Radiotherapy and Oncology 197 (2024) 110329

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Standard versus fractionated high-dose cisplatin plus radiation for locally advanced head and neck cancer: Results of the CisFRad (GORTEC 2015-02) randomized phase II trial

Christian Borel [a,*,1], Xu-Shan Sun [b,c,1], Alexandre Coutte [d], Guillaume Bera [e], Christian Sire [e], Sylvie Zanetta [f], Marc Alfonsi [g], Guillaume Janoray [h], Thierry Chatellier [i], Muriel Garcia-Ramirez [j], Elisabeta Gherga [b], Yasser Hammoud [c], Mickaël Burgy [a,k], Nelly Etienne-Selloum [a,k], Adeline Pechery [l], Marie-Hélène Girard-Calais [l], Michel Velten [a,m], Jean-Pierre Pignon [n], Mathilde Wanneveich [l], Jean Bourhis [o]

[a] Institut de Cancérologie Strasbourg Europe, Strasbourg, France
[b] Hôpital Nord Franche-Comté, Montbéliard, France
[c] Centre Hospitalo-Universitaire Besançon, Besançon, France
[d] Centre Hospitalo-Universitaire Amiens-Picardie-Site Sud, Amiens, France
[e] Centre Hospitalier Bretagne Sud, Lorient, France
[f] Centre Georges-François Leclerc, Dijon, France
[g] Institut Sainte Catherine, Avignon, France
[h] Centre Hospitalier Régional Universitaire Tours, Tours, France
[i] Centre d'Oncologie de l'Estuaire, Saint-Nazaire, France
[j] Hôpital Robert Boulin, Libourne, France
[k] Laboratory of Bioimaging and Pathology, University of Strasbourg, UMR7021 CNRS, Illkirch, France
[l] Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) - Centre Hospitalo-Universitaire Bretonneau, Tours, France
[m] Université de Strasbourg, UMR-S1113 IRFAC Inserm, Strasbourg, France
[n] Service de Biostatistique et d'Epidémiologie, Gustave-Roussy Cancer Campus, Villejuif, France
[o] CHUV – Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

ARTICLE INFO

Keywords:
Squamous Cell Carcinoma of Head and Neck
Locally advanced
Chemoradiotherapy
Cisplatin
Cisplatin pharmacokinetic

ABSTRACT

Background: Chemoradiotherapy with high-dose cisplatin (HD-Cis: 100 mg/m^2 q3w for three cycles) is the standard of care (SOC) in locally advanced head and neck squamous cell carcinoma (LA-HNSCC). Cumulative delivered dose of cisplatin is prognostic of survival, even beyond 200 mg/m^2 but high toxicity compromises its delivery.

Aim: Cisplatin fractionation may allow, by decreasing the peak serum concentration, to decrease toxicity. To date, no direct comparison was done of HD-Cis versus fractionated high dose cisplatin (FHD-Cis).

Methods: This is a multi-institutional randomized phase II trial, stratified on postoperative or definitive chemoradiotherapy, comparing HD-Cis to FHD-Cis (25 mg/m^2/d d1-4 q3w for 3 cycles) in patients with LA-HNSCC. The primary endpoint was the cumulative delivered cisplatin dose.

Results: Between December 2015 and April 2018, 124 patients were randomized. Median cisplatin cumulative delivered dose was 291 mg/m^2 (IQR: 251;298) in the FHD-Cis arm and 274 mg/m^2 (IQR: 198;295) in the HD-Cis arm ($P = 0.054$). The proportion of patients receiving a third cycle of cisplatin was higher, with a lower proportion of grade 3–4 acute AEs in the FHD-Cis arm compared to the HD-Cis arm: 81 % vs. 64 % ($P = 0.04$) and 10 % vs. 17 % ($P = 0.002$), respectively.

With a median follow-up of 48 months (IQR: 41;55), locoregional failure rate, PFS and OS were similar between the two arms.

* Corresponding author at: Medical Oncology Department, ICANS – Institut de Cancérologie Strasbourg Europe, 17 rue Albert Calmette – BP 23025 – 67033 Strasbourg, France.
E-mail address: c.borel@icans.eu (C. Borel).

[1] C.B. and XS.S. contributed equally to this work.

https://doi.org/10.1016/j.radonc.2024.110329
Received 2 January 2024; Received in revised form 28 April 2024; Accepted 1 May 2024
Available online 19 May 2024

Conclusion: Although the primary endpoint was not met, FHD-Cis allowed more cycles of cisplatin to be delivered with lower toxicity, when compared to SOC. FHD-Cis concurrently with RT is a treatment option which deserves further consideration.

Introduction

Chemoradiotherapy (CRT) is the standard of care in locally advanced head and neck squamous cell carcinoma (LA-HNSCC), either post-operatively in patients at high-risk of recurrence [1,2] or as definitive CRT [3,4]. High-dose cisplatin, i.e. 100 mg/m^2 every 3 weeks for 3 cycles (HD-Cis) has thus become the reference modality [4,5]. However, this treatment is associated with high toxicity (>80 % grade $\geq$ 3) [2,3], which compromises its administration, especially regarding the cumulative dose of cisplatin delivered concurrently with radiotherapy, as commonly 30–50 % of patients cannot receive the third cycle [1,5]. Indeed, the cumulative dose of cisplatin is not only prognostic of locoregional control but also of survival: 200 mg/m^2 seems to be the minimal active dose [6,7], but in fact the benefit seems to continue beyond 200 mg/m^2 [8,9], except for HPV-positive oropharyngeal carcinomas [5,10].

The toxicity of high-dose cisplatin seems to be partly related to the extent of the peak serum concentration, so fractionating the dose with a weekly administration, should decrease it [11]. Thus, the radiosensitization regimen in the form of weekly administration of 40 mg/m^2 cisplatin (Cis-40) for 6 to 7 cycles has been adopted by many teams with encouraging results in terms of toxicity, and efficacy improvement compared to RT alone, but at the time we initiated this trial in 2015 without evidence of at least equivalent results in terms of outcomes compared to HD-Cis [12,13].

Furthermore, fractionating the 100 mg/m^2 dose over 4 days i.e., 25 mg/m^2/d every 3 weeks (FHD-Cis) could allow for higher cumulative doses of cisplatin than the Cis-40 regimen and perhaps less toxicity given the lower daily doses.

Based on this rationale, we initiated in 2015 a randomized phase II trial, the GORTEC 2015–02 CisFRad study, comparing standard CRT (HD-Cis) to CRT with fractionated cisplatin (FHD-Cis); the primary endpoint being the cumulative dose of cisplatin delivered during radiation therapy.

Patients and Methods

Trial design

CisFRad is a multi-institutional, randomized, superiority phase II study conducted in ten centers of the French "Groupe d' Oncologie Radiothérapie Tête Et Cou" (GORTEC) registered with ClinicalTrial.gov (NCT03330249).

After signing an informed consent, patients were randomly assigned in a 1:1 ratio to CRT with 3-weekly high dose cisplatin (HD-Cis) or 3-weekly fractionated high dose cisplatin (FHD-Cis) (Supplementary Fig. A1). Randomization was carried out by block of four and stratified by center and type of CRT (definitive or postoperative).

Eligibility criteria

Eligible patients had histologically proven locally advanced stage III or IV (UICC 7th edition) squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx that was non operated or inoperable, and therefore eligible for definitive CRT, or had high-risk post-operative tumor characteristics with positive or close margins ($\leq$1 mm) and/or positive nodes with extracapsular extension. They were aged 18 to 70, had an ECOG-PS 0, 1 or 2, adequate organ function with a calculated creatinine clearance $\geq$ 60 mL/min.

The main criteria for non-inclusion were as follows: carcinomas of the nasopharynx, sinuses or nasal cavities, non-squamous histology, presence of distant metastases, previous neoadjuvant systemic chemotherapy, or peripheral neuropathy > grade 1. The inclusion and exclusion criteria are described in detail in the protocol.

Study end points

The primary endpoint was the cumulative dose of cisplatin delivered during radiotherapy compared between the two arms. Secondary end points were toxicity, time-dependent outcomes, and cisplatin pharmacokinetic.

Toxicity was evaluated using CTCAE version 4.0, and according to the number of serious adverse events (SAEs) and hospitalizations. Outcomes included overall survival (OS), progression-free survival (PFS) and locoregional failure rate (LRF) as described in Appendix 1.

Treatments

In the standard arm (HD-Cis), patients received cisplatin at a dose of 100 mg/m^2 every 3 weeks for 3 cycles on D1, D22, and D43 of radiotherapy. In the fractionated experimental arm (FHD-Cis), patients received cisplatin at a dose of 25 mg/m^2/d from D1 to D4, D22 to D25, and D43 to D46 of radiotherapy. Chemotherapy was not continued after completion of radiotherapy.

Cisplatin was administered with antiemetics and corticosteroids according to the practice of each center. Only hydration modalities (normal saline: 4000 mL in 9 h in the HD-Cis arm and 2000 mL in 4 h and 15 min in the FHD-Cis arm) and cisplatin infusion rate were standardized to ensure comparability of pharmacokinetic characteristics: 100 mg/m^2 in 3 h in the HD-Cis arm and 25 mg/m2 in 45 min in the FHD-Cis arm, i.e. 0.55 mg/m^2 per minute as described in Appendix 1.

Criteria for dose reduction or delay were prespecified in the protocol. For patients requiring post-operative CRT, this was performed within 8 weeks after surgery.

RT was delivered with high-energy photons of 6–10 MV using LINAC or tomotherapy whenever possible 1 to 2 h after cisplatin infusion. Intensity-modulated radiation therapy (IMRT) was mandatory. Target volumes were outlined in the protocol. In summary, three PTVs were defined: tumor or surgical bed (PTV1), intermediate-risk areas (PTV2), and high-risk nodal areas (PTV3). Two treatment schedules were used: sequential conventional (SQ) or simultaneous integrated boost (SIB). For patients treated with definitive CRT, PTV1 received 70 Gy in 35 fractions regardless of schedule, PTV2 received 50 Gy at a rate of 2 Gy per session in the SQ schedule or 56 to 59.5 Gy with 1.6 to 1.7 Gy per session in the SIB schedule, and PTV3 received 60 Gy at a rate of 2 Gy per session in the SQ schedule and 63 Gy at a rate of 1.8 Gy per session in the SIB schedule. For patients treated with postoperative CRT, PTV1 received 66 Gy in 33 fractions regardless of schedule, PTV2 received 50 Gy at a rate of 2 Gy per session in the SQ schedule or 54.12 Gy with 1.64 Gy per session in the SIB schedule, and PTV3 received 60 Gy at a rate of 2 Gy per session in the SQ schedule and 59.4 Gy at a rate of 1.8 Gy per session in the SIB schedule.

Cisplatin pharmacokinetic study

Centers wishing to participate in the cisplatin pharmacokinetic study had to declare themselves at the site initiation visit. Technical aspects of the cisplatin pharmacokinetic study are described in Appendix 1 and shown in Fig. A2.

Statistical analysis

In a retrospective series, the mean cumulative dose of cisplatin for patients in the standard arm (HD-Cis) was estimated to 245 mg/m^2 and 283 mg/m^2 in the fractionated experimental arm (FHD-Cis) with a standard deviation (SD) of 59 mg/m^2. The required number of patients calculated with a power of 90 % and an alpha of 0.05 was 124 in total, 62 patients in each arm. The analysis was performed in intent-to-treat (ITT).

A sensitivity analysis was performed per-protocol with the patients who received at least 1 cycle of cisplatin and for whom all inclusion criteria were validated.

For categorical variables, comparisons were made by a Chi2 test or by a Fisher test where appropriate; for quantitative variables, Student's *t* test or Wilcoxon test were used and for censored data, log-rank test.

All tests were two-sided with a 5 % alpha level. The analysis of the primary endpoint was stratified by the type of indication for CRT (definitive or postoperative).

Survival curves were estimated using the Kaplan Meier method. Hazard ratio (HR) and 95 % confidence interval were based on Cox model estimate stratified on CRT modalities. The first analysis was performed at the data cutoff of July 15, 2020. An additional follow-up analysis for time-dependent outcomes was performed at the data cut-off of May 23, 2022. Statistical analyses were performed with SAS software (version 9.4) and SAS Enterprise Guide (version 8.2).

Results

Between December 2015, and April 2018, 124 patients were randomized in ten centers: 65 patients in the standard arm (HD-Cis) and 59 patients in the fractionated arm (FHD-Cis). Two patients were excluded from the analysis because one was under legal guardianship (HD-Cis arm) and the other withdrew consent (FHD-Cis arm). Thus, 122 patients were included in the **ITT** analysis of the primary endpoint and of time-

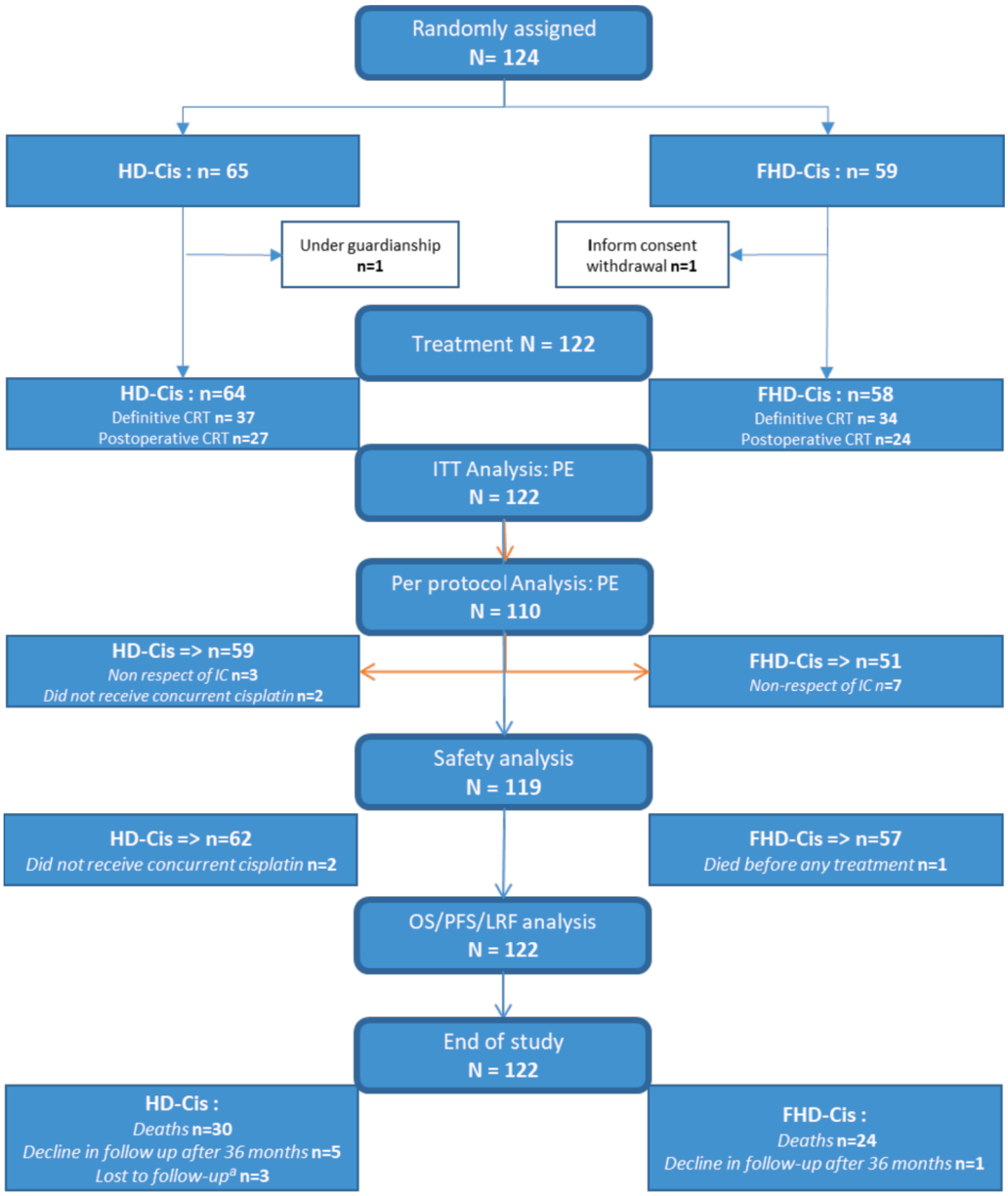

Fig. 1. CONSORT diagram. FHD-Cis, Fractionated High-Dose cisplatin; HD-Cis, High-Dose cisplatin; CRT, chemoradiotherapy; ITT, Intent To Treat; LRF, Loco-Regional Failure; OS, Overall Survival; PFS, Progression-Free Survival; PE, Primary End Point; IC, Inclusion Criteria; [a]3 patients lost to follow-up after 32, 40 and 41 months.

dependent outcomes. In the per-protocol analysis of the primary endpoint, 110 patients were included: 10 patients did not respect inclusion criteria (see Appendix 1 for description) and 2 patients did not receive concomitant cisplatin. For the safety analysis, 119 patients were considered because 3 patients did not receive concomitant cisplatin (Fig. 1).

The baseline characteristics of patients were generally well balanced between the treatment arms. However, there was a slight excess of T4 and N3 in the HD-Cis arm. The p16 status was known for 54 of the 60 oropharyngeal tumors (90 %).

In the FHD-Cis arm, the proportion of p16-positive oropharyngeal tumors was numerically higher than in the HD-Cis arm [29 % (17/58) vs. 17 % (11/64)], and the proportion of hypopharyngeal tumors was lower [10 % (6/58) vs. 17 % (11/64)]. These proportions were not significantly different ($P = 0.11$ and $P = 0.31$, respectively) (Table 1).

In the ITT analysis, three patients did not receive cisplatin (two patients in the HD-Cis arm who received carboplatin and 5FU and one patient in the FHD-Cis arm died rapidly before any treatment), so the dose of cisplatin received was considered zero.

Median cisplatin cumulative dose was 291 mg/m^2 [interquartile range (IQR): 251; 298] in the FHD-Cis arm (n = 58) and 274 mg/m^2 (IQR: 198; 295) in the HD-Cis arm (n = 64) ($P = 0.054$). Cumulative cisplatin dose in three categories showed similar results with more patients in the ≥ 280 mg/m^2 group (71 % vs 50 %) and less in the < 200 mg/m^2 group (17 % vs 31 %) for the FHD-Cis arm compared to the HD-Cis arm. The percentage of patients who received the three scheduled cycles of cisplatin was significantly greater in the FHD-Cis arm: 81 % vs 64.1 % in the HD-Cis arm ($P = 0.04$) (Table 2).

Moreover, fewer patients in the FHD-Cis arm required cisplatin dose reductions than in the HD-Cis arm: 9 % (5/55) vs. 19 % (11/58) at the second cycle and 28 % (13/47) vs. 56 % (23/41) at the third cycle.

In the per-protocol analysis, results on median cumulative dose were similar, but the difference was significant ($P = 0.02$). The other results of the per-protocol analysis were also similar to the ITT analysis (Supplementary Table A1).

Fractionating the 100 mg/m^2 dose over 4 days resulted in a 28 % decrease in the mean maximum concentration (Cmax) ($P < 0.0001$) and a 26 % increase in the mean Area Under the Curve (AUC) ($P = 0.003$) of ultra-filterable cisplatin in the FHD-Cis arm compared to the HD-Cis arm as shown in Supplementary Fig. A3, Tables A2-A3 and described in Appendix 1.

All treated patients received IMRT. Seventy-one patients were planned for definitive CRT and fifty-one for postoperative CRT (Table 1). Radiation delivery was similar in both arms for both total dose and duration. The percentage of patients who had a radiotherapy interruption was also similar for the definitive modality, but higher in the HD-Cis arm for the postoperative group (HD-Cis vs FHD-Cis: 70 % vs 38 %) (Supplementary Table A4).

Acute toxicity was assessed in the 119 patients who received at least one cisplatin infusion (Table 3). The differences were mainly hematological, particularly neutropenia. The grade 3–4 neutropenia rate was 27 % (17/62) in the HD-Cis arm versus 9 % (5/57) in the FHD-Cis arm ($P = 0.009$). The grade 3–4 anemia rate also increased in the HD-Cis arm: 13 % (8/62) versus 0 % (0/57) in the FHD-Cis arm. There were two grade 3–4 thrombocytopenia in the HD-Cis arm vs zero in the FHD-Cis arm.

There were no significant differences in terms of creatinine elevation and hearing toxicity between the two arms.

However, all-grade creatinine elevation in the HD-Cis arm was 42 % (26/62) versus 33 % (19/57) in the FHD-Cis arm. For hearing toxicity, when considering grade ≥ 2 toxicities, there were seven in the HD-Cis arm versus three in the FHD-Cis arm.

Overall, the toxicities more typical of the CRT combination, i.e. mucositis and dysphagia, were not influenced by the fractionating of cisplatin, except for skin toxicity in the radiation field, with 12 grade 3 toxicities in the HD-Cis arm versus 4 in the FHD-Cis arm.

Overall, there were more patients with at least one grade 3–4 adverse event in the HD-Cis arm than in the FHD-Cis arm: 69 % (43/62) and 54

Table 1
Pretreatment Characteristics of Patients in the Intent-to Treat Population.

Characteristic	HD-Cis (n = 64)	FHD-Cis (n = 58)	Total (n = 122)
Age			
Median, years (IQR)	61 (57–66)	61 (55–65)	61 (56–65)
Sex No (%)			
Male	54 (84)	49 (85)	103 (84)
Female	10 (16)	9 (15)	19 (16)
ECOG PS No (%)[a]			
0	32 (51)	31 (53)	63 (52)
1	29 (46)	25 (43)	54 (45)
2	2 (3)	2 (3)	4 (3)
Tobacco use No (%)			
Current	21 (33)	20 (35)	41 (34)
Former	37 (58)	31 (53)	68 (56)
Never	6 (9)	7 (12)	13 (11)
Primary site No (%)			
Oral cavity	11 (17)	13 (22)	24 (20)
Oropharynx	31 (48)	29 (50)	60 (49)
Larynx	11 (17)	9 (16)	20 (16)
Hypopharynx	11 (17)	6 (10)	17 (14)
Hypopharynx + Oropharynx		1 (2)	1 (1)
Oropharynx p16 status[b]			
p16 positive	11 (41)	17 (63)	28 (52)
p16 negative	16 (59)	10 (37)	26 (48)
T stage No (%)[c]			
T1	6 (9)	2 (4)	8 (7)
T2	13 (20)	22 (39)	35 (29)
T3	20 (31)	15 (26)	35 (29)
T4	25 (39)	18 (32)	43 (36)
N stage No (%)			
N0	10 (16)	6 (10)	16 (13)
N1	14 (22)	9 (16)	23 (19)
N2	32 (50)	40 (69)	72 (59)
N3	8 (13)	3 (5)	11 (9)
TNM stage			
Stage II	3 (5)	1 (2)	4 (3)
Stage III	12 (19)	12 (21)	24 (20)
Stage IV	49 (77)	45 (78)	94 (77)
Planned CRT modalities[d]			
Definitive	37 (58)	34 (59)	71 (58)
Post-operative	27 (42)	24 (41)	51 (42)
High risk features			
In the post-operative setting[df]			
Close or positive margins	13 (50)	12 (48)	25 (49)
Extra capsular extension	17 (65)	17 (68)	34 (67)

HD-Cis, High-dose Cisplatin; FHD-Cis, Fractionated High-Dose Cisplatin; [a] Data missing for one patient in the HD-Cis arm; [b] Data missing for four patients in the HD-Cis arm and two patients in the FHD-Cis arm; [c] Data missing for one patient in the FHD-Cis arm (post-operative setting); [d] stratification factor; [f] eight patients had close or positive margins and extra capsular extension.

Table 2
Cumulative delivered dose of cisplatin in the intention to treat population.

	HD-Cis (n = 64)	FHD-Cis (n = 58)	*P*-value[a]
Cum. Dose mg/m^2			
Median	274	291	0.054
Q1; Q3	198; 295	251; 298	
Cum. Dose No (%)			
<200 mg/m^2	20 (31)	10 (17)	0.07[b]
200–279 mg/m^2	12 (19)	7 (12)	
≥ 280 mg/m^2	32 (50)	41 (71)	
Received 3 cycles of cisplatin No (%)	41 (64)	47 (81)	0.04

HD-Cis, High-dose cisplatin; FHD-Cis, Fractionated High-Dose Cisplatin; No, number of patients; Cum., cumulative; Q1/Q3: first and third interquartile; [a] Test stratified on postoperative vs definitive chemoradiotherapy; [b] Test for trends stratified on postoperative vs definitive chemoradiotherapy.

Table 3
Acute Adverse Events in ≥ 10 % of patients.

	HD-Cis n = 62		FHD-Cis n = 57	
Adverse Event No patients (%)	Any Grade	Grade 3–4	Any Grade	Grade 3–4
At least one severe toxicity – Hematologic		43 (69)		31 (54)
Anemia	59 (95)	8 (13)[h]	52 (91)	0 (0)[h]
Neutropenia	45 (73)	17 (27)[i]	20 (35)	5 (9)[i]
Thrombocytopenia	31 (50)	2 (3)	26 (46)	0 (0)
Non hematologic				
Dermatitis [a]	50 (91)	12 (22)[j]	47 (82)	4 (7)[j]
Mucositis [b]	48 (84)	14 (25)	43 (75)	13 (23)
Dysphagia [c]	45 (80)	19 (34)	42 (75)	17 (30)
Hypokalemia	33 (53)	2 (3)	22 (39)	1 (2)
Vomiting	31 (50)	3 (5)	30 (53)	3 (5)
Xerostomia [d]	17 (44)	0 (0)	27 (64)	0 (0)
Creatine elevation	23 (37)	3 (5)	18(31)	1 (2)
Hypoalbuminemia [e]	21 (34)	1 (2)	10 (18)	0 (0)
Hyponatremia	21 (34)	3 (5)	16 (28)	0 (0)
Hearing disturbance	19 (31)	2 (3)	15(26)	2 (4)
Hypomagnesemia [f]	16 (26)	1 (2)	15 (27)	0 (0)
Neck edema[g]	9 (23)	0 (0)	15 (36)	0 (0)
Transaminase elevation [e]	10 (16)	1 (2)	11 (19)	0 (0)
Hypocalcemia	10 (16)	0 (0)	11 (19)	0 (0)
Fever	10 (16)	0 (0)	7 (12)	0 (0)
Hyperbilirubinemia [e]	7 (11)	0 (0)	5 (9)	0 (0)

HD-Cis, High-Dose Cisplatin; FHD-Cis, Fractionnated High-Dose Cisplatin; [a] skin toxicity in the radiation field; [d] Data missing for 7 patients in the HD-Cis arm; [b] Data missing for 5 patients in the HD-Cis arm; [c] Data missing for 6 patients in the HD-Cis arm and for 1 patient in the FHD-Cis arm; [d] Data missing for 23 patients in the HD-Cis arm and for 15 patients in the FHD-Cis arm; [e] Data missing for one patient in the HD-Cis arm; [f] Data missing for one patient in the FHD-Cis arm; [g] Data missing for 22 patients in the HD-Cis arm and for 15 patients in the FHD-Cis arm; [h]$P = 0.006$; [i]$P = 0.009$; [j]$P = 0.03$.

% (31/57), respectively.

In addition, when all acute toxicities were pooled, there were significantly fewer grade 3–4 toxicities in the FHD-Cis arm:10 % (50/487) compared to the HD-Cis arm: 17 % (95/563) ($P = 0.002$).

There were 51 acute serious adverse events (SAEs) related to CRT (Appendix 1, Supplementary Table A5). The rate of patients with at least one SAE was lower in the FHD-Cis arm, 21 % (12/57), compared to the HD-Cis arm, 34 % (21/62).

Four types of events were associated with 88 % of SAEs (FHD-Cis/HD-Cis): 6 febrile and/or septic neutropenia resulting in one toxic death in the HD-Cis arm (2/4), 15 acute renal function impairments all leading to hospitalization (5/10), 16 sepsis (6/10) and 8 mucositis and/or dysphagia (4/4). Considering the first three types of SAEs more likely to have been influenced by cisplatin fractionation, there were fewer patients with at least one SAEs of special interest in the FHD-Cis arm compared to the HD-Cis arm: 18 % (10/57) versus 27 % (17/62) respectively.

Toxicities were considered late when they occurred more than 3 months after CRT. Late toxicities were assessed in 44 patients out of 57 (77 %) in the FHD-Cis arm and 48 patients out of 62 (77 %) in the HD-Cis arm. Rates of patients with at least one late grade 3–4 toxicity were 9 % (4/44) in the FHD-Cis arm and 6 % (3/48) in the HD-Cis arm ($P = 0.71$) (Supplementary Table A6).

With a median follow-up of 48 months (IQR: 41; 55), there were no significant differences in time-dependent outcomes (HR stratified by type of CRT) in the FHD-Cis arm compared to the HD-Cis arm: 3-year LRF rates were 28 % vs. 24 % with a HR of 1.09 (95 %CI: 0.52–2.29) (Fig. 2A), 3-year PFS rates were 50 % vs. 52 % with a HR of 0.93 (95 % CI: 0.57–1. 52) (Fig. 2B), and the 3-year OS rates were 62 % vs. 63 % with a HR of 0.86 (95 %CI: 0.50–1.47), respectively (Fig. 2C, Appendix 1, Supplementary Tables A7-A8).

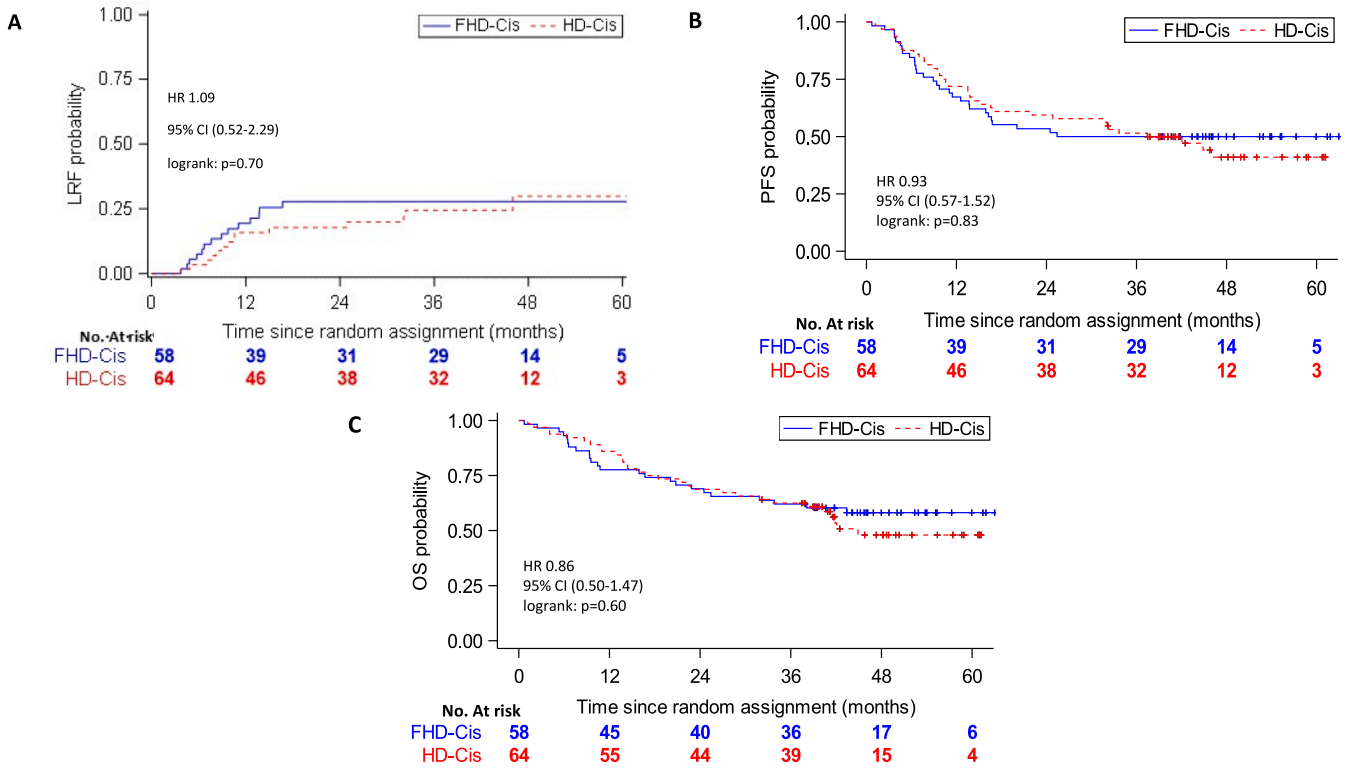

Fig. 2. (A) Kaplan-Meier curve for loco-regional failure (LRF). (B) Kaplan-Meier curve for progression-free survival (PFS). (C) Kaplan-Meier curve for overall survival (OS). The symbol "+" indicate censored observations. HRs were computed using a stratified Cox proportional hazards model and *P* values were from a stratified log-rank test.

Discussion

Results from the GORTEC 2015–02 trial showed that although the cumulative dose of cisplatin administered concurrently with radiotherapy was numerically higher in the fractionated arm (FHD-Cis) than in the standard arm (HD-Cis), this difference was not significant ($P = 0.054$) which means that primary endpoint was not met.

However, the percentage of patients receiving a third cycle of cisplatin was significantly higher in the FHD-Cis arm than in the HD-Cis arm [81 % vs. 64 % ($P = 0.04$)], with significantly fewer grade 3–4 acute adverse events [10 % vs. 17 % ($P = 0.002$)] and fewer cisplatin dose reductions.

In the per-protocol analysis, the cumulative dose of cisplatin administered concurrently with radiotherapy was significantly higher in the FHD-Cis arm than in the HD-Cis arm ($P = 0.02$).

It should be noted that there was an imbalance in the number of patients between the 2 arms (65 patients in the HD-Cis arm vs. 59 in the FHD-Cis arm). This imbalance is explained by the randomization procedure as some centers that enrolled few patients did not complete their blocks.

To our knowledge, this study is the first to show that a modification of the cisplatin administration scheme allows to obtain this result which was not achieved with any weekly fractionating regimen to date. Indeed, studies using weekly fractionating of cisplatin, either at a dose of 30 mg/m^2 (W3W study [14]) or at a dose of 40 mg/m^2 (JCOG1008 study [15], CONCERT study [16]) delivered median cumulative doses ranging from 210 mg/m^2 to 240 mg/m^2 that were always lower than, or not significantly different from, the cumulative dose delivered in the standard arm (Table 4).

The importance of the cumulative dose of cisplatin concurrent with radiotherapy was highlighted as early as 2011 when it appeared that 20 mg/m^2 weekly was an insufficient dose not providing any benefit compared to radiotherapy alone [17]. The minimal cumulative active dose appears to be 200 mg/m^2 as shown in the RTOG 0129 and SAAK trials, however these trials included potential confounding factors, i.e. altered fractionating of the radiotherapy which was either moderately accelerated or bifractionated [6,7].

In the W3W trial, patients in the weekly cisplatin 30 mg/m^2 (Cis-30) arm received a median cumulative dose of 210 mg/m^2 and 42 % received less than 200 mg/m^2. This resulted in a significant decrease in the locoregional control rate from 73.1 % at 2 years in the standard arm to 58.5 % in the weekly Cis-30 arm. Moreover, the benefit of increasing the cumulative dose of cisplatin appeared to continue beyond 200 mg/m^2, as even patients in the Cis-30 arm who received a cumulative dose greater than 200 mg/m^2 also had a significant decrease in locoregional control rate compared with those in the standard arm [14]. The continued benefit of a cumulative cisplatin dose beyond 200 mg/m^2 was also well demonstrated in Strojan's *meta*-analysis where an absolute survival benefit of 2.2 % was obtained each time an additional 10 mg/m^2 was administered [9]. It seems likely that high-risk patients, i.e. HPV-negative and/or having a high tumor burden (T4 and/or N3), may require a high cumulative dose of cisplatin above 200 mg/m^2 [18]. The administration of such doses is difficult to achieve, the more so since these patients suffer often from multiple co-morbidities.

In our study, despite a higher cumulative dose of cisplatin delivered in the FHD-Cis arm, there was no significant difference in LRC, PFS or OS. However, it should be noted that our study was not powered for this purpose.

The higher proportion of p16-positive oropharyngeal tumors and the lower proportion of hypopharyngeal tumors may have favored the time dependent outcomes of the FHD-Cis arm compared to the HD-Cis arm, but these proportions were not significantly different.

Ultimately, the benefit of fractionating the administration of cisplatin remains the reduction of acute toxicity. Four types of toxicities of particular interest can be considered more likely to be influenced by cisplatin fractionating: neutropenia, infections, renal and hearing toxicity [15].

Grade 3–4 neutropenias were significantly decreased in the Cis-30 arm of the W3W study with a decrease in febrile neutropenia [14]. Infections were significantly reduced in the weekly arms of the W3W and JCOG1008 Studies [14,15]. Renal toxicity as well as hearing impairment were significantly reduced in the weekly arms of the JCOG1008 and CONCERT Studies [15,16].

In our study, we also found a significant decrease in grade 3–4 neutropenias and numerically less febrile neutropenias, infections, renal toxicity and grade ≥ 2 hearing impairment.

In general, grade 3–4 acute toxicities were less frequent in the fractionated vs standard arms in the W3W study, in the JCOG1008 study and in the CONCERT study as well as in our study.

The disadvantage of fractionated cisplatin is the increased number of infusions: twelve in the FHD-cis arm versus seven for weekly dosing versus three for standard dosing. However, fractionated administration over 4 h can be done on an outpatient basis, whereas standard administration over 9 h requires inpatient treatment.

The results of our pharmacokinetic study of ultra-filterable cisplatin, which represents the active form not bound to proteins, are in line with those of Nagai et al, namely that it was the decrease in Cmax observed with fractionating the dose that would induce a decrease in toxicity [11]. In addition, fractionating the dose resulted in a 26 % increase in the AUC, it is reasonable to expect that efficacy will at least be maintained.

Conclusion

The 4-day fractionated regimen did not significantly increase the cumulative dose of cisplatin administered concurrently with radiotherapy compared to the standard schedule. Therefore, the study did not meet its primary endpoint.

However, the percentage of patients receiving a third cycle of cisplatin was significantly higher in the FHD-Cis arm, while toxicity was

Table 4
Cumulative delivered dose of cisplatin in four randomized trials.

CDDP mg/m^2 schema	W3W[14] 93 % post-op CRT		JCOG-1008[15] Post-op CRT		CONCERT[16] Definitive CRT		CisFRad 58 % definitive CRT	
	Weekly Cis-30	3-weekly Cis-100	Weekly Cis-40	3-weekly Cis-100	Weekly Cis-40	3-weekly Cis-100	3-weekly FHD-Cis	3-weekly HD-Cis
No. pts	150	150	129	132	133	133	58	64
Median	210	300	239	280	240[b]	225[b]	291[c]	274[c]
IQR	180–210	200–300	199–277	250–299	0-280[a]	0-300[a]	251–298	198–295
<200 % pts	42 %	5 %	NA	NA	19.5 %	22.5 %	17.2 %	31.3 %
≥ 280 % pts	NA	NA	NA	NA	28.5 %	36.8 %	70.7 %[d]	50.0 %[d]

CDDP, cisplatin; Cis-30, 30 mg/m^2 weekly cisplatin; Cis-100, 100 mg/m^2 three-weekly cisplatin; Cis-40, 40 mg/m^2 weekly cisplatin; HD-Cis, High-dose cisplatin; FHD-Cis, Fractionated High-Dose Cisplatin; CRT, chemoradiotherapy; pts, patients; NA, not available; [a] range; [b] $P = 0.31$; [c] $P = 0.054$; [d] $P = 0.02$.

significantly reduced. The 4-day fractionated high-dose cisplatin regimen appears to be an alternative worth considering, not only for patients with borderline HD-Cis eligibility, but also for those at high risk who definitely need a third cycle of full-dose cisplatin.

Prior presentation

Presented at the European Society for Medical Oncology Annual Meeting, Virtual Meeting, 2020 (abstr. 914MO, Mini Oral Abstract Session).

Support

Supported by the *Centre Paul Strauss* for the pharmacokinetic study under Grant No SGBXJFELPRDXYK4G.

CRediT authorship contribution statement

Christian Borel: Writing – Review & editing, Writing – original draft, Conceptualization, Resources, Investigation. **Xu-Shan Sun:** Writing – review & editing, Resources, Investigation. **Alexandre Coutte:** Writing – review & editing, Resources, Investigation. **Guillaume Bera:** Writing – review & editing, Resources, Investigation. **Christian Sire:** Writing – review & editing, Resources, Investigation. **Sylvie Zanetta:** Writing – review & editing, Resources, Investigation. **Marc Alfonsi:** Writing – review & editing, Resources, Investigation. **Guillaume Janoray:** Writing – review & editing, Resources, Investigation. **Thierry Chatellier:** Writing – review & editing, Resources, Investigation. **Muriel Garcia-Ramirez:** Writing – review & editing, Resources, Investigation. **Elisabeta Gherga:** Writing – review & editing, Investigation. **Yasser Hammoud:** Writing – review & editing, Investigation. **Mickaël Burgy:** Writing – review & editing, Resources, Investigation. **Nelly Etienne-Selloum:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis. **Adeline Pechery:** Writing – review & editing, Methodology, Data curation. **Marie-Hélène Girard-Calais:** Writing – review & editing, Methodology, Data curation. **Michel Velten:** Writing – review & editing, Methodology, Data curation. **Jean-Pierre Pignon:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Mathilde Wanneveich:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Jean Bourhis:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We thank all the GORTEC team and especially Fanny Louat and Natacha Collin-Batailhou for data monitoring and Pascale Adam and Pascal Garaud for data management.

We thank Professor Georges Noël and Doctor Yoann Pointreau for their proofreading and suggestions.

We thank Professor Etienne Chatelut for the cisplatin assays, Mrs. Sophie Bayer for the management of blood samples for cisplatin pharmacokinetics.

We thank the Paul Strauss Center for their grant for the pharmacokinetic study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110329.

References

[1] Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL, Greiner RH, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 2004;350:1945–52. https://doi.org/10.1056/NEJMoa032641.

[2] 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. N Engl J Med 2004;350:1937–44. https://doi.org/10.1056/NEJMoa032646.

[3] Adelstein DJ, Li Y, Adams GL, Wagner Jr H, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 2003;21:92–8. https://doi.org/10.1200/JCO.2003.01.008.

[4] Lacas B, Carmel A, Landais C, Wong SJ, Licitra L, Tobias JS, 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. https://doi.org/10.1016/j.radonc.2021.01.013.

[5] Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomized controlled phase 3 trial. Lancet 2019;393:51–60. https://doi.org/10.1016/S0140-6736(18)32752-1.

[6] Nguyen-Tan PF, Zhang Q, Ang KK, Weber RS, Rosenthal DI, Soulieres D, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol 2014;32:3858–66. https://doi.org/10.1200/JCO.2014.55.3925. Epub 2014 Nov 3.

[7] Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 2004;22:4665–73. https://doi.org/10.1200/JCO.2004.12.193.

[8] Ghi MG, Paccagnella A, Floriani I, Garavaglia D. Concomitant chemoradiation in locally advanced head and neck squamous cell carcinoma: A literature-based meta-analyse on the platinum concomitant chemotherapy. J Clin Oncol 2011;29:5534. https://doi.org/10.1200/jco.2011.29.15_suppl.5534.

[9] Strojan P, Vermorken JB, Beitler JJ, Saba NF, Haigentz Jr M, Bossi P, et al. Cumulative cisplatin dose in concurrent chemoradiotherapy for head and neck cancer: A systematic review. Head Neck 2016;38:E2151–8. https://doi.org/10.1002/hed.24026.

[10] Spreafico A, Huang SH, Xu W, Granata R, Liu CS, Waldron JN, et al. Impact of cisplatin dose intensity on human papillomavirus-related and -unrelated locally advanced head and neck squamous cell carcinoma. Eur J Cancer 2016;67:174–82. https://doi.org/10.1016/j.ejca.2016.08.013.

[11] Nagai N, Kinoshita M, Ogata H, Tsujino D, Wada Y, Someya K, et al. Relationship between pharmacokinetics of unchanged cisplatin and nephrotoxicity after intravenous infusions of cisplatin to cancer patients. Cancer Chemother Pharmacol 1996;39:131–7. https://doi.org/10.1007/s002800050548.

[12] Sharma A, Mohanti BK, Thakar A, Bahadur S, Bhasker S. Concomitant chemoradiation versus radical radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: a phase II randomized trial. Ann Oncol 2010;21:2272–7. https://doi.org/10.1093/annonc/mdq219. Epub 2010 Apr 28.

[13] Ghosh-Laskar S, Kalyani N, Gupta T, Budrukkar A, Murthy V, Sengar M, et al. Conventional radiotherapy versus concurrent chemoradiotherapy versus accelerated radiotherapy in locoregionally advanced carcinoma of head and neck: Results of a prospective randomized trial. Head Neck 2016;38:202–7. https://doi.org/10.1002/hed.23865.

[14] Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, et al. Once-a-Week Versus Once-Every-3-Weeks Cisplatin Chemoradiation for Locally Advanced Head and Neck Cancer: A Phase III Randomized Noninferiority Trial. J Clin Oncol 2018;36:1064–72. https://doi.org/10.1200/JCO.2017.74.9457.

[15] Kiyota N, Tahara M, Mizusawa Y, Kodaira T, Fujii H, Yamazaki T, et al. Weekly Cisplatin Plus Radiation for Postoperative Head and Neck Cancer (JCOG1008): A Multicenter, Noninferiority, Phase II/III Randomized Controlled Trial. J Clin Oncol 2022;40:1980–90. https://doi.org/10.1200/JCO.21.01293. Epub 2022 Mar 1.

[16] Sharma A, Kumar M, Bhasker S, Thakar A, Pramanik R, Biswas A, et al. An open-label, noninferiority phase III RCT of weekly versus three weekly cisplatin and radical radiotherapy in locally advanced head and neck squamous cell carcinoma (ConCERT trial). J Clin Oncol 2022;40:6004. https://doi.org/10.1200/JCO.2022.40.16_suppl.6004.

[17] Quon H, Leong T, Haselow R, Leipzig B, Cooper J, Forastiere A. Phase III study of radiation therapy with or without cis-platinum in patients with unresectable squamous or undifferentiated carcinoma of the head and neck: an intergroup trial of the Eastern Cooperative Oncology Group (E2382). Int J Radiat Oncol Biol Phys 2011;81:719–25. https://doi.org/10.1016/j.ijrobp.2010.06.038. Epub 2010 Oct 1.

[18] Kharouta MZ, Patil N, Torres-Saavedra P, Wang GM, Damico N, Deshane A, et al. Nomogram for predicting survival in patients receiving definitive chemoradiation for locally advanced squamous cell carcinoma of the head and neck. A secondary analysis of NRG/RTOG 0129, 0522 and 016. Ann Oncol 2021;32:863. https://doi.org/10.1016/j.annonc.2021.08.1273.