

Concurrent weekly cisplatin and simultaneous integrated boost intensity-modulated radiotherapy of locally advanced squamous cell carcinoma of the head and neck

Současné podávání cisplatinu jednou týdně a radioterapie s modulovanou intenzitou svazku s využitím simultánního integrovaného boostu při léčbě pokročilého skvamocelulárního karcinomu hlavy a krku

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Summary

Background: Radiotherapy of locally advanced head and neck cancer represents a major clinical challenge. Any treatment intensification aiming at improved treatment outcomes potentially results in a higher toxicity. The search for optimal treatment schedule involving conventional or altered fractionation of radiotherapy and the frequency and dose of concomitant cisplatin or other systemic agents has been spanning over several decades. **Purpose:** To evaluate long-term outcomes and toxicity of accelerated chemoradiotherapy of locally advanced squamous cell carcinoma of the head and neck (LA SCCHN). **Patients and methods:** Forty patients with stage III and IVA (TNM, 7th Ed.) LA SCCHN were treated with accelerated radiotherapy with a total dose of 67.5 Gy in 6 weeks delivered with simultaneous integrated boost intensity-modulated radiotherapy (SIB IMRT) and concomitant weekly cisplatin 40 mg/m². Five-year outcomes and early and late toxicity were evaluated. **Results:** With the median follow-up of 47.8 months, a 5-year locoregional control rate (LCR) was 56.5%, distant control rate (DCR) was 87% and 5-year progression-free survival (PFS) and overall survival (OS) were 37 and 45%, respectively. Cisplatin cumulative dose of ≥ 200 mg/m² was administered in 83% of patients. Grade ≥ 2 late toxicity with dietary change was observed in 21 (53%) patients. Human papillomavirus (HPV) status determined by p16 immunohistochemistry was the only significant factor in 5-year treatment outcomes analysis with LCR 100 vs. 41% ($P < 0.01$), DCR 100 vs. 78% ($P = 0.154$), PFS 80 vs. 23% ($P = 0.01$) and OS 80 vs. 34% ($P = 0.03$) for HPV positive oropharyngeal cancer (OPC) and other HPV negative LA SCCHN. **Conclusion:** High proportion of patients with LA SCCHN received an adequate cumulative dose of concurrent cisplatin with accelerated radiotherapy with SIB IMRT. This study demonstrated that chemoradiotherapy with weekly cisplatin resulted in favorable local control rate and survival in patients with HPV+ OPC.

Key words

radiotherapy – cisplatin – head and neck cancer – oropharyngeal cancer – human papillomavirus

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

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Souhrn

Východiska: Radioterapie lokálně pokročilého karcinomu hlavy a krku představuje velkou klinickou výzvu. Jakákoli intenzifikace léčby s cílem zlepšit léčebné výsledky vede k vyšší toxicitě. Hledání optimálního režimu léčby zahrnujícího konvenční nebo alterovanou frakcionaci radioterapie a dávky a frekvence současně podávané cisplatinu nebo jiných systémových léčiv trvá již několik desetiletí. **Cíl:** Zhodnotit dlouhodobé výsledky a toxicitu akcelerované chemoradioterapie lokálně pokročilého skvamocelulárního karcinomu hlavy a krku (locally advanced squamous cell carcinoma of the head and neck – LA SCCHN). **Soubor pacientů a metody:** Čtyřicet pacientů s LA SCCHN stadií stadia III nebo IVA (7. vydání klasifikace TNM) bylo současně léčeno akcelerovanou radioterapií při celkové dávce 67,5 Gy aplikované v 6 týdnech prostřednictvím radioterapie s modulovanou intenzitou svazku s využitím simultánního integrovaného boostu (simultaneous integrated boost intensity-modulated radiotherapy – SIB IMRT) a cisplatinou podávanou 1× týdně v dávce 40 mg/m². Byly hodnoceny 5leté výsledky léčby a časná i pozdní toxicita. **Výsledky:** Při mediánu doby trvání follow-up 47,8 měsíce byla 5letá míra lokoregionální kontroly (locoregional control rate – LCR) 56,5 %, 5letá míra distanční kontroly (distant control rate – DCR) 87 %, 5leté přežití bez progresu (progression-free survival – PFS) 37 % a 5leté celkové přežití (overall survival – OS) 45 %. Kumulativní dávka cisplatinu ≥ 200 mg/m² byl podána u 83 % pacientů. Pozdní toxicita stupně ≥ 2 s dietním opatřením byla pozorována u 21 (53 %) pacientů. Přítomnost lidského papilomaviru (human papillomavirus – HPV) určená imunohistochemickým stanovením proteinu p16 byla jediným významným faktorem analýzy 5letých výsledků léčby, přičemž u pacientů s HPV pozitivním orofaryngeálním karcinomem (oropharyngeal cancer – OPC) a ostatními HPV negativními LA SCCHN byly hodnoty LCR 100 vs. 41 % ($p < 0,01$), DCR 100 vs. 78 % ($p = 0,154$), PFS 80 vs. 23 % ($p = 0,01$) a OS 80 vs. 34 % ($p = 0,03$). **Závěr:** Vysokému procentu pacientů s LA SCCHN byla podána adekvátní kumulativní dávka cisplatinu podávaná současně při akcelerované radioterapii pomocí SIB IMRT. Tato studie prokázala, že chemoradioterapie s cisplatinou podávanou 1× týdně pacientům s HPV+ OPC vedla k příznivým výsledkům týkajícím se lokální kontroly a přežití.

Klíčová slova

radioterapie – cisplatinu – nádory hlavy a krku – orofaryngeální karcinom – lidský papilomavirus

Introduction

Radiotherapy of locally advanced head and neck cancer represents a major clinical challenge. Any treatment intensification aiming at improved treatment outcomes potentially results in a higher toxicity. The search for optimal treatment schedule involving conventional or altered fractionation of radiotherapy and the frequency and dose of concomitant cisplatin or other systemic agents has been spanning over several decades. All this endeavor is complicated by the establishment of human papillomavirus-associated oropharyngeal cancer (HPV+ OPC), as a new entity with distinct biology.

We evaluated long-term treatment outcomes and toxicity of accelerated fractionation based on simultaneous integrated boost (SIB) delivered by intensity-modulated radiotherapy (IMRT), which may require a lower cumulative dose of concurrent cisplatin [1,2], in a cohort of prospectively treated patients. Radiotherapy was combined with weekly administration of cisplatin, a schedule that needs further testing in HPV positive and HPV negative LA SCCHN.

Materials and methods

A retrospective analysis of acute and late toxicity and long-term treatment out-

comes was conducted for the cohort of consecutive patients with LA SCCHN treated with accelerated SIB IMRT with concurrent weekly cisplatin at the Department of Radiation Oncology of the East Slovakia Institute of Oncology (ESIO). The treatment protocol was approved by the institutional Ethics Committee of the ESIO and the study was conducted in compliance with recognized international standards including the Declaration of Helsinki.

Diagnostic workup and treatment

We identified 40 consecutive patients with LA SCCHN between January 2013 and October 2014. All patients included into the study met the following criteria: squamous cell carcinoma (SCC) of oral cavity, oropharynx, hypopharynx and larynx in stages III and IVA (TNM, 7th Ed.), World Health Organization performance status 0 – 1 and no contraindication for cisplatin. All patients were seen by members of the multidisciplinary head and neck cancer team. Routine pretreatment workup consisted of medical history, physical examination of the head and neck, direct endoscopy under general anesthesia, dental and nutritional evaluation, CT imaging of the head and neck and chest X-ray. The HPV status in oropharynx carcinoma patients was assessed by p16 immunohis-

tochemistry [3]. All patients signed the informed consent.

In all patients, step-and-shoot IMRT with accelerated SIB was used. The prescribed total radiation doses were 67.5 Gy for the gross tumor planning target volume (PTV_High), 60 Gy for the clinical target volume (PTV_Mid) and 54 Gy for the prophylactic neck irradiation (PTV_Low) in 30 fractions of 2.25/2.0/1.8 Gy per fraction over 6 weeks. The planning target volumes were defined as follows:

- PTV_High: all CT visible tumor and clinically visible mucosal spread with an isotropic 7 mm margin;
- PTV_Mid: gross tumor volume with a 10-mm edited margin for a primary and the whole involved nodal area for nodal metastases with a 5 mm margin;
- PTV_Low: nodal areas according to consensus recommendations [4] with a 5 mm margin.

The patients were treated daily, 5 times a week, with no compensation of missing days. Portal imaging or megavoltage cone-beam CT was used for weekly setup verification.

Intravenous cisplatin 40 mg/m² was administered before radiotherapy weekly with a maximum of 6 courses unless pre-specified criteria for chemotherapy stopping were met.

Prophylactic feeding tubes were not utilized. Reactive nasogastric tube was inserted in the case of > 10% weight loss. Examinations by a dietician and a dentist were scheduled before the start of the therapy and when necessary.

The patients were seen by a radiation oncologist weekly during the treatment with documentation of acute side effects, oral intake, weight loss, whole blood count and biochemistry profile. Common Terminology Criteria of Adverse Events (CTCAE), version 4.0, were used for acute and late toxicity assessment [5].

After treatment completion, follow-up visits were scheduled in 3-month intervals in year 1, in 4-month intervals in year 2, and in 6-month intervals afterwards. Each visit consisted of a history of symptoms and physical examination with endoscopic evaluation when needed. In the case of suspected recurrence, patients were referred for radiologic evaluation and examination under anesthesia with biopsies.

Statistical analysis

The endpoints of analysis included locoregional control rate (LCR), distant control rate (DCR), progression-free survival (PFS), overall survival (OS) and toxicity. All survival data were calculated from the date of the first fraction of radiotherapy. The closeout date for survival was December 1, 2019. Cumulative survival data were calculated using the Kaplan – Meier method. Univariate and multivariate analyses using the Cox regression model were performed for the total cohort patients to determine the prognostic significance of the following factors: HPV status, cisplatin cumulative dose, overall treatment time (OTT) prolongation, stage and tumor site. Univariate analysis using the Cox regression model was subsequently performed for the subgroup of HPV negative SCCHN patients. The analyses were performed by the statistical program SPSS for Windows version 18.0 (IBM SPSS Statistics for Windows, Armonk, NY).

Results

We included 40 patients (median age 54 years, range 34–64 years) with oral

Tab. 1. Patient and treatment characteristics.

Characteristics	All patients N (%)	HPV+ OPC N (%)
number of patients	40	10
age (years)		
range	34–64	41–64
median	56	51
sex		
female	6 (15)	2 (20)
male	34 (85)	8 (80)
location of primary tumor		
oropharynx	23 (58)	10 (100)
larynx	3 (7)	–
hypopharynx	8 (20)	–
oral cavity	6 (15)	–
stage (TNM 7th Ed.)		
III	16 (40)	5 (50)
IVA	24 (60)	5 (50)
retrospective HPV+ OPC TNM 8 th Ed. reclassification stage	NA	
I		5 (50)
II		5 (50)
HPV status		
p16+	10 (25)	10 (100)
p16–	30 (75)	0 (0)
smoking history		
≤ 10 pack/years	10 (25)	4 (40)
smoker	30 (75)	6 (60)

HPV+ OPC – human papillomavirus positive oropharyngeal cancer, N – number, NA – not analyzed, TNM – tumor-node- metastases

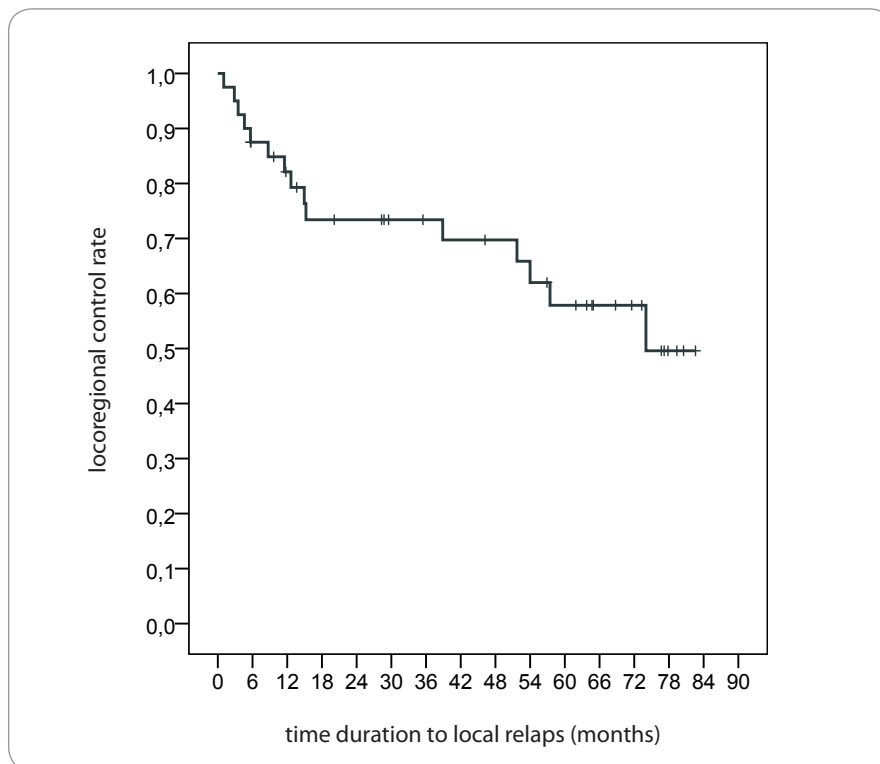
cavity, laryngeal, hypopharyngeal and oropharyngeal cancers in stages III and IVA. The HPV status was assessed by p16 immunohistochemistry and was positive in 10 (25%) patients and negative in 30 (75%) patients. The characteristics of all patients and the HPV+ OPC subgroup are in Tab. 1.

Median OTT prolongation was 7 days (0–13 days) mostly due to holidays and machine service. No measures were taken to compensate for treatment breaks. Cisplatin cumulative dose of at least 80% of the planned dose, i. e. ≥ 200 mg/m², was delivered in 34 (85%) and < 200 mg/m² in

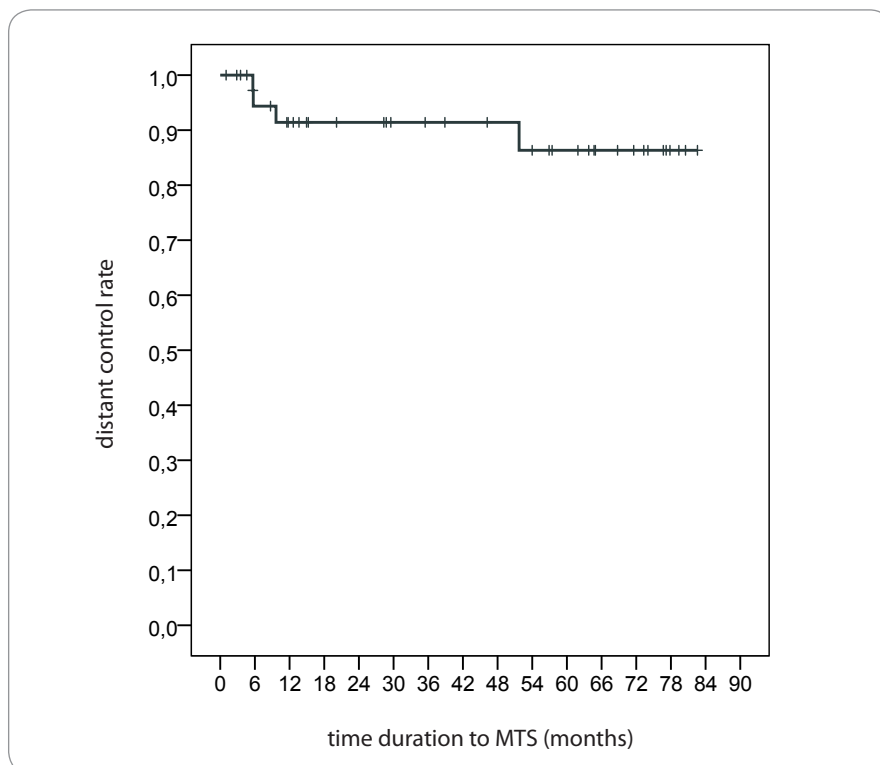
6 (15%) patients. The reasons for not completing 6 courses included hematologic toxicity in 4 patients, renal toxicity in 1 patient and general condition deterioration in 1 patient. In HPV– and HPV+ OPC subgroups, 50 and 80% of patients received both ≥ 200 mg/m² cisplatin doses with OTT prolongation less than one week. Salvage and upfront neck dissection were performed in 1 and 2 cases, respectively.

Treatment outcomes

With the median follow-up of 47.8 months (range 5–82 months), locoregional fail-



Graph 1. Five-year locoregional control rate for all 40 study patients.



Graph 2. Five-year distant control rate for all 40 study patients.

ure was identified in 12 (30%) patients out of 40. Six patients (15%) developed distant metastases, with concurrent

1 local and 1 locoregional failure. The 5-year LCR and DCR were 56.5 and 87%, respectively (Graphs 1, 2).

At the time of evaluation, 25 patients had died; none of treatment-related toxicity, 17 of disease progression, 5 of second primary malignancy (4 of lung cancer and 1 of stomach cancer) and 3 of other causes. The 5-year PFS and OS were 37 and 45%, respectively (Graph 3).

We performed an analysis of known prognostic factors in all patients and in the p16 negative subgroup to exclude HPV association as the most prominent confounding factor. The HPV status, cisplatin cumulative dose (< 200 mg/m² vs. ≥ 200 mg/m²) and OTT prolongation (≤ 7 days vs. > 7 days) were significant for the 5-year LCR, PFS and OS in univariate analysis, while the stage, tumor site, gender and smoking status were not. The multivariate analysis confirmed HPV status as the only significant factor in the 5-year treatment outcomes analysis for HPV+ OPC and HPV- LA SCCHN with LCR 100 vs. 41% (P < 0.01), DCR 100 vs. 78% (P = 0.154), PFS 80 vs. 23% (P = 0.01) and OS 80 vs. 34% (P = 0.03), respectively (Graphs 4, 5).

The site of the primary tumor, stage, age, gender, smoking status and OTT prolongation were not significant in OS, PFS or LCR; neither for all patients nor for the p16 negative subgroup.

Toxicity

Twenty-one patients (53%) developed G2 mucositis and in 15 patients (38%) G3 mucositis was observed. Reactive feeding tubes were placed on treatment in 8 (20%) patients with a median duration of placement of 6 weeks (2–17 weeks).

Clinically significant G3 hematologic toxicity was observed in 5 (13%) patients (2× anemia, 2× neutropenia and 1× thrombocytopenia) which led to cisplatin dose reduction or hospital stay prolongation. Other G3 toxicities involved nausea and vomiting in 3 (8%) patients, acute kidney injury in 1 (2.5%) patient and dermatitis in 1 (2.5%) patient.

At least one grade ≥ 2 late toxicity was observed in 21 patients (53%) (Tab. 2). Dietary change was caused mostly by dysphagia in 11 (28%) patients, xerostomia in 6 (15%) patients and mandibular osteoradionecrosis in 1 (2.5%) patient, trismus in 1 (2.5%) patient and periph-

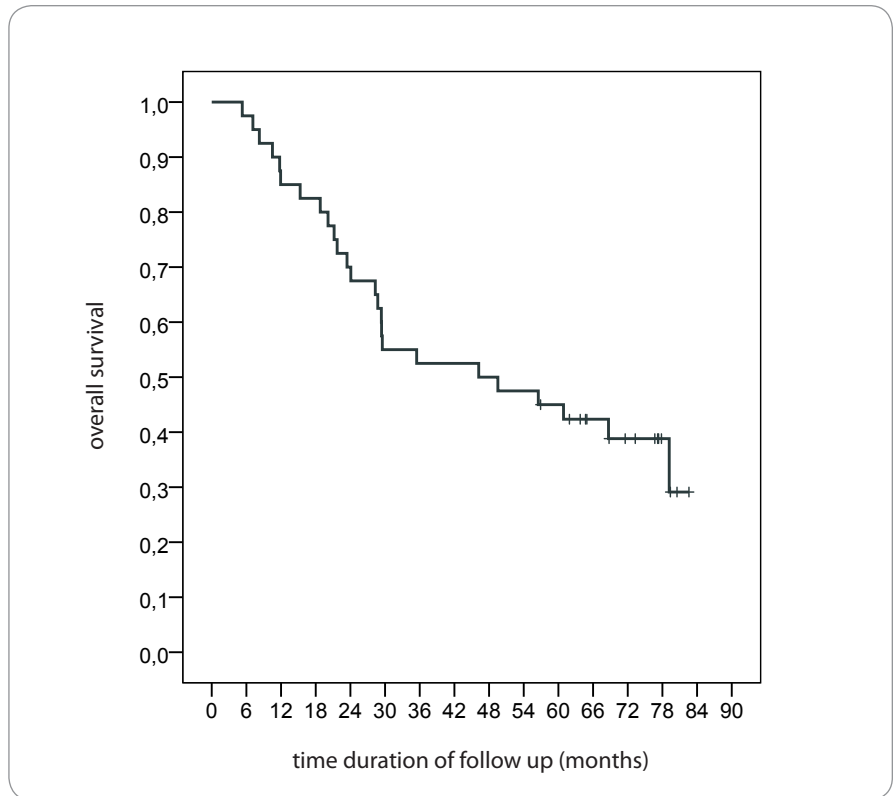
eral neuropathy in 1 (2.5%) patient. One patient (2.5%) suffered from G3 dysphagia one year after chemoradiotherapy and had nasogastric tube placement with some oral intake for 8 months. No patient with a controlled tumor suffered from malnutrition. Severe peripheral motor and sensory neuropathy was diagnosed in 1 (2.5%) patient with p16-OPC, with gradual onset of 6 months after the treatment resulting in severe symptoms limiting self-care.

Discussion

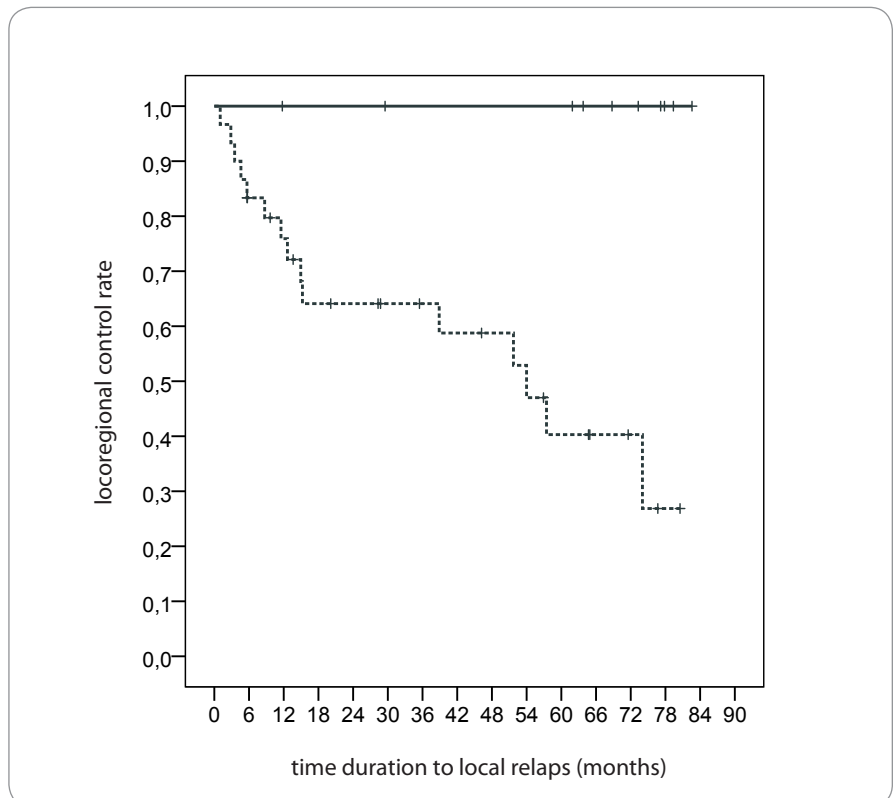
Historically, efforts in treatment outcomes improvement and toxicity reduction have been focused on three principal areas: technology development, altered fractionation and optimization of systemic treatment. We incorporated all these aspects into the treatment protocol. We involved IMRT, a rather new technology at that time with treatment acceleration by delivery of SIB and administration of concomitant weekly cisplatin.

Dosimetric and planning studies have mostly documented the superiority of various IMRT techniques over 2D or 3D techniques, both in conformity and dose distribution [6–8], as well as sparing organs at risk (OARs).

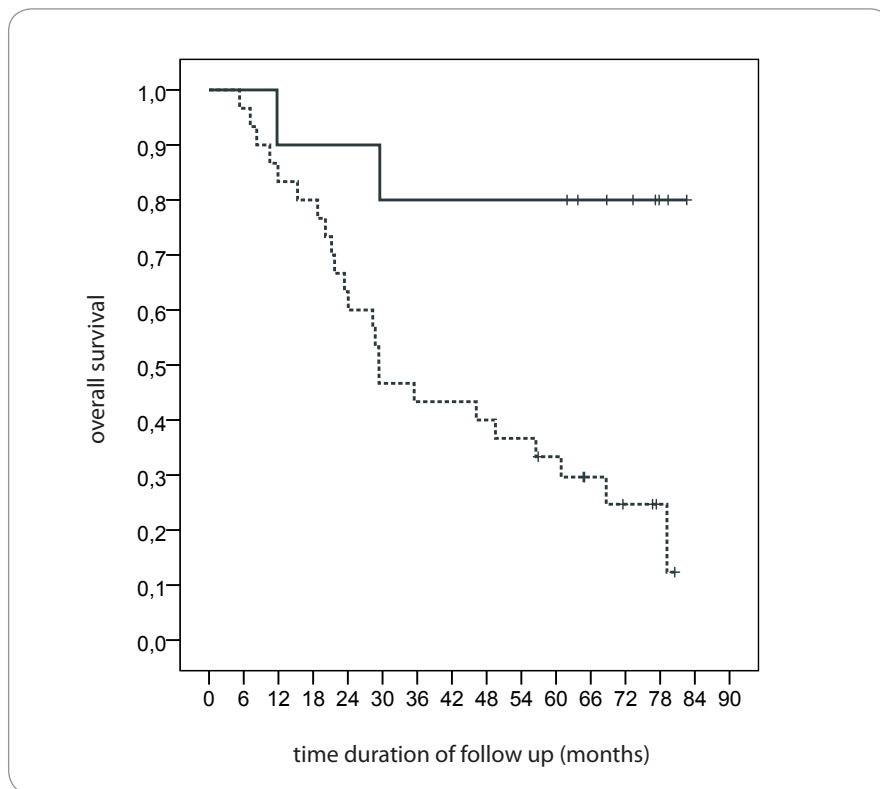
We may expect significant reduction of grade 2–4 xerostomia in IMRT treated patients as has been shown by Gupta et al [9] in the analysis of 7 prospective randomized controlled trials including 1,155 patients. Intensity-modulated radiotherapy led to a risk reduction of 36% in grade > 2 acute xerostomia and a reduction of 56% in grade > 2 late xerostomia. We observed a 15% cumulative incidence of late G2 and none G3 xerostomia. The recorded proportion of patients suffering from parotid glands damage (15%) was also low in comparison to the benchmark study of Nutting et al (38% at 12 months and 29% at 14 months) [10]. This observation might have been due to the true effect of IMRT parotid sparing but also due to low concordance between late toxicity grading by CTCAE in our population and LENT SOMA scale in the study of Nutting et al [11]. In general, the occurrence of clinically significant local late ef-



Graph 3. Five-year overall survival for all 40 study patients.



Graph 4. Five-year locoregional control rate for patients with human papillomavirus positive oropharyngeal cancer (solid line) and other locally advanced squamous cell head and neck carcinoma patients (dotted line).



Graph 5. Five-year overall survival for human papillomavirus positive oropharyngeal cancer patients (solid line) and other locally advanced squamous cell head and neck carcinoma patients (dotted line).

Tab. 2. Results of late toxicity evaluation of all 40 study patients.

Adverse event	Grade 1 – N (%)	Grade 2 – N (%)	Grade 3 – N (%)
dysphagia	6 (15)	10 (25)	1 (2.5)
dry mouth	16 (40)	6 (15)	0
mandibular osteoradionecrosis	4 (10)	1	0
trismus	0	1	0
brachial plexopathy	0	1	0
peripheral motor and sensory neuropathy	0	0	1 (2.5)

N – number

fects other than dysphagia and xerostomia was low with only 3 grade 2 and no grade ≥ 3 events recorded.

Dosimetric comparison of SIB IMRT with sequential boost IMRT is equivocal with studies suggesting better dose conformity and OAR sparing [12,13], leading to fewer side effects [14,15] with SIB IMRT, while others showed superiority of sequential boost IMRT [16,17]

due to a better coverage of the high dose regions, conformity and homogeneity, with fewer monitor units being used. Recent metaanalysis [18] compared sequential boost IMRT with SIB IMRT in head and neck cancer including 7 studies with a total of 1,049 patients. Interestingly, there was no difference in any of the endpoints used: OS (P = 0.71), PFS (P = 0.79), local recurrence-free sur-

vival (P = 0.91) and distant metastasis-free survival (P = 0.63) including no difference in side effects. We chose SIB IMRT planning as it was more practical using a single plan from the start and allowed irradiation of three clearly different (risk-wise) areas at the same time. Moreover, this technique enables acceleration of the treatment by shortening the OTT to 6 weeks by moderate hypofractionation in high risk PTV. Acceleration without reduction of the total dose has been shown to offer significant benefit on locoregional control over conventional fractionation [19,20].

There is no consensus on dose per fraction neither in high risk nor in prophylactic PTVs for acceleration with SIB. We used radiobiological considerations summarized by Mohan et al [21]. Calculations had been made for 42 days of OTT which we were unable to achieve. With the median of one week of radiotherapy prolongation, the potential benefit of acceleration on local control might have been lost. Conversely, undesirable OTT prolongation might have decreased the rate of acute G3 mucositis, G3 dermatitis and feeding tubes placements in comparison to a similar series of patients [22–24].

Optimal administration of radiotherapy and cisplatin in the definitive treatment remains unsolved, despite the fact that doses of 100 mg/m² applied every 3 weeks were both suggested and largely practiced in the past 3 decades [25,26]. Common clinical practice of a weekly administration of cisplatin, mostly at a dose of 40 mg/m² is based on the expected lower toxicity and potentially better radiosensitization, theoretically leading to a better therapeutic ratio. Unfortunately, high quality and multiple prospective randomized trials investigating the issue of concurrent scheduling of cisplatin are strikingly lacking. We opted for weekly cisplatin in our protocol, anticipating lower toxicity. The treatment adherence was good with cisplatin cumulative dose ≥ 200 mg/m² delivered in the high proportion of patients, similarly to the study by Noronha et al [27]. Grade 3 acute hematologic and non-hematologic toxicity was low, comparable to weekly cisplatin arms in recent meta-

analyses [28–30] which points to a better systemic toxicity profile of weekly administration in comparison to a 3-weekly schedule [31].

We observed one case of irreversible peripheral neuropathy, both motoric and sensory, limiting the patient's daily activities. Neuropathy is rare at cumulative doses of $\leq 300 \text{ mg/m}^2$ and cisplatin dose intensity does not appear to enhance the severity of the neuropathy [32].

The HPV status assessed by surrogate p16 expression was the only risk factor determining treatment outcomes. Better compliance of HPV+ OPC in patients with both radiotherapy and chemotherapy and no case in stage III (TNM, 8th Ed.) might have been contributed to striking differences in LCR, PFS and OS between the subgroups with HPV+ OPC and other LA SCCHN. No local or distal recurrence was observed during a long-term follow-up in HPV+ OPC patients despite a history of smoking in a half of them.

Recently, 3-weekly cisplatin has been established as a standard concomitant schedule in HPV+ OPC [33,34]. A weekly cisplatin schedule may represent a reasonable alternative for this subgroup of patients in stages I and II as a component of treatment de-escalation strategies. Very likely, a weekly dose of cisplatin may be reduced to the cumulative dose of $\leq 200 \text{ mg/m}^2$ [35].

With no IVB patients included, we considered outcomes of our protocol in HPV– LA SCCHN suboptimal. We believe that weekly cisplatin would not compensate for significant OTT prolongation in this group of patients.

Optimized treatment of an individual patient should be thoroughly considered to provide an appropriate balance between various factors in the decision-making process. This applies especially in the case when treatment optimization is still facing challenges, in both HPV– and HPV+ patients [36,37].

We understand that there are considerable limitations in interpretation of our rather small, single-arm observational study. Nevertheless, the excellent 5-year treatment outcomes observed in a subgroup of HPV+ OPC patients included in

this study (5-year LCR, DCR, PFS and OS of 100%, 100%, 80% and 80%, respectively) emphasize the need for further refinement of cytoreduction strategies as a part of treatment de-intensification protocols in HPV+ OPC patients. In 157 HPV+ OPC patients treated with primary chemoradiotherapy to a dose of 60 Gy with concurrent weekly cisplatin 40 mg/m^2 within NRG-HN002, 80.9% had ≥ 5 cycles of cisplatin and the observed 2-year PFS and OS were 90.5 and 96.7%, respectively [38]. Similarly, in two prospective trials, Chera et al reduced primary chemoradiation dose to 60 and 54 Gy at high-risk areas and regions of subclinical microscopic spread in combination with weekly cisplatin 30 mg/m^2 , respectively. In these trials, the 2- and 3-year locoregional control, distant metastases-free survival and OS were 95–100%, 91–100% and 95% with no grade ≥ 3 late adverse event observed in either of the studies, respectively [39, 40]. More randomized controlled trials and long-term follow-up is undoubtedly necessary to refine the use of weekly cisplatin in patients with HPV+ OPC.

We believe that the choice of cisplatin schedule may be based on the HPV status. Currently, we continue to treat patients with stages I and II HPV+ OPC with weekly cisplatin in a de-escalation protocol while other patients with LA SCCHN receive SIB IMRT accelerated radiotherapy for 6 weeks with three-weekly cisplatin.

Conclusion

A high proportion of patients with LA SCCHN received an adequate cumulative dose of concurrent cisplatin with accelerated radiotherapy with SIB IMRT. This study demonstrated that chemoradiotherapy with weekly cisplatin resulted in a favorable local control rate and survival in patients with HPV+ OPC. Despite limitations in the size and the design of our study, the results suggest that weekly cisplatin administration may be considered an appropriate option in primary concomitant chemoradiotherapy of stages I and II HPV+ OPC.

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