 patients were in the fluorouracil/cisplatin–CRT-arm (5 due to toxicity). The patients in both arms received a median 100% of the prescribed dose for all of the 3 cytostatic agents (cisplatin, paclitaxel, fluorouracil). 88.3% of the patients in arm A and 81.6% in arm B received the prescribed cisplatin-dose; however, 15 patients had to be switched to carboplatin at some point (8 in arm A, 7 in arm B). The cumulative paclitaxel dose

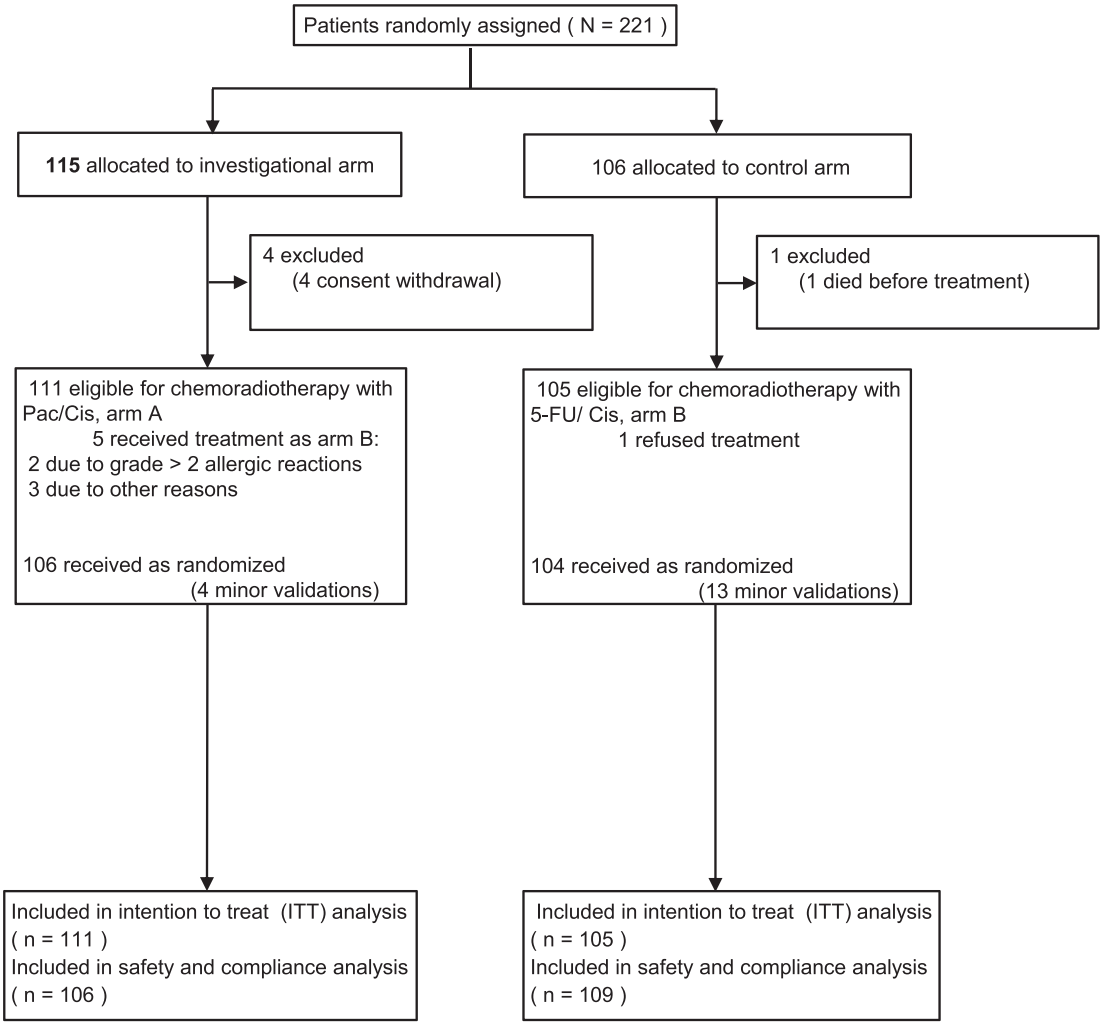


Fig. 1. CONSORT diagram. All efficacy analyses were conducted based on "intention to treat" (ITT). Toxicities were analyzed in the "safety set".

had to be reduced in 44%, and the fluorouracil dose in 24% of the cases. The mean cumulative dose per square meter was 136 mg/m^2 (0–160 mg/m^2) for paclitaxel, 5669 mg/m^2 (0–7000 mg/m^2) for fluorouracil and 157 and 187 mg/m^2 for cisplatin for arms A and B, respectively.

The most common grade ≥3 toxicities during and up to 6 weeks after completion of CRT occurred as functional and clinical mucositis (59.4% and 47.2% versus 64.2% and 48.6% for arm A and arm B, respectively, p-values: 0.48 and 0.42), as well as grade 3 dysphagia (81.1% versus 77.1%, p = 0.72). Mean weight loss during treatment was similar in both arms: 3.3 kg in arm A and 2.8 kg in arm B (p = 0.37) and maximal weight loss up to 6 weeks after treatment was 6.3 and 6.6 kg, respectively (p = 0.78). The only acute adverse events demonstrating a statistically significant difference between the arms were hematological toxicities with grade 3–4 anemia and grade 3–4 leukocytopenia being more frequent in arm B (Table 2) and grade 3 infections, with 32% in arm A and 16.5% in arm B (p = 0.01). No grade 4 infection and no treatment related deaths occurred.

The rates of PEG-dependence, as surrogate for severe dysphagia, 6 and 12 months after treatment were 9% versus 10.5% (p = 1.00) and 8.1% versus 9.5% (p = 0.805) for arm A and arm B repectively.

After a median follow-up of 3.7 years (range, 3.2–4.1, arm A 3.7, arm B 3.76 and 4.13 and 4.67 respectively for living patients), the 3y-DFS was 48.4% in arm A and 58.2% in arm B (HR: 0.82, 95% CI: 0.56–1.21, p = 0.51). The 3y-OS in arm A amounted to 59.2% and in arm B to 64.6% (HR: 0.82, 95% CI: 0.54–1.24, p = 0.49) (Fig. 2a and b). A total of 20.3% of the patients in arm A and 17.7% in arm B experienced locoregional failure at 3 years (p = 0.97) (Suppl. Fig. 1a). Distant metastases occurred in 12.7% and 10% of the cases in arm A and arm B, respectively (p = 0.47) (Suppl. Fig. 1b). After three years, the rate of death was 18.8% and 14.2% in arm A and B, respectively (p = 0.30) (Suppl. Fig. 1c). The oncological results were similar in the as-treated and per-protocol analyses (Suppl. Fig. 2a and b).

For p16-positive, oropharyngeal cases, the 3y-DFS and 3y-OS-rates were 84.6% vs. 83.9% (HR: 0.98, 95% CI: 0.16–5.89, p = 0.65) and 92.3% vs. 83.5% (HR: 2.08, 95% CI: 0.22–20.0, p = 0.76) for arms A and B, respectively (Fig. 3a and b). There was no significant difference in the 3y-DFS according to smoking status (current smoker vs. rest, p = 0.18), age (≥70 vs. younger, p = 0.93), tumor site (oropharyngeal vs. other, p = 0.61), or non-smokers (p = 0.52, Fig. 3c and d). A direct comparison for all subgroups can be found in Fig. 4a and b.

Discussion

The present trial investigated the efficacy of paclitaxel/cisplatin concomitant to a slightly reduced total dose of radiotherapy for the

Table 1
Patient and tumor characteristics.

Characteristic	Paclitaxel + Cisplatin (Arm A) (n = 111)		Fluorouracil + Cisplatin (Arm B) (n = 105)		p-Value
	No.	%	No.	%	
Age, years					
Mean	60.04		59.87		
SD	8.55		8.24		0.882
Range	36–80		38–59		
Sex					
Male	86	77.5	86	81.9	0.500
Female	25	22.5	19	18.1	
Body weight					
Mean	72.62		73.51		0.682
SD	16.3		15.64		
Range	41–129		44–137		
Smoking history					
Never smoker	13	11.7	11	10.5	
Former smoker	37	33.3	34	32.4	0.807
Current smoker	47	42.3	52	49.5	
Missing	14	12.6	8	7.6	
ECOG performance					
0	76	68.5	66	62.9	0.473
1	35	31.5	38	36.2	
Missing	0	0	1	1	
Tumor Site					
Oral Cavity	19	17.1	11	10.5	0.173
Oropharynx	51	45.9	53	50.5	0.586
Hypopharynx	29	26.1	16	15.2	0.065
Supraglottic larynx	10	9.0	10	9.5	1.00
Multilevel-tumor	2	1.8	15	14.3	0.001
T stage					
1	5	4.5	3	2.9	
2	4	3.6	9	8.6	0.452
3	42	37.8	37	35.2	
4	60	54.1	56	53.3	
N-stage					
N0	15	13.5	15	14.3	
N1	14	12.6	8	7.6	
N2a	3	2.7	2	1.9	0.601
N2b	33	29.7	41	39.0	
N2c	45	40.5	37	35.2	
N3	1	0.9	2	1.9	
UICC/AJCC stage					
III	18	16.2	11	10.5	0.237
IV	93	83.8	94	89.5	
Grading					
G1	5	4.5	5	4.8	
G2	65	58.6	57	54.3	0.705
G3	37	33.3	41	39.0	
Missing	4	3.6	2	1.9	
p16 – status					
Positive	25	22.5	24	22.9	
Negative	57	51.4	53	50.5	1.00
Missing	29	26.1	28	26.7	

definitive treatment of locoregionally advanced SCCHN. Although we recognize that both the systemic treatments used here cannot be internationally considered as reference schemes, the "standard" arm is widely used in german-speaking countries. The main hypothesis was an improved outcome in terms of DFS, based on previous phase I–II data [12,14,26], suggesting that the implementation of low dose paclitaxel in combination with platin during CRT could improve DFS. Particularly, one previous randomized RTOG-trial demonstrated that the combination of paclitaxel with standard CRT was feasible and could improve the 2-year-DFS from 38.2% to 51.3%, compared with the cisplatin/fluorouracil-arm [16]. The cumulative paclitaxel and cisplatin doses used in this randomized phase II trial were similar to the present study. Thus, the goal of proving a benefit of 10% in 3y-DFS in favor of the paclitaxel/cisplatin–CRT-arm appeared reasonable.

The trial was stopped early due to slow accrual after a blinded interim analysis. The standard arm showed a trend for improved 3y-DFS in the overall population (58% vs. 48%), as well as in almost all subgroups (Fig. 4). Thus, the rejection of the null hypothesis has been highly unlikely, and the trial was terminated prematurely due to futility. Altogether, the outcome in both arms was good and the 3y-DFS is comparable to other similar, recent, prospective trials [27,28], despite a low percentage of p16-positive oropharyngeal cases [27].

These findings appear somewhat surprising when considering that a recent comprehensive analysis on concurrent taxane-based

Table 2
Acute toxicities during and up to 6 weeks after treatment.

Toxicity during treatment	Paclitaxel + Cisplatin (Arm A)		Fluorouracil + Cisplatin (Arm B)		*p*-Value
	No.	%	No.	%	
Anemia					
<3	102	96.2	94	86.2	**0.015**
3	2	1.9	10	9.2	
4	0	0	2	1.8	
Missing	2	1.9	3	2.8	
Leukocytopenia					
<3	87	82.1	69	63.3	**0.002**
3	17	16	33	30.3	
4	0	0	4	3.7	
Missing	2	1.9	3	2.8	
Thrombocytopenia					
<3	101	95.3	100	91.7	0.328
3	1	0.9	5	4.6	
4	2	1.9	1	0.9	
Missing	2	1.9	3	2.8	
Creatinine elevation					
<3	102	96.2	105	96.3	
3	2	1.9	1	0.9	0.62
4	0	0	0	0	
Missing	2	1.9	3	2.8	
Vomiting					
<3	102	96.2	106	97.2	
3	2	1.9	0	0	0.244
4	0	0	0	0	
Missing	2	1.9	3	2.8	
Dermatitis					
<3	74	69.8	69	63.3	
3	28	26.4	37	33.9	0.181
4	2	1.9	0	0	
Missing	2	1.9	3	2.8	
Acute Dysphagia					
<3	18	17	21	19.3	
3	86	81.1	84	77.1	0.723
4	0	0	0	0	
Missing	2	1.9	4	3.7	
Mucositis (clinical)					
<3	54	50.9	53	48.6	
3	48	45.3	53	48.6	0.419
4	2	1.9	0	0	
Missing	2	1.9	3	2.8	
Mucositis (functional)					
<3	40	37.7	36	33	0.476
3	63	59.4	70	64.2	
4	0	0	0	0	
Missing	3	2.8	3	2.8	
Pain					
<3	77	72.6	78	71.6	1
3	27	25.5	28	25.7	
4	0	0	0	0	
Missing	2	1.9	3	2.8	
Allergic reactions					
<3	102	96.2	106	97.2	0.244
3	1	0.9	0	0	
4	1	0.9	0	0	
Missing	2	1.9	3	2.8	
Infections					
<3	70	66	88	80.7	**0.01**
3	34	32.1	18	16.5	
Missing	2	1.9	3	2.8	

CRT as primary treatment for locoregionally advanced SCCHN indicated improved OS and less toxicity with the use of taxane-based CRT regimens compared with phase 2–3 trials without taxanes [29]. Interestingly, studies with taxane-based regimens in that analysis mostly used a combination with platinum, which led the authors to the assumption that the improved survival observed should be attributed to this combination rather than to the implementation of taxanes alone [12,30–34]. Taken together, an abundance of data examining different SCCHN-treatments advocated utilization of a combined cisplatin/paclitaxel CRT-strategy as a promising option, yet we failed to observe any significant differences to the standard arm.

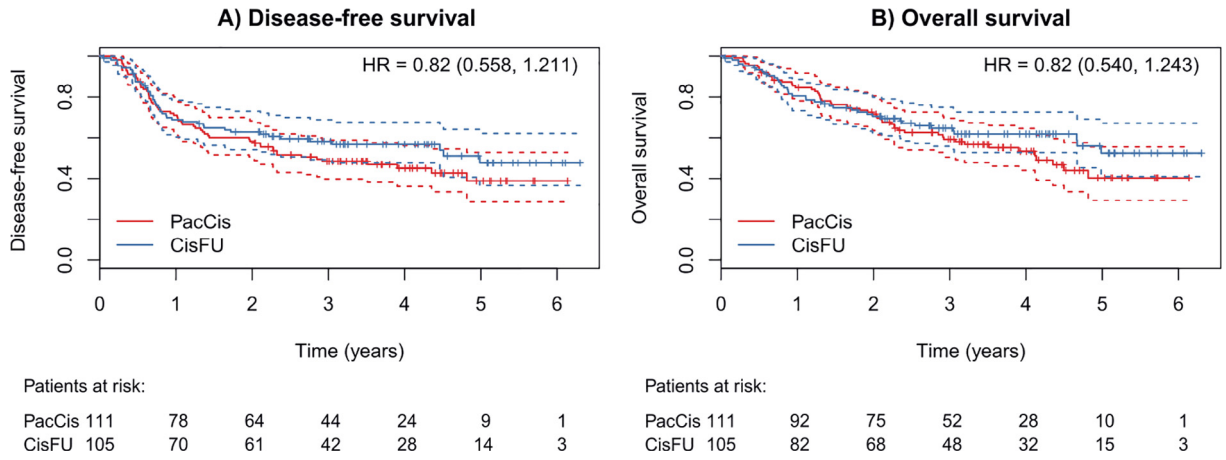


Fig. 2. Disease-Free (a) and Overall survival (b) for both treatment arms, including hazard ratios.

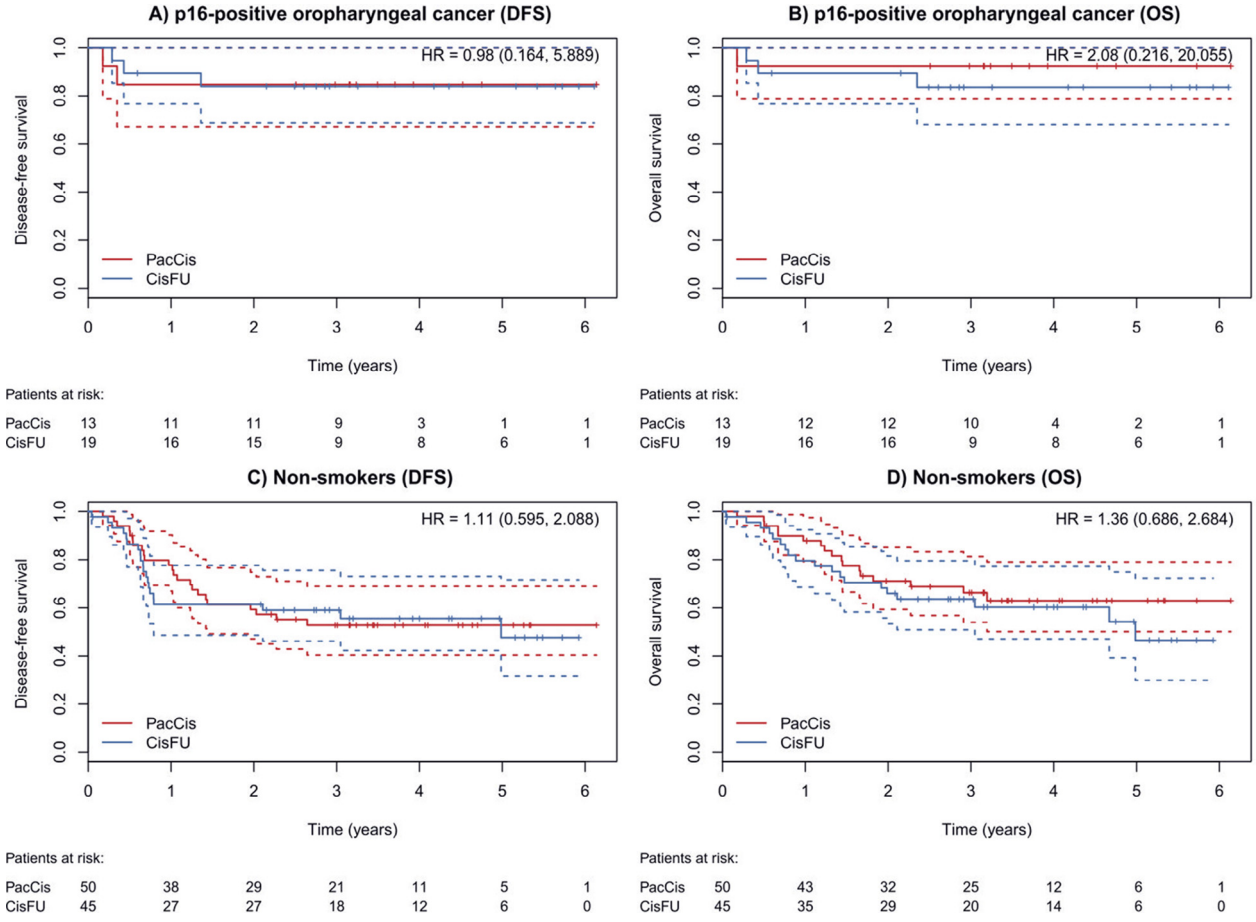


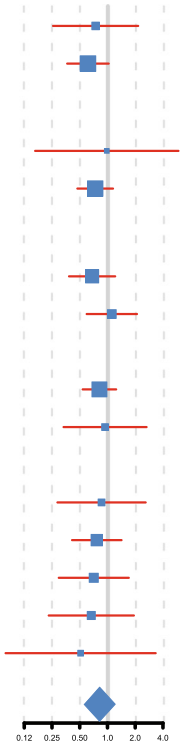
Fig. 3. Disease-Free and Overall survival for p16-positve oropharyngeal cancer patients (a, b), and non-smokers (c, d).

A possible explanation for the, at best, equivalent or even inferior 3y-DFS of the experimental arm is the slightly reduced total dose of radiation applied. There is a well established dose-tumor control relationship in radiotherapy of SCCHN [35]. Here, the addition of paclitaxel seems to compensate for the reduced total radiation dose in the experimental arm, both in terms of local tumor control and distant failure even though the dose was lower compared with previous smaller trials [12,14]. However, in these trials, more than 93% of the patients had a Karnofsky score of 90–100%, treatment was applied completely in the in-patient setting and toxicities were considerable (88% received blood transfusion, 36% granulocyte stimulating factor).

No significant differences regarding radiation-induced adverse events could be observed, despite the lower total RT-dose in arm A. The similar rates of mucositis, dermatitis, pain, and dysphagia may be attributed to the relatively aggressive HART regimen along with the radiosensitizing effects of paclitaxel. Overall, the experimental treatment was well tolerated and no significant rates of drop outs due to toxicity or incompliance were observed. Infections were more common in the experimental arm, but no cases

A) Disease-free survival

	Observed Events / N (PacCis)	Observed Events / N (CisFU)	adjusted HR (95% CI)
p16 status			
positive	8 / 25	6 / 24	0.744 (0.257, 2.151)
negative	38 / 57	24 / 53	0.614 (0.366, 1.030)
p16 status / tumor location			
p16+ oropharynx	2 / 13	3 / 19	0.983 (0.164, 5.889)
other	52 / 84	32 / 66	0.736 (0.472, 1.147)
Current smoking			
yes	26 / 47	21 / 52	0.681 (0.383, 1.211)
no	23 / 50	20 / 45	1.115 (0.595, 2.088)
Age			
< 70	51 / 95	40 / 91	0.818 (0.539, 1.241)
>= 70	9 / 16	6 / 14	0.942 (0.334, 2.654)
Tumor location			
oral cavity	9 / 19	5 / 11	0.862 (0.287, 2.595)
oropharynx	23 / 51	18 / 53	0.766 (0.413, 1.420)
hypopharynx	18 / 29	7 / 16	0.710 (0.296, 1.701)
larynx	8 / 10	7 / 10	0.668 (0.231, 1.932)
multilevel tumor	2 / 2	9 / 15	0.511 (0.078, 3.332)
Total	**60 / 111**	**46 / 105**	**0.822 (0.558, 1.211)**



B) Overall survival

	Observed Events / N (PacCis)	Observed Events / N (CisFU)	adjusted HR (95% CI)
p16 status			
positive	5 / 25	5 / 24	1.157 (0.334, 4.008)
negative	34 / 57	20 / 53	0.609 (0.347, 1.068)
p16 status / tumor location			
p16+ oropharynx	1 / 13	3 / 19	2.083 (0.216, 20.055)
other	46 / 84	26 / 66	0.705 (0.434, 1.147)
Current smoking			
yes	24 / 47	16 / 52	0.576 (0.306, 1.085)
no	17 / 50	19 / 45	1.357 (0.686, 2.684)
Age			
< 70	46 / 95	34 / 91	0.767 (0.491, 1.199)
>= 70	6 / 16	6 / 14	1.499 (0.482, 4.666)
Tumor location			
oral cavity	8 / 19	4 / 11	0.931 (0.279, 3.105)
oropharynx	19 / 51	17 / 53	0.904 (0.470, 1.740)
hypopharynx	16 / 29	6 / 16	0.743 (0.290, 1.900)
larynx	7 / 10	5 / 10	0.490 (0.143, 1.679)
multilevel tumor	2 / 2	8 / 15	0.138 (0.017, 1.112)
Total	**52 / 111**	**40 / 105**	**0.819 (0.540, 1.243)**

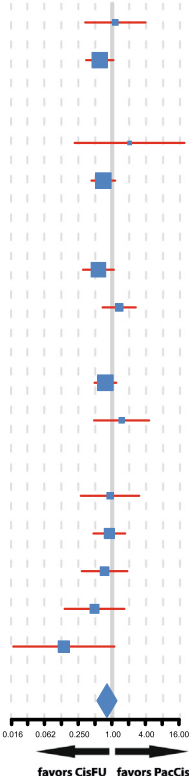


Fig. 4. Forest-plots for a) Disease-Free and b) Overall survival.

of grade 4–5 infections were observed. Moreover, high grade hematological toxicities were significantly more common in the standard arm.

Interestingly, the experimental regimen did not show any tendency for worse DFS or OS as compared to the standard arm in the p16-positive oropharyngeal subgroup. However, this should be considered in the context of low numbers of p16-positive cases, which makes it difficult to draw safe conclusions. For this cohort, the DFS and OS rates seem to be identical, and the equivalence or even the superiority of the experimental arm cannot be statistically ruled out, despite the lower radiotherapy dose. When the PacCis-trial was designed, the prognostic relevance of the HPV/p16-status was not established and the first landmark trials on this topic [27,36] only emerged later. Thus, we performed a post hoc analysis of the p16-status which was balanced in both arms, and the survival of the positive patients was significantly superior. A recent prospective phase II trial for p16-positive SCCHN demonstrated that CRT with paclitaxel and a total radiotherapy dose $\leq$60 Gy yielded reduced toxicity compared to historical data and excellent results concerning PFS [37]. This could represent a possible de-escalation strategy for these patients showing an improved outcome in the present, as well as in other, published trials [38,39]. A further subgroup that might profit from the reduced dose are non-smokers, for whom DFS and OS were equal in both arms.

This study has limitations. Firstly, the premature termination reduced the power to reject the null hypothesis. Secondly, the experimental arm varied two treatment components, and the reduced RT dose may have compromised any potential benefit of paclitaxel. This could be considered as the main limitation of the trial, but the optimism associated with taxane use at this time, together with the toxicities observed in our previous, phase II trials, led to this questionable decision. Thirdly, p16 status was not used as a stratification factor, and evaluation of the disease 6 weeks after the end of treatment could be somewhat premature, as HPV positive disease often needs a longer time to neck node clearance. Despite that, this is the first randomized phase III trial implementing a taxane-based concomitant CRT and, thus, the results are important and hypothesis generating.

Cisplatin-based CRT combined with paclitaxel and a slightly reduced RT-dose is not superior to a standard regimen, but is feasible, associated with less hematological toxicity but more grade 3 infections and similar rates of late PEG-dependence. Future trials should explore the possibility of implementing similar strategies for p16-positive non-smokers with oropharyngeal cancer with the purpose of de-escalation.

Conflict of interest statement

All authors declare that they have no potential conflict of interest relevant to this manuscript.

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Role of the funding source

The funding source had no role in the design of this study or any role during its execution, analyses, interpretation of the data, or decision to submit results.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

All authors have approved publication of the present manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.01.016.

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