# Dose-limiting toxicities due to cisplatin chemoradiotherapy after short hydration schemes in comparison with long hydration schemes in head and neck squamous cell carcinoma patients (HydraCis)

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**Abstract**

**INTRODUCTION** Cisplatin dose-limiting toxicity (CDLT), often due to cisplatin-induced nephrotoxicity, is common during cisplatin-based chemoradiotherapy (CRT) in patients with head and neck squamous cell carcinoma (HNSCC). Currently, different strategies consisting of hydration using different saline infusions and varying timeframes are used to combat cisplatin-induced nephrotoxicity. The aim of this study was to assess whether a short hydration (SH) scheme in comparison with a long hydration (LH) scheme leads to less CDLT, specifically due to nephrotoxicity, in HNSCC patients.

**MATERIAL AND METHODS** In this Dutch multicenter retrospective cohort study, HNSCC patients from the Antoni van Leeuwenhoek (AvL) and Amsterdam University Medical Center, location Vrije Universiteit Medical Center (Amsterdam UMC), who were treated with 40 mg/m$^2$ (Cis40) or 100 mg/m$^2$ (Cis100) cisplatin-based CRT, were included. The AvL administered a LH scheme, whereas the Amsterdam UMC administered a SH scheme. The primary outcome was the incidence of CDLT due to nephrotoxicity. CDLT was defined as any toxicity resulting in dose-reduction of ≥50%, treatment delay of at least four days, or early treatment cessation of cisplatin. Data was collected from patients from January 1$^{st}$ 2020 until July 1$^{st}$ 2022. For each patient data was collected until one month after treatment. Chi-square and Fisher's exact tests were performed to assess differences in incidence.

**RESULTS** In total, 112 patients (AvL 68 patients versus Amsterdam UMC 44 patients) receiving Cis40 and 100 patients (AvL 23 patients versus Amsterdam UMC 77 patients) receiving Cis100 were included. For patients receiving the Cis100 SH scheme, less CDLT due to nephrotoxicity (n = 9 (39%) versus n = 13 (17%), p = 0.024), less treatment changes (n = 14 (61%) versus n = 29 (38%), p = 0.049), and a higher mean cumulative cisplatin dose (230 mg/m$^2$ ± 55 versus 259 mg/m$^2$ ± 62, p = 0.008) were observed as compared to patients receiving the Cis100 LH scheme. In patients receiving Cis40, no significant differences in CDLT were observed.

**CONCLUSION** The current study demonstrates that the Cis100 SH scheme is associated with less treatment changes due to CDLT, particularly nephrotoxicity, compared to the Cis100 LH scheme. This resulted in a higher cumulative cisplatin dose in patients receiving the SH scheme. Therefore, for HNSCC patients receiving Cis100, the SH scheme is preferable.

**KEY WORDS** Cisplatin chemoradiotherapy, head and neck squamous cell carcinoma, short hydration, nephrotoxicity, creatinine.

# 1 INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is with 3,174 new cases and 921 deaths in 2021 the eighth most common cancer in the Netherlands (1). The incidence is estimated to continue to rise and expected to increase with up to 30% by 2030 worldwide. That is, 1.08 million new HNSCC patients annually (2). HNSCC has multiple origins. It can arise as a result of excessive alcohol consumption or tobacco-derived carcinogens, or both (3). HNSCC can also arise as a result of infectious agents, like the Epstein-Barr virus (EBV) and the Human papillomavirus (HPV) (3-5). EBV-positive HNSCC is specifically associated with nasopharyngeal carcinoma (6). HPV-positive HNSCC is specifically associated with oropharyngeal carcinoma and commonly has a more favorable survival than HPV-negative HNSCC (4, 5). More than 50% of the HNSCC patients present with advanced disease at diagnosis (large tumor,

regional and/or distant metastases) (1). Treatment for patients with locally and/or regionally advanced (stage lll-IV) HNSCC consists of concurrent cisplatin-based chemoradiotherapy (CRT), in a primary or adjuvant setting in high-risk patients (7). The standard chemotherapy regimen consists of cisplatin given at 100 mg/m$^2$ body surface area (BSA) (Cis100) every three weeks (8). Additionally, a phase ll/lll randomized controlled trial from Kiyota et al. shows that a weekly administration of 40 mg/m$^2$ BSA (Cis40) in patients with postoperative high-risk locally advanced HNSCC is non-inferior to Cis100 (2, 7). However, according to a meta-analysis from Szturz et al. there is still a lack of evidence to claim that Cis40 is non-inferior compared to Cis100 in primary CRT (9). It might be preferable to administer Cis40 in patients with pre-existing renal injury or hearing loss (10) and Cis40 was preferable in the Antoni van Leeuwenhoek (AvL) during the Covid-19 pandemic because it induced less fragility in CRT patients.

Cisplatin-based CRT is commonly associated with severe, dose-limiting acute adverse events, like nephrotoxicity, neutropenia, thrombocytopenia, ototoxicity, nausea, infections and weight loss (9). Cisplatin-induced nephrotoxicity is a common dose-limiting adverse event in clinical practice with a prevalence of 33% of the treated patients (11). It typically arises at approximately ten days after treatment (11, 12). Nephrotoxicity arises during cisplatin therapy when cisplatin accumulates in the renal proximal tubules. Cisplatin accumulation has been shown to originate from changes in expression of the proximal tubule organic cation transporter 2 (OCT2). It then results in activation of complex signaling pathways that generate tubular cell injury and cell death (11, 13). Contrarily, according to a review of Strojan et al., a cumulative dose of cisplatin in CRT for HNSCC patients has a significant positive correlation with survival. According to this review, the recommended cumulative dose of cisplatin is at least 200 mg/m$^2$. It therefore claims the more cisplatin is administered, the higher the beneficial effect of the therapy (14). Treatment changes caused by cisplatin dose-limiting toxicity (CDLT) due to nephrotoxicity might therefore diminish treatment effectivity.

Studies have shown that hydration can limit the incidence and degree of nephrotoxicity because of reduction in urine cisplatin concentrations, cisplatin half-life, and proximal tubule transit time (11, 15). Multiple hydration regimens exist between different hospitals, and even within hospitals. Momentarily, no definite conclusions can be drawn regarding the optimal hydration scheme (11). However, long hydration (LH) schemes are considered the standard hydration regimen for HNSCC patients. LH schemes consist of a liter saline solution that is administered two to four times over 13 to 24 hours. On the other hand, short hydration (SH) schemes consist of a two to four liters saline solution that is administered over two to six hours (11). The SH scheme is therefore substantially less time-consuming, which can be beneficial for the patient as well as the physician. Additionally, longer hydration prolongs the hospital stay of patients and therefore increases health care costs (16, 17).

According to a retrospective cohort study from Niggebrugge et al., the SH scheme is preferable in comparison with the LH scheme in patients with non-small-cell lung cancer (NSCLC). This study compared the SH and LH scheme in NSCLC patients with cisplatin-based chemotherapy. The SH scheme resulted in statistically significant and clinically relevant less decrease in renal function compared to the LH scheme. Additionally, fewer SH patients had to stop the treatment due to nephrotoxicity (16). However, standard cisplatin treatment for NSCLC patients is lower-dosed than standard treatment for HNSCC patients (70 versus 100 mg/m$^2$). Therefore, it is not yet clear which hydration scheme is preferable in HNSCC patients. According to a small, retrospective, unpublished study at the University Medical Center Utrecht (UMCU), 34% of the patients receiving the LH scheme had CDLT due to nephrotoxicity in comparison with 5% of the patients receiving the SH scheme. However, 15% of the patients receiving the LH scheme had CDLT due to ototoxicity in comparison with 25% of the patients receiving the SH scheme. To further investigate the effects of the SH scheme, the aim of the current study is to determine the CDLT, specifically due to nephrotoxicity, caused by cisplatin-based CRT after a SH scheme in comparison with a LH scheme in patients with HNSCC.

# 2 MATERIAL AND METHODS

**2.1 Study design and setting**

In this Dutch multicenter retrospective cohort study, patients from the Antoni van Leeuwenhoek (AvL) and Amsterdam University Medical Center, location Vrije Universiteit Medical Center (Amsterdam UMC), with HNSCC who were treated with Cis100 CRT triweekly or Cis40 CRT weekly, were included.

The following inclusion criteria were used: ≥1 cycle with cisplatin-based CRT in the AvL or Amsterdam UMC for HNSCC, age ≥18 years, a serum creatinine value available ≤1.5 month before the first cisplatin cycle (creatinine at baseline) and at least one serum creatinine value available within one month after the last cisplatin cycle administration. Patients who were previously treated with cisplatin were excluded.

**2.2 Hydration schemes**

The AvL administered a LH scheme in HNSCC patients, whereas the Amsterdam UMC administered a SH scheme in HNSCC patients. There is no official SH scheme in the Amsterdam UMC for Cis100. However, the Amsterdam UMC's hydration scheme is substantially shorter than in the AvL and therefore this hydration scheme is referred to as SH scheme in this study (Table 1).

**2.3 Outcomes**

The primary outcome was the incidence of CDLT due to nephrotoxicity. Secondary outcomes consisted of CDLT due to ototoxicity and overall CDLT. CDLT was defined as toxicity resulting in dose-reduction of ≥50%, a treatment delay of at least four days, or early treatment cessation of cisplatin (18). Additionally, nephrotoxicity was measured based on the increased creatinine using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 as secondary outcome (11). Furthermore, the delta serum creatinine (ΔCR) was assessed for each patient (ΔCR = maximum creatinine during cisplatin-based CRT – creatinine at baseline). All ΔCR's were used to calculate the average ΔCR for the total population of the LH and SH schemes, respectively.

**2.4 Data extraction**

All data were extracted from the Electronic Patient Records (EPR). The following variables were collected: patient ID; gender; age, length, weight, body mass index (BMI) and body surface area (BSA) at the start of the first cycle; The Union for International Cancer Control's (UICC) Tumor Node Metastasis (TNM) stage based on the TNM8 (19); tumor location; chemotherapy protocol from primary and adjuvant CRT patients (including starting date cisplatin, number of cisplatin cycles, cause of protocol change); hydration protocol; cumulative cisplatin dose; creatinine at baseline in µmol/L; maximum creatinine in µmol/L; CDLT and cause of CDLT; HPV and EBV-status. The tumor location was determined based on the Dutch Head and Neck Audit (DHNA). Data was collected from patients that started and finished cisplatin-based CRT between January 1$^{st}$ 2020 until July 1$^{st}$ 2022. For each patient data was collected until one month after treatment.

**2.5 Statistical analyses**

Statistical analyses were performed in IBM SPSS Statistics version 27.0 (IBM, Chicago, USA). A p-value of <0.05 was considered statistically significant. Variables consisted of continuous and categorical variables. Normality of continuous variables was investigated using the Shapiro-Wilk test. Normally distributed variables were shown as means ± standard deviation (SD) and compared between hydration schemes using the independent T-Test. Non-normally distributed variables were shown as medians with an interquartile range (IQR) and compared between hydration schemes using the Mann-Whitney U-test. The categorical baseline characteristics were shown as frequencies with

corresponding percentages. Chi-square and Fisher's exact tests were used for analyzing differences between the frequencies of each hydration scheme.

### 2.6 Ethical approval

The AvL's Institutional Review Board (IRB) and the Amsterdam UMC's Medical Ethical Research Committee (METC) approved the design of this study and granted ethical approval (IRBd22-217 and METC ID 2022.0724, respectively).

# 3 RESULTS

### 3.1 Treatment and baseline characteristics

The total study population consisted of 112 patients receiving Cis40 (Table 2) and 100 patients receiving Cis100 (Table 3). Of the patients receiving Cis40, 68 patients from the AvL and 44 patients from the Amsterdam UMC were included. Of the patients receiving Cis100, 23 patients from the AvL and 77 patients from the Amsterdam UMC were included. In total ten patients were excluded for various reasons (Figure 1). In patients receiving Cis40, the BMI, surgical status and HPV-status differed statistically significant between the LH and SH scheme (Table 2). In patients receiving Cis100, the EBV-status, tumor location and TNM8-stage differed statistically significant (Table 3).

#### 3.2.1 Cisplatin 40 mg/m$^2$ dose-limiting toxicities

Of the patients receiving Cis40, 33 (49%) patients receiving the LH scheme and 22 (50%) patients receiving the SH scheme underwent a treatment change (p = 0.879) (Figure 2). Patients receiving the LH scheme experienced more early treatment cessation (n = 25; 37%) and fewer delays (n = 3; 4%) of cisplatin chemotherapy compared to patients receiving the SH scheme with 10 (23%) early treatment cessations and 9 (21%) delays. In 5 (7%) patients receiving the LH scheme and 3 (7%) patients receiving the SH scheme, treatment underwent multiple interventions with first a delay of treatment later a stop of treatment. Dose reductions of ≥50% were not observed in these patients, only <50%. The number of treatment changes due to overall-CDLT was comparable in the LH and SH scheme (LH scheme n = 31 (46%) versus SH scheme n = 18 (41%), p = 0.626). Non-CDLT treatment changes were for example due to preference of the patient or logistical reasons. CDLT due to nephrotoxicity was observed in 12 (18%) patients receiving the LH scheme and in 3 (7%) patients receiving the SH scheme (p = 0.100). Only in 1 (2%) patient receiving the LH scheme CDLT due to ototoxicity was observed (p = 1.000).

#### 3.2.2 Cisplatin 100 mg/m$^2$ dose-limiting toxicities

Of the patients receiving Cis100, 14 (61%) patients receiving the LH scheme and 29 (38%) patients receiving the SH scheme underwent a treatment change (p = 0.049) (Figure 2). Patients receiving the LH scheme experienced more early treatment cessation (n = 13; 57%) and fewer delays (n = 0; 0%) of cisplatin chemotherapy compared to patients receiving the SH scheme with 20 (26%) early treatment cessations and 6 (8%) delays. In 1 (4%) patient receiving the LH scheme and 3 (4%) patients receiving the SH scheme, treatment underwent multiple interventions with first a delay of treatment later a stop of treatment. Dose reductions of ≥50% were not observed in these patients, only dose reductions <50%. The number of treatment changes due to overall-CDLT was comparable in the LH and SH scheme (LH scheme n = 11 (48%) versus n = 29 (38%), p = 0.383). Non-CDLT treatment changes only happened in patients receiving the LH scheme, which was in two patients because of the Covid-19 pandemic and in one patient because of the patients' preference. CDLT due to nephrotoxicity was observed in 9 (39%) patients receiving the LH scheme and in 13 (17%) patients receiving the SH scheme (p = 0.024). CDLT due to ototoxicity was observed in 0 (0%) patients receiving the LH scheme and 6 (8%) patients receiving the SH scheme (p = 0.332).

### 3.3.1 Creatinine increase in cisplatin 40 mg/m$^2$

In patients receiving the Cis40 LH scheme, the median creatinine values increased from 71 µmol/L [IQR 63-80] to 94 µmol/L [IQR 79-113] and in patients receiving the Cis40 SH scheme from 71 µmol/L [IQR 61-87] to 84 µmol/L [IQR 68-96] (p = 0.007). In patients receiving the LH scheme, the median ΔCR was 14 µmol/L [IQR 4-43] compared to 10 µmol/L [IQR 4-17] in patients receiving the SH scheme (p = 0.020) (Figure 3).

Furthermore, if nephrotoxicity is based on creatinine increased according to the CTCAE v5.0, 26 (38%) patients have an increased creatinine ≥ grade 1 in patients receiving the LH scheme compared to 7 (16%) patients receiving the SH schemes (Figure 4). In patients receiving the LH scheme, 3 (4%) patients had an increased creatinine of grade 2 and 1 (2%) patient had an increased creatinine of grade 3 (p = 0.043).

### 3.3.2 Creatinine increase in cisplatin 100 mg/m$^2$

In patients receiving the Cis100 LH scheme, the median creatinine values increased from 69 µmol/L [IQR 60-80] to 122 µmol/L [IQR 100-141] and in patients receiving the Cis100 SH scheme from 69 µmol/L [IQR 56-79] to 109 µmol/L [IQR 89-129] (p = 0.066). In patients receiving the LH scheme, the median ΔCR was 57 µmol/L [IQR 29-76] compared to 33 µmol/L [IQR 18-55] in patients receiving the SH scheme (p = 0.048) (Figure 3).

Furthermore, if nephrotoxicity is based on creatinine increased according to the CTCAE v5.0, 17 (74%) patients have an increased creatinine ≥ grade 1 in patients receiving the LH scheme compared to 46 (60%) in patients receiving the SH scheme (Figure 4). In patients receiving the LH scheme, 4 (17%) patients had an increased creatinine of grade 2. In patients receiving the SH scheme, 9 (12%) patients had an increased creatinine of grade 2 and 2 (3%) patients had an increased creatinine of grade 3 (p = 0.518).

# 4 DISCUSSION

This study demonstrates the effect of the SH versus LH scheme on CDLT in HNSCC patients undergoing cisplatin-based CRT. In this study, less treatment changes, particularly because of less frequent nephrotoxicity, were associated with the Cis100 SH scheme compared to the Cis100 LH scheme. Furthermore, the SH scheme was associated with a smaller ΔCR, regardless of the dosing schedule of cisplatin. For Cis40, less nephrotoxicity was observed according to the CTCAE v5.0 in patients receiving the SH scheme compared to patients receiving the LH scheme.

For Cis100, the SH scheme was associated with a statistically significant lower number of treatment changes, and in particular fewer CDLT due to nephrotoxicity. For Cis100, more early treatment cessations and less delays were observed in patients receiving the LH scheme in comparison with patients receiving the SH scheme. More delay instead of early treatment cessation of cisplatin can imply that the recommended cumulative cisplatin dose of at least 200 mg/m$^2$ is reached more frequently in patients receiving the SH scheme. However, the number of patients that reached the recommended cumulative cisplatin dose was comparable in both hydration schemes and in both dosages (cumulative cisplatin ≥200 mg/m$^2$ Cis40 p = 1.000 versus Cis100 p = 0.169). On the other hand, the mean cumulative cisplatin dose was statistically significant higher in patients receiving the Cis100 SH scheme. According to a study of Strojan et al. (14), the more cisplatin that is administered, the higher the beneficial effect of cisplatin-based CRT. Therefore, the Cis100 SH scheme might give a more beneficial effect of cisplatin-based CRT compared to the Cis100 LH scheme.

The SH scheme was associated with a statistically significant smaller ΔCR compared to the LH scheme, irrespective of the cisplatin dosing schedule. For Cis40, the SH scheme also was associated with a lower maximum creatinine. Furthermore, a statistically significant lower number of patients receiving the Cis40 SH scheme was observed with an increased creatinine based on the CTCAE v5.0. This, however, did not result into statistically significant treatment changes.

In this study, the SH and LH scheme were compared. However, a difference between the Cis40 and Cis100 results can also be observed. A higher incidence of CDLT due to nephrotoxicity was observed for Cis100 compared to Cis40. This is in line with other studies where more severe nephrotoxicity was observed in Cis100 compared to Cis40 (7, 9). The incidence of CDLT due to ototoxicity did not differ statistically significant between dosing schedules. Since Cis40 and Cis100 are not directly compared, no statements of significance between the two dosages can be made.

The influence of the SH versus the LH scheme on CDLT due to nephrotoxicity has been investigated in previous studies (11, 16, 17, 20-22). In these studies, lower dosages of cisplatin (≤70 mg/m$^2$) were investigated compared to the current study. Furthermore, treatment groups showed more diversity such as different indications and different types of chemotherapy. The study from Niggebrugge et al. (16) focused on a single type of chemotherapy and a single indication (NSCLC). However, chemotherapy in NSCLC patients is also lower-dosed (≤70 mg/m$^2$) than in HNSCC patients. The observed preferable effects of the SH scheme in this study are, however, in line with the previous studies. It is plausible that forced diuresis due to hydration in a short time leads to a higher flow in the kidneys which might lead to less cisplatin accumulation and therefore less CDLT due to nephrotoxicity. To our knowledge, this is the first real-world study to evaluate the impact of the SH versus LH regimen for patients receiving Cis100, focused on HNSCC patients.

The SH scheme could influence clinical practice by shortening hospital admission, which might be favorable for the patient and health care costs (16, 17). A disadvantage, however, can be that the SH scheme will clinically transport hydration from one-night-hospitalization to short admission in a day care bed. In this way, monitoring the patient will only be for a short while. Since HNSCC patients, might be frail, monitoring the patient for one night could be perceived as preferable in some hospitals. Longer observational time on the day care unit could be a solution, but logistically this is not always possible. In general, HPV-positive oropharyngeal patients have better clinical outcomes, are less fragile and have 58% reduction in risk of death (4, 5). Therefore, admission to a day care bed for HPV-positive oropharyngeal patients could be considered if one would not want to jeopardize the safety of a longer observation.

There are several limitations to this Dutch multicenter retrospective cohort study. First, hydration schemes were differentiated based on duration and volume of hydration in this study. However, other differences in the hydration schemes were also present. Hydration schemes between the AvL and Amsterdam UMC differed in electrolyte additives and hydration design. Contrarily to the Amsterdam UMC, which includes a total of 5g $MgSO_4$ and 50 mmol KCl in Cis40 hydration, the AvL includes 1.5g $MgSO_4$, 60 mmol KCl and 900 mg $C_{12}H_{22}CaO_{14}$. Electrolyte additives for Cis100 hydration consists of 10g $MgSO_4$ and 100 mmol KCl in the Amsterdam UMC compared to 1.5g $MgSO_4$, 60 mmol KCl and 870mg $C_{12}H_{22}CaO_{14}$ in the AvL. Magnesium-depletion has a substantial additive effect on cisplatin-induced nephrotoxicity (23). Preloading magnesium, dosed 600mg, before administration of cisplatin was previously shown to statistically significant reduce cisplatin-induced nephrotoxicity (23-25). Furthermore, adding magnesium is believed to contribute to the feasibility and safety of the SH schemes in patients with high-dose cisplatin (>75 mg/m$^2$) (11). Additionally, a non-randomized interventional study showed that triple electrolyte supplementation with magnesium, calcium and potassium decreases the risk of nephrotoxicity after chemotherapy with cisplatin at a dose of ≥50 mg (26). This suggests an advantage for the AvL's LH scheme. However, the results show otherwise. Whether this is due to the electrolyte supplementation or hydration design of the hydration regimen cannot be concluded due to this study design. Second, this study design did not take effectivity of cisplatin-based CRT into consideration. However, the surrogate parameter, the recommended cumulative cisplatin dose of 200 mg/m$^2$ was considered. The latter was chosen because of the follow-up time. Additionally, the surrogate parameter is highly predictive for the survival of HNSCC patients (14). Third, this study was conducted in two different hospitals. Heterogeneity between two hospitals can cause confounding because of different documentation in EPR's. In different hospitals, different choices can be made, like regarding the Covid-19 pandemic. In two patients in the AvL the pandemic led to treatment changes during cisplatin-based CRT. Furthermore, physicians decided to switch from Cis100 to Cis40-based CRT in the AvL. In the Amsterdam UMC, no differences in treatment were made

based on the pandemic. Fourth, nephrotoxic co-medication and renal comorbidities were not taken into account in this study. However, the findings of this study are representative for daily clinical practice as patients were only excluded if they had been treated with cisplatin before. Lastly, Cis40 baseline characteristics were not comparable for the BMI, HPV-status and surgical status. Consequently, it is plausible that the ΔCR might be affected because possible risk factors for cisplatin-induced nephrotoxicity are alcohol ingestion (more HPV-positive patients means less alcohol-induced HNSCC) and diabetes mellitus (7). This might be associated with more CDLT due to nephrotoxicity for Cis40. However, CDLT due to nephrotoxicity for Cis40 did not differ statistically significant between the hydration schemes. The difference in surgical status can be explained because the AvL treats all HNSCC patients with Cis40 since the Covid-19 pandemic. Cis40 is only preferred in the Amsterdam UMC for postoperative HNSCC patients. Cis100 baseline characteristics were not comparable for the EBV-status, tumor location and TNM8-stage. These variables might have an impact on prognosis and survival but they are not believed to impact CDLT (2, 27).

Future recommendations would be to further investigate CDLT due to nephrotoxicity in HPV-positive compared to HPV-negative oropharyngeal patients to look into the possibility of monitoring HPV-positive oropharyngeal patients for a short while. In addition, CDLT due to ototoxicity in both hydration schemes could be further investigated since the CDLT due to ototoxicity results were not as expected. Furthermore, the effect of addition and dose of different electrolytes like magnesium, potassium and calcium gluconate to the different hydration schemes could be further investigated. Additionally, the differences in toxicity between Cis40 and Cis100 should be further investigated. Currently this study, called the CISLOW-study (NL76533.041.21), is executed in a prospective manner in the UMCU, Amsterdam UMC and the AvL.

# 5 CONCLUSION

This study demonstrates that patients with HNSCC receiving the Cis100 SH scheme had statistically significant less treatment changes, mostly due to less frequent nephrotoxicity. This resulted in a higher cumulative cisplatin dose. The SH scheme was also associated with a statistically significant smaller ΔCR compared to the LH scheme, irrespective of dosing schedule. In conclusion, the current study demonstrates that the Cis100 SH scheme is associated with less CDLT compared to the Cis100 LH scheme, particularly caused by less CDLT due to nephrotoxicity. This resulted in a higher delivered cisplatin dose. Therefore, the SH scheme is preferable to treat HNSCC patients receiving Cis100.

# 6 CONFLICTS OF INTEREST

No conflicts of interest to be declared.

# 7 AWKNOWLEDGEMENTS

I would like to thank the educational team.

# 8 APPENDICES

**Table 1: Hydration schemes administered during cisplatin-based chemoradiotherapy in 40 mg/m² and 100 mg/m² in the Antoni van Leeuwenhoek and Amsterdam UMC.** Sodium chloride (NaCl); Magnesium sulfate ($MgSO_4$); Potassium chloride (KCl); Calcium gluconate ($C_{12}H_{22}CaO_{14}$).

| | **Cis40 Long hydration scheme (AvL)** | **Cis40 Short hydration scheme (Amsterdam UMC)** | **Cis100 Long hydration scheme (AvL)** | **Cis100 Long hydration scheme (Amsterdam UMC)** |
|---|---|---|---|---|
| **Hydration fluid** | NaCl 0.9% | NaCl 0.9% | NaCl 0.9% | NaCl 0.9% |
| **Prehydration** | | | | |
| **Volume (L)** | 1 | 1 | 2*1 | 1 |
| **Infusion time (h)** | 2 | 2 | 13 | 2 |
| **Prehydration electrolytes** | 500 mg $MgSO_4$<br>20 mmol KCl<br>300 mg $C_{12}H_{22}CaO_{14}$ | 2 g $MgSO_4$<br>20 mmol KCl | - | 2 g $MgSO_4$<br>20 mmol KCl |
| **Rinse** | | | | |
| **Volume (L)** | - | 0.05 | - | 0.05 |
| **Infusion time (h)** | - | 1/12 | - | 1/12 |
| **Cisplatin** | | | | |
| **Volume (L)** | 1 | 0.5 | 0.5 | 0.4 |
| **Infusion time (h)** | 4 | 1 | 4 | 3 |
| **Rinse** | | | | |
| **Volume (L)** | - | 0.1 | - | 0.05 |
| **Infusion time (h)** | - | 1/6 | - | 1/12 |
| **Hydration during cisplatin** | | | | |
| **Volume (L)** | 1 | - | 3*1 | - |
| **Infusion time (h)** | 2 | - | 18 | - |
| **Added electrolytes during cisplatin** | 500 mg $MgSO_4$<br>20 mmol KCl<br>300 mg $C_{12}H_{22}CaO_{14}$ | - | 3*500 mg $MgSO_4$<br>3*20 mmol KCl<br>3*290 mg $C_{12}H_{22}CaO_{14}$ | - |
| **Post-hydration** | | | | |
| **Volume (L)** | 1 | 1.5 | 4*1 | 4 |
| **Infusion time (h)** | 12 | 2 | 24 | 20 |
| **Post-hydration electrolytes** | 500 mg $MgSO_4$<br>20 mmol KCl<br>300 mg $C_{12}H_{22}CaO_{14}$ | 3 g $MgSO_4$<br>30 mmol KCl | - | 8 g $MgSO_4$<br>80 mmol KCl |
| **Total hydration** | | | | |
| **Volume (L)** | 4 | 3.15 | 9.5 | 5.5 |
| **Infusion time (h)** | 20 | 5.25 | 59 | 25 1/6 |

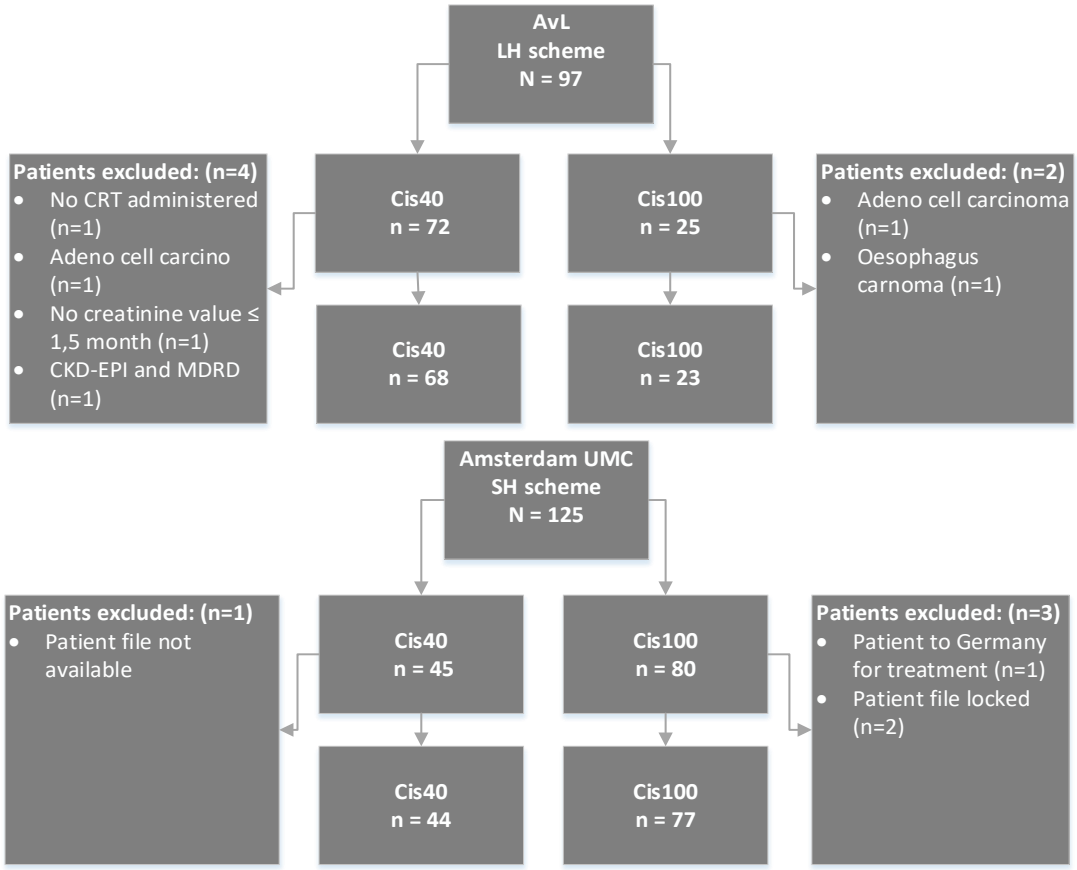


**Figure 1: Selection procedure of 100 mg/m$^2$ and 40 mg/m$^2$ cisplatin-based chemoradiotherapy patients in the AvL and Amsterdam UMC.**

**Table 2: Patient characteristics of patients receiving 40 mg/m² cisplatin-based chemoradiotherapy.** Abbreviations: IQR = Interquartile Range; HPV = Human Papillomavirus; EBV = Epstein-Barr Virus; UICC TNM-stage = The Union for International Cancer Control's (UICC) Tumor Node Metastasis stage based on the TNM8.
Continuous data are displayed as mean ± standard deviation or median [IQR]; categorical data as number (%).

| | **Long hydration scheme (n = 68)** | **Short hydration scheme (n = 44)** | **p-value** |
|---|---|---|---|
| **Sex** *n (%)* | | | |
| Male | 53 (78) | 34 (77) | 0.934 |
| **Age (y)** *Median [IQR]* | 60 [55-66] | 63 [56-69] | 0.244 |
| **Body Surface Area (BSA) ($m^2$)** *Mean ± SD* | 1.92 ± 0.21 | 1.98 ± 0.22 | 0.109 |
| **Body Mass Index (BMI) ($kg/m^2$)** *Mean ± SD* | 24 ± 4 | 26 ± 4 | 0.033 |
| **Creatinine at baseline (µmol/L)** *Median [IQR]* | 71 [63-80] | 71 [61-87] | 0.825 |
| **Cumulative cisplatin** *n (%)* **≥ 200 mg/m²** | 61 (90) | 40 (91) | 1.000 |
| **Cumulative cisplatin dose (mg)** *Mean ± SD* | 242 ± 57 | 243 ± 51 | 0.879 |
| **Primary or adjuvant treatment** *n (%)* Primary treatment | 59 (87) | 26 (59) | 0.001 |
| **HPV-status** *n (%)* **HPV-positive** | 25 (37) | 7 (16) | 0.017 |
| **EBV-status** *n (%)* **EBV-positive** | 2 (3) | 0 (0) | 0.519 |
| **Tumorlocation** *n (%)* | | | |
| **Oral cavity** | 10 (15) | 12 (27) | 0.061 |
| **Nasopharynx** | 2 (3) | 1 (2) | |
| **Oropharynx** | 37 (54) | 12 (27) | |
| **Hypopharynx** | 10 (15) | 7 (16) | |
| **Larynx** | 4 (6) | 8 (18) | |
| **Unknown primary** | 3 (4) | 3 (7) | |
| **Sinonasal** | 2 (3) | 1 (2) | |
| **UICC TNM-stage** | | | 0.112 |
| **Stage I** | 3 (4) | 5 (11) | |
| **Stage II** | 9 (13) | 3 (7) | |
| **Stage III** | 21 (31) | 6 (14) | |
| **Stage IVA** | 21 (31) | 17 (39) | |
| **Stage IVB** | 13 (19) | 13 (30) | |
| **Stage IVC** | 1 (2) | 0 (0) | |

**Table 3: Patient characteristics of patients receiving 100 mg/m² cisplatin-based chemoradiotherapy.** * 101 tumor locations with only 100 patients because one patient in the SH scheme had a HNSCC double tumor. Abbreviations: IQR = Interquartile Range; HPV = Human Papillomavirus; EBV = Epstein-Barr Virus; UICC TNM-stage = The Union for International Cancer Control's (UICC) Tumor Node Metastasis stage based on the TNM8.
Continuous data are displayed as mean ± standard deviation or median [IQR]; categorical data as number (%).

| | **Long hydration scheme (n = 23)** | **Short hydration scheme (n = 77)** | **p-value** |
|---|---|---|---|
| **Sex** *n (%)*<br>**Male** | 17 (74) | 50 (65) | 0.422 |
| **Age (y)**<br>*Median [IQR]* | 57 [52-64] | 60 [56-65] | 0.436 |
| **Body Surface Area (BSA) ($m^2$)**<br>*Mean ± SD* | 1.93 ± 0.21 | 1.96 ± 0.22 | 0.629 |
| **BMI ($kg/m^2$)**<br>*Median [IQR]* | 24 [22-28] | 24 [22-28] | 0.997 |
| **Creatinine at baseline (µmol/L)**<br>*Median [IQR]* | 69 [60-80] | 69 [56-79] | 0.635 |
| **Cumulative cisplatin** *n (%)*<br>**≥ 200 $mg/m^2$** | 18 (78) | 69 (90) | 0.169 |
| **Total cumulative cisplatin (mg)**<br>*Mean ± SD* | 230 ± 55 | 260 ± 62 | 0.008 |
| **Primary or adjuvant treatment** *n (%)*<br>**Primary treatment** | 22 (96) | 72 (94) | 1.000 |
| **HPV-status** *n (%)*<br>**HPV-positive** | 8 (35) | 35 (46) | 0.473 |
| **EBV-status** *n (%)*<br>**EBV-positive** | 3 (13) | 1 (1) | 0.037 |
| **Tumorlocation*** *n (%)* | | | |
| **Oral cavity** | 2 (9) | 1 (1) | 0.003 |
| **Nasopharynx** | 5 (22) | 1 (1) | |
| **Oropharynx** | 10 (44) | 46 (60) | |
| **Hypopharynx** | 4 (17) | 9 (12) | |
| **Larynx** | 1 (4) | 13 (17) | |
| **Unknown primary** | 1 (4) | 2 (3) | |
| **Sinonasal** | 0 (0) | 5 (7) | |
| **UICC TNM-stage** | | | |
| **Stage I** | 2 (9) | 19 (25) | 0.001 |
| **Stage II** | 3 (13) | 6 (8) | |
| **Stage III** | 2 (9) | 30 (40) | |
| **Stage IVA** | 11 (48) | 14 (18) | |
| **Stage IVB** | 5 (22) | 7 (9) | |
| **Stage IVC** | 0 (0) | 0 (0) | |

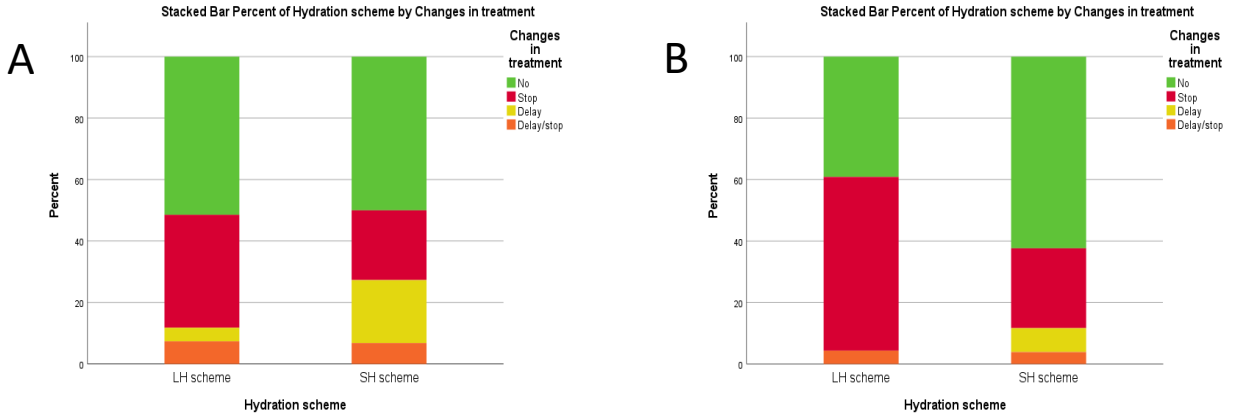


**Figure 2: Stacked bar of percentage of treatment changes in the long hydration (LH) and short hydration (SH) scheme of A.Patients receiving 40 mg/m² cisplatin-based chemoradiotherapy and B. Patients receiving 100 mg/m² cisplatin-based chemoradiotherapy.** A. LH scheme $n_{total}$ = 68 patients versus SH scheme $n_{total}$ = 44 patients. B. LH scheme $n_{total}$ = 23 patients versus SH scheme $n_{total}$ = 77 patients.

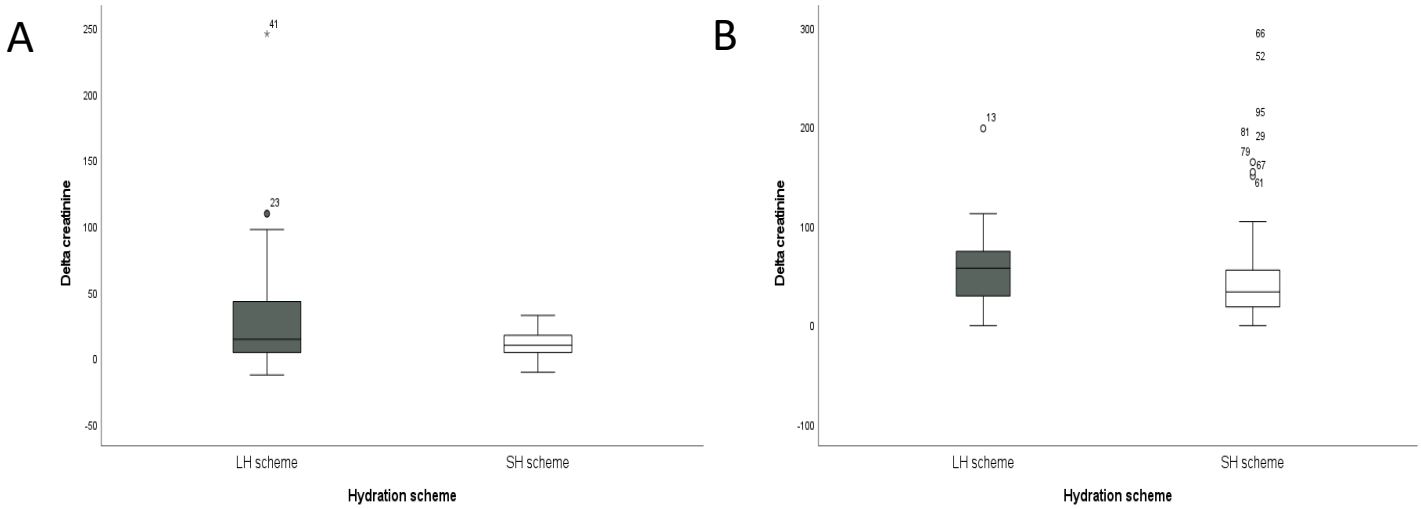


**Figure 3: Delta creatinine (µmol/L) in A. Patients receiving 40 mg/m² cisplatin-based chemoradiotherapy and B. Patients receiving 100 mg/m² cisplatin-based chemoradiotherapy in the long hydration (LH) and short hydration (SH) scheme.**

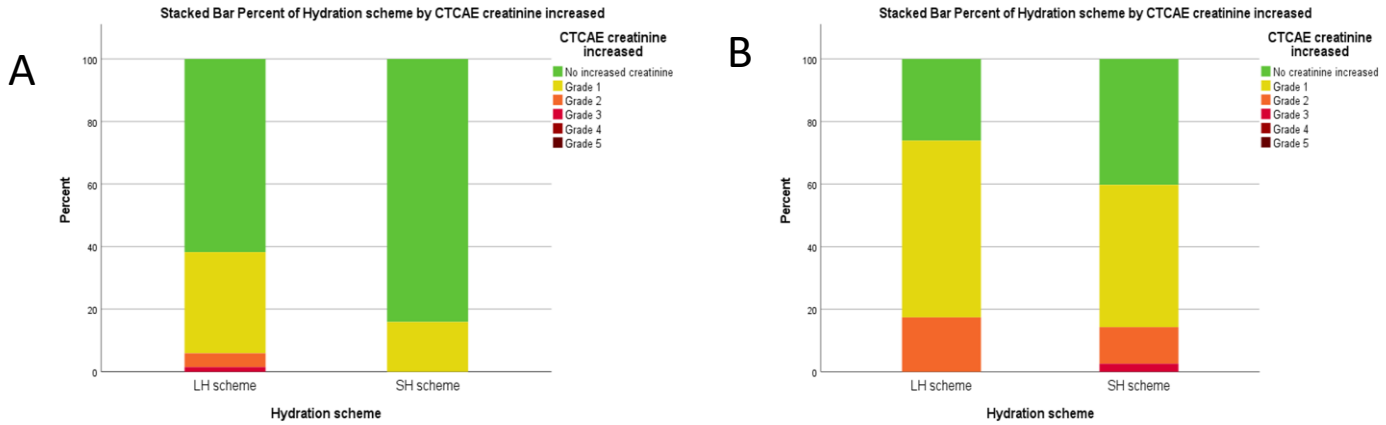


**Figure 4: Nephrotoxicity in the long hydration (LH) and short hydration (SH) scheme based on creatinine increased according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 in A. Patients receiving 40 mg/m² cisplatin-based chemoradiotherapy and B. Patients receiving 100 mg/m² cisplatin-based chemoradiotherapy.** A. Describes $n_{total}$ = 68 LH scheme patients and $n_{total}$ = 44 SH scheme patients. p = 0.043. B. Describes $n_{total}$ = 23 LH scheme patients and $n_{total}$ = 77 SH scheme patients. p = 0.518. Grade 1 = > ULN – 1.5 * ULN; Grade 2 = > 1.5 – 3.0 * baseline or > 1.5 – 3.0 * ULN; Grade 3 = > 3.0 * baseline or > 3.0 – 6.0 * ULN; Grade 4 = > 6.0 * ULN.

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