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Survival and toxicity of weekly cisplatin chemoradiotherapy versus three-weekly cisplatin chemoradiotherapy for head and neck cancer: A systematic review and meta-analysis endorsed by the Italian Association of Radiotherapy and Clinical Oncology (AIRO)

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ABSTRACT

Purpose: To evaluate efficacy and toxicity of weekly cisplatin chemoradiotherapy versus three-weekly cisplatin chemoradiotherapy and identify differences in clinical outcomes and severe toxicity rate.
Methods: PICOS/PRISMA methods were used to identify studies on PubMed, EMBASE and Cochrane Library, 2005–2019.
Results: Six randomized clinical trials (554 patients) were identified. Weekly cisplatin was not associated with significant overall survival (HR 1.13, 95 % CI 0.84–1.51) and progression-free survival (HR 1.23, 95 %CI 0.91–1.65) improvement compared with three-weekly regimen. Severe acute toxicity (RR 0.95), treatment compliance to chemotherapy (RR 1.67) and radiotherapy (RR 0.61) were similar between regimens.
Conclusion: Weekly cisplatin is not associated with better clinical outcomes compared to three-weekly cisplatin. Three-weekly cisplatin chemoradiotherapy should be considered the standard approach in the management of locally advanced head and neck cancer. Methodologically robust RCTs designs are needed to improve the quality of evidence. Differences on long-term toxicity and cost-effectiveness remain to be tested.

1. Introduction

Squamous cell carcinoma of the head and neck (SCCHN) represents a heterogeneous group of malignancies and its incidence is increasing over the years (Siegel et al., 2020). The standard treatment for locally advanced SCCHN is concomitant chemoradiotherapy for organ preservation strategy, unresectable tumors and for those patients with post-operative high risk pathologic features (Pignon et al., 2009). Cisplatin-based chemotherapy is the most frequent regimen combined to radiotherapy due to its radiosensitizing properties and its toxicity profile

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Table 1
PICO Criteria.

Population	Patients with SCCHN treated with concomitant chemoradiotherapy
Intervention	Weekly CDDP based chemotherapy
Control	Three-weekly CDDP based chemotherapy
Outcomes	OS, OS for adjuvant chemoradiotherapy, OS in HPV + patients, LRC in adjuvant chemoradiotherapy, MFS in HPV + patients, PFS, G3−4 acute toxicity, RT interruptions, CDDP dose intensity, death treatment related, G3−4 late toxicity

SCCHN: squamous cell carcinoma of the head and neck; CDDP: cisplatin; OS: overall survival; HPV: human papillomavirus; LRC: loco-regional control; MFS: metastasis-free survival; PFS: progression-free survival; G: grade.

does not overlap with the commonest radiation-related side effects (Strojan et al., 2016). Even if the optimal cisplatin dose is not well defined, a cumulative dose of 200 mg/m^2 seems to be sufficient (Strojan et al., 2016; National Comprehensive Cancer, 2020). Among various schedules, the highest evidence for a benefit in locoregional control and overall survival is for cisplatin 100 mg/m^2 given every 3 weeks (three weekly), up to 300 mg/m^2 (National Comprehensive Cancer, 2020). However, this regimen seems to be associated with high rates of severe acute toxicity as hematological and renal complications (National Comprehensive Cancer, 2020). Therefore, in clinical practice, other schedules are tested to supposedly decrease the toxicity profile. In this sense, weekly cisplatin is often used because of a possible more favorable toxicity profile, being supposed to reach the dose of 200 mg/m^2 with increased patient's compliance (Ang, 2004; Ghi et al., 2011). Five randomized controlled trials had tested the efficacy, toxicity and compliance of weekly versus three-weekly cisplatin administered concurrently to radiotherapy for SCC HN treatment. Szturz et al. reviewed the available data of 59 prospective trials enrolling a total of 5, 582 patients (Szturz et al., 2017). No statistically significant difference in terms of overall survival was observed between low-dose weekly and high-dose three-weekly cisplatin but, as the authors reported, these results should be interpreted in light of the several limitations. Recently, a

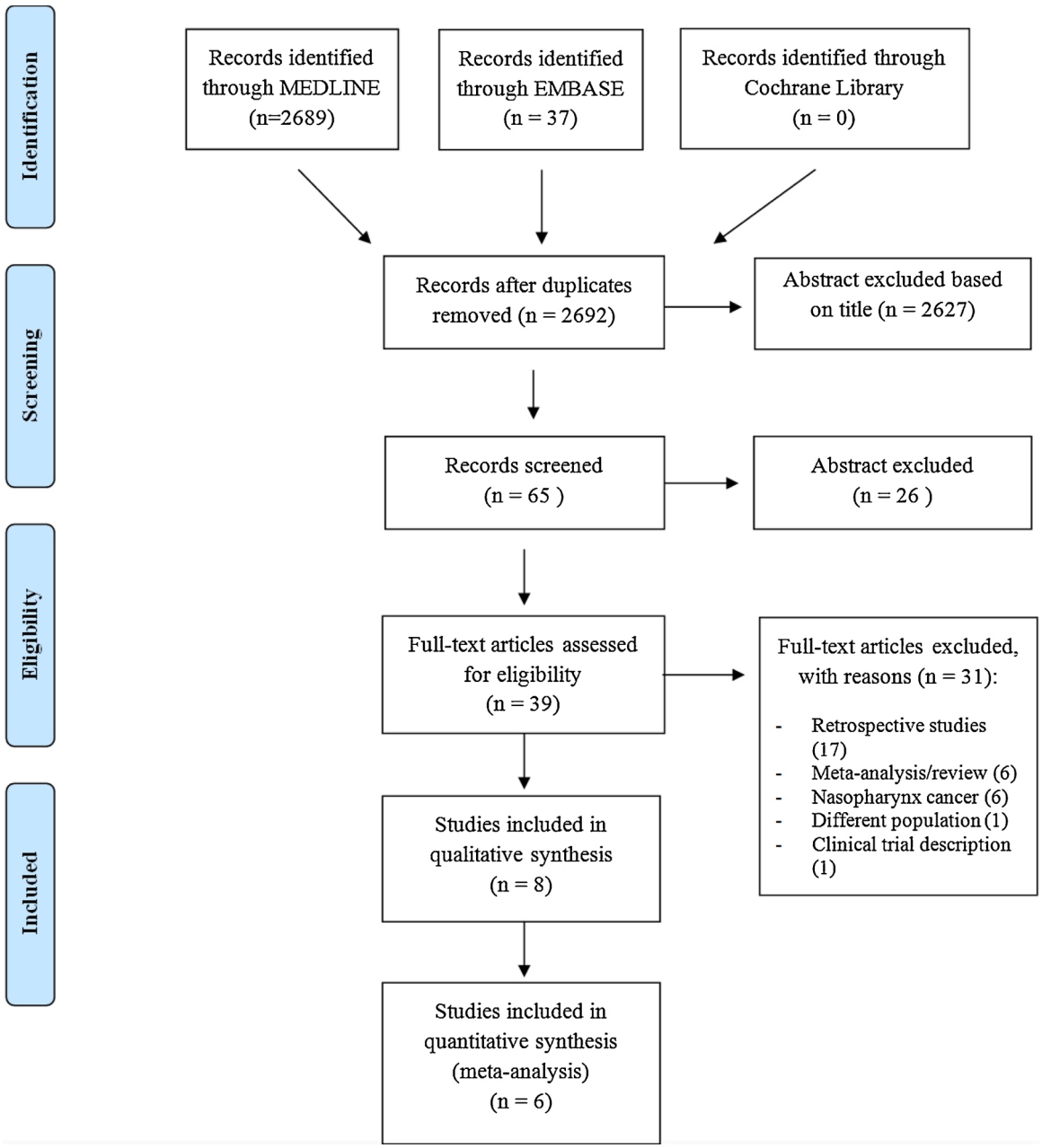

Fig. 1. PRISMA diagram flow diagram describing the data collection process following the PRISMA convention.

Table 2
Details of the included studies.

Author	Trial		Patients						
	enrollment time	type	population	total	weekly CDDP	three-weekly CDDP	Median FU	Primary end point	Consideration
Nair et al. (2017)	2013–2014	phase IIb RCT	stage III-IV SCC of oropharynx, hypopharynx and larynx	55	24	31	26 months	DFS	no predetermined sample size was calculated. No cumulative toxicity data reported
Nanda et al. (2019a)	2011–2013	prospective RCT	stage III-IV SCC of oropharynx	60	29	31	28 months	NA	Cobalt-60 teletherapy machine
Noronha et al. (2018)	2013–2017	phase III RCT	stage III-IV SCC of oral cavity, oropharynx, hypopharynx and larynx	300	150	150	22 months	LRC	due to slow recruitment, data analysis was performed before complete FU
Tsan et al. (2012)	2008–2010	phase III RCT	post-operative SCC of oral cavity	50	24	26	12 months	PFS	due to slow recruitment, trial was ended before the 371 scheduled patients
Rawat et al. (2016)	2013–2014	prospective RCT	stage III-IV SCC of oral cavity, oropharynx, hypopharynx and larynx	59	30	29	8 months	NA	no predetermined sample size was calculated. Standard three-field RT technique
Sahoo et al. (2017)	2011–2012	prospective RCT	stage III-IV SCC of oral cavity, oropharynx, hypopharynx and larynx	30	15	15	7 months	disease response	no predetermined sample size was calculated. Cobalt-60 teletherapy machine

CDDP: cisplatin; FU: follow-up; DFS: disease-free survival; SCC: squamous cell carcinoma; NA: not available; LRC: loco-regional control; PFS: progression-free survival.

further randomized trial was published and no significant differences in terms of overall response, complete response and acute toxicities were recorded (Nanda et al., 2019a). The Association of Radiotherapy and Clinical Oncology (AIRO) decided to perform a systematic review and a meta-analysis to address the clinical questions related to cisplatin regimen in SCCHN. The aim was to provide a grade of recommendation, assessment, development and evaluation (GRADE) evidence in a structured and transparent way to help clinicians during the daily decision-making process.

2. Methods

2.1. Data sources

This systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The inclusion criteria for the literature search was defined using the Population, Intervention, Control, Outcome, (PICO; Table 1) approach. Computerized search from PubMed, Embase and The Cochrane Library was conducted by two independent researchers (LB and FDF), with a specialization in radiation oncology. The selection of keywords and related Medical Subject Headings (MeSH terms) were the following: “head and neck cancer”, “radiotherapy/chemoradiotherapy”, “cisplatin/cisplatin dosage”, “weekly/triweekly” (Supplementary Material).

The search was restricted to English article and to the period from 2005/01/01–2019/09/10 and were included studies of patients who underwent definitive chemoradiation for SCCHN or adjuvant chemoradiation for resected locally advanced SCCHN. In order to minimize the possible effect of natural history on treatment response, studies that enrolled participants with nasopharynx, paranasal sinus, thyroid and salivary gland cancer were excluded. Similarly, studies with other schedules of administration of cisplatin (e.g. daily), use in combination with other drugs or administration not in concurrent setting were excluded.

2.2. Data extraction and trials selection

The systematic search produced 2693 results, which were screened by title and abstract leading to the exclusion of 2653 articles. The remaining 39 manuscripts were evaluated with full-text assessment and 31 of them were excluded due to study type, clinical trial description and different analyzed population (Fig. 1). Of the final 8 studies, 6 were randomized controlled trials (RCTs) and 2 had a retrospective design. Retrospective analyses were included only for those outcomes which were not addressed in RCT.

Extracted data include author, year, title, study design, sample size, study population, data on radiotherapy (dose, technique), cisplatin dose administration (low dose or high dose), survival outcome, severe acute and late toxicity, treatment-related mortality and compliance to treatment.

2.3. Outcomes

According to the GRADE framework, a panel of experts in the field of head and neck oncology were solicited to make an overall rating of confidence in estimates of effect for the following outcomes, which they deemed important or critical (Guyatt et al., 2011): overall survival for the entire population (OS), OS for adjuvant chemoradiotherapy, OS in human papillomavirus (HPV)-positive patients (based on p16 expression by immunohistochemistry), loco-regional control (LRC) after adjuvant chemoradiotherapy, metastasis free survival (MFS) in HPV-positive patients, progression free survival (PFS) (outcomes of benefit), and severe (grade 3–4) acute toxicity, radiation therapy interruptions (treatment compliance), cisplatin dose intensity, treatment-related deaths, severe (grade 3–4) late toxicity (outcomes of harm).

2.4. Statistical analysis

Data analysis was performed using Review Manager (RevMan) version 5.3 (http://www.cochrane.org). The grading of recommendations assessment, development and evaluation (GRADE) system was used to rate quality of evidence and grade strength of recommendations for all included studies (Guyatt et al., 2011). The individual and pooled hazard ratios (HR) with 95 % confidence intervals (CI), as well as the pooled risk ratio (RR) were calculated using a fixed- or random-effects model. Since no individual patient data were available, survival probabilities were extracted for each of the included studies based on reported numbers and estimations from Kaplan-Meier curves. A significant two-way p value for comparison was defined as $p < 0.05$. Statistical heterogeneity among studies was examined using both the Cochrane Q statistic (significant at $p < 0.1$) and the I^2 value (significant heterogeneity if > 50 %) (Higgins et al., 2003).

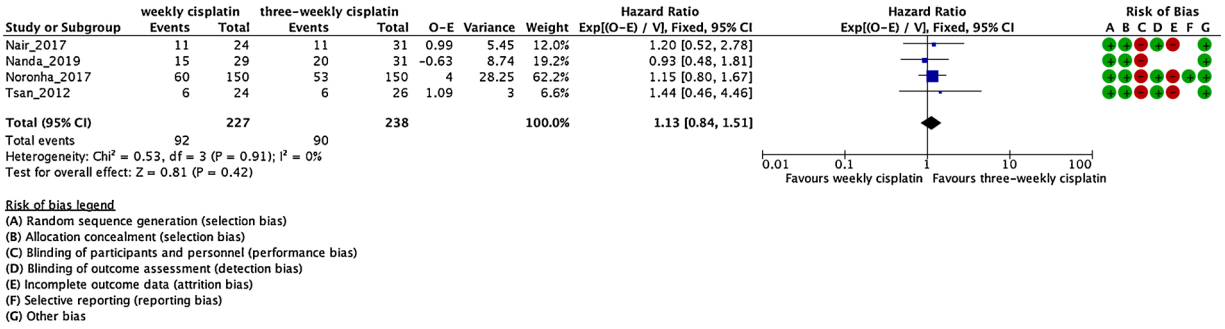

Fig. 2. Forest plot of overall survival.

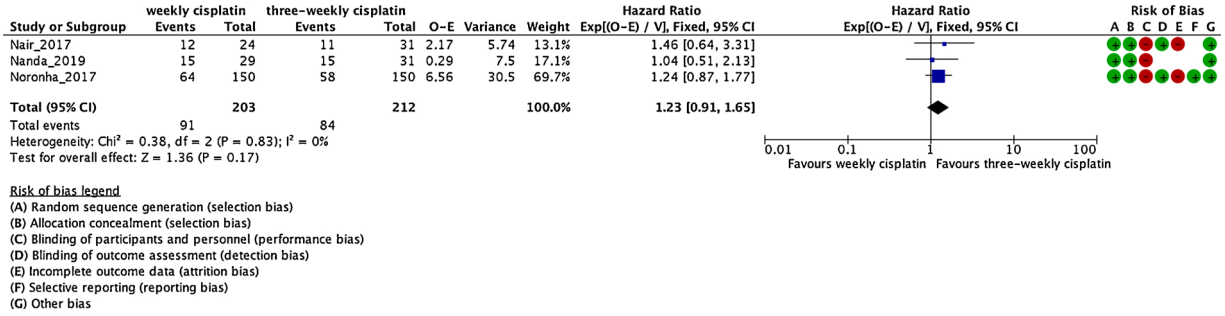

Fig. 3. Forest plot of progression-free survival.

3. Results

3.1. Studies characteristics

The main characteristics of the retrieved studies are summarized in Table 2. Overall, six RCTs, reporting on 554 patients, were included in the final analysis (Nanda et al., 2019a; Nair et al., 2017; Nanda et al., 2019b; Noronha et al., 2018; Tsan et al., 2012; Rawat et al., 2016). Five studies were conducted in India (Nanda et al., 2019a; Nair et al., 2017; Nanda et al., 2019b; Tsan et al., 2012; Rawat et al., 2016) and one in Taiwan (Noronha et al., 2018). Weekly cisplatin regimen included 30 mg/m^2 (n = 2 studies (Nanda et al., 2019b; Rawat et al., 2016)), 35 mg/m^2 (n = 1 study (Tsan et al., 2012)) and 40 mg/m^2 (n = 3 studies (Nanda et al., 2019a; Nair et al., 2017; Noronha et al., 2018)), respectively. In total, four RCTs (465 patients) were available for the OS and PFS outcomes (Nanda et al., 2019a; Nair et al., 2017; Noronha et al.,

Table 3
Quality of evidence and strength of recommendation: summary of findings.

Weekly cisplatin compared to three-weekly cisplatin for head and neck squamous cell carcinoma			
Patient or population: HNSCC Intervention: Weekly cispaltin (CDDP 30−40 mg/mq) Comparison: Three-weekly cisplatin (CDDP 100 mg/mq)			
Outcomes	N° of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95 % CI)
Overall survival (OS) assessed with: Kaplan-Meier Product Limit follow up: median 22 months	465 (4 RCTs)	⨁x̂x̂x̂ VERY LOW [a,b,c,d,e,f,g,h]	**HR 1.13** (0.84 to 1.51)
Progression free survival (PFS) assessed with: Kaplan-Meier Product Limit follow up: median 22 months	415 (3 RCTs)	⨁x̂x̂x̂ VERY LOW [b,c,d,e,f,i,j,k]	**HR 1.23** (0.91 to 1.65)

*The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI). CI: Confidence interval; HR: Hazard Ratio.
GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Explanations.
a. multiplicity (drop control for multiple comparison).
b. open label studies.
c. total dose 66 Gy (2 Gy fr).
d. included only adjutant CRT in oral cavity cancer.
e. Cobalto RT.
f. no predetermined sample size was calculated.
g. planned 371 patients, but ended after 55 patients due to slow recruitment.
h. analysis performed before complete follow-up.
i. not applicable.
j. included only oropharynx.
k. sample size calculation not specified.

2018), six RCTs (554 patients) for the acute toxicity evaluation (Nanda et al., 2019a; Nair et al., 2017; Nanda et al., 2019b; Noronha et al., 2018; Tsan et al., 2012; Rawat et al., 2016) and four RCTs (224 patients) for the treatment tolerability analysis (Nanda et al., 2019a; Nair et al., 2017; Noronha et al., 2018; Tsan et al., 2012). Subgroup analysis on both adjuvant and HPV-related groups and meta-analysis on late toxicity were not performed because of the limited number of trials and patients (Sahoo et al., 2017; Perez et al., 2017). Acute toxicity was graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) and/or the Radiation Therapy Oncology Group (RTOG) scale. Median follow-up was 17 months (7–28 months).

3.2. Outcomes of benefit

Overall, weekly cisplatin chemotherapy was not associated with a significant reduction in the risk of death (HR = 1.13, 95 %CI = 0.84–1.51; p = 0.42) compared to three-weekly cisplatin (Fig. 2). Similarly, it was not correlated to a statistically significant decrease (HR = 1.23, 95 %CI = 0.91–1.65; p = 0.17) in the risk of relapse compared to standard three-weekly regimen. Details are shown in Fig. 3. Evidence of recommendation concerning the comparison of weekly cisplatin chemoradiotherapy versus three-weekly cisplatin chemoradiotherapy for both survival outcomes was graded as very low, given the quality assessment – including the risk of bias, inconsistency, indirectness and imprecision – in the included studies (Table 3).

3.3. Outcomes of harm

There were no notable differences in severe acute toxicity (RR = 0.95, 95 %CI = 0.78–1.15; p = 0.60) between weekly and three-weekly cisplatin regimen. Fig. 4 listed subgroup analysis stratified by type of severe acute toxicity. The risk of severe acute anemia (RR = 0.90, 95 % CI = 0.50–1.63; p = 0.73), neutropenia (RR = 0.78, 95 %CI = 0.23–2.70; p = 0.70), thrombocytopenia (RR = 0.88, 95 %CI = 0.31–2.53; p = 0.81) and oral mucositis (RR = 1.05, 95 %CI = 0.79–1.35; p = 0.79) was similar between groups. It was not possible to extract data on severe late toxicity.

Concerning treatment compliance, of the 224 patients included, 55 (24.6 %) received a cumulative dose of cisplatin lower than 200 mg/m^2. Compliance with concomitant chemotherapy was not significantly different (RR = 1.67, 95 %CI = 0.55–5.04; p = 0.36) between the 2 chemotherapy strategies. Compliance with RT was similar between groups (RR = 0.61, 95 %CI = 0.30–1.24; p = 0.18). Treatment compliance details are shown in Fig. 5.

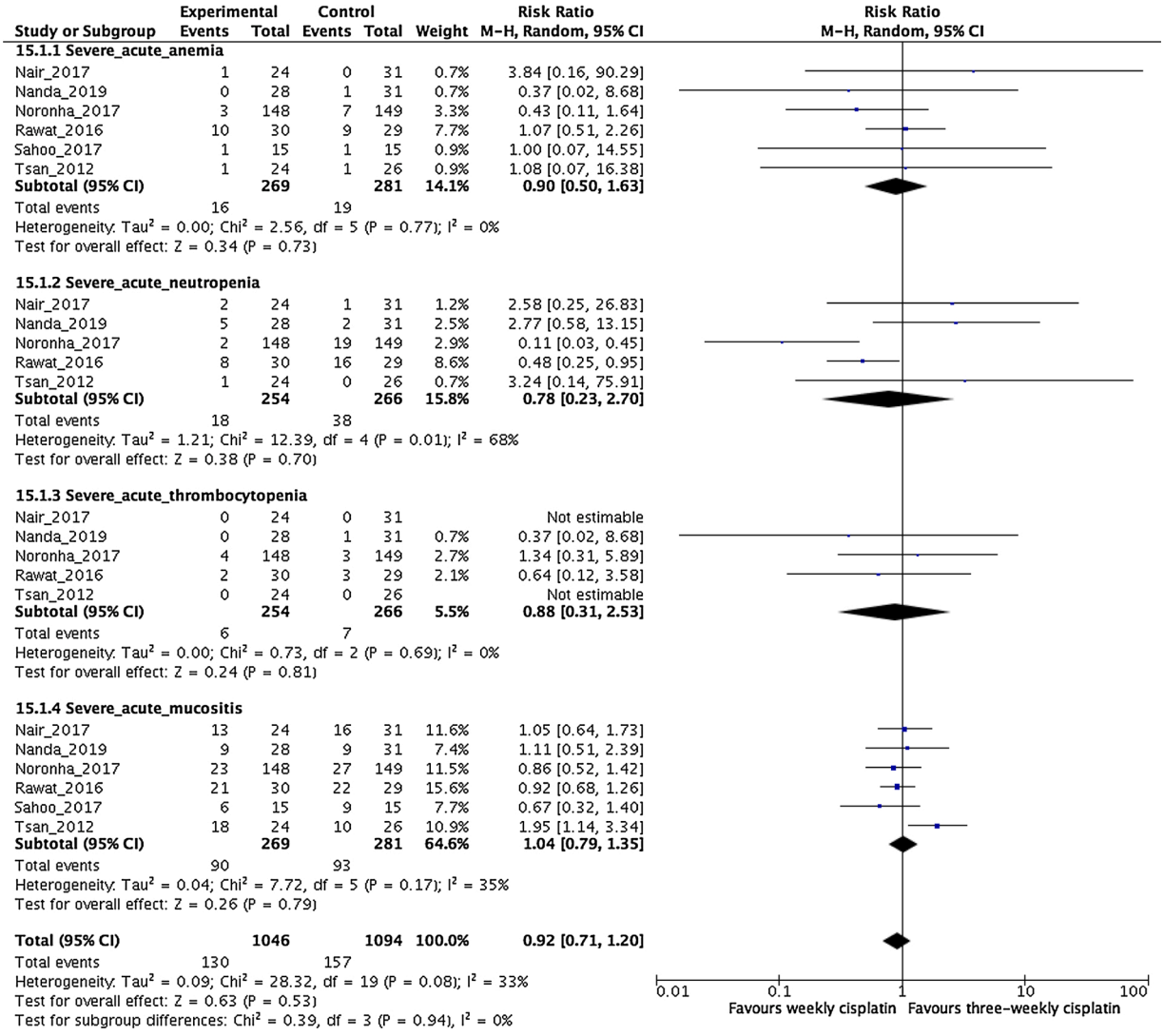

Fig. 4. Forest plot of severe acute toxicity – subgroup analysis.

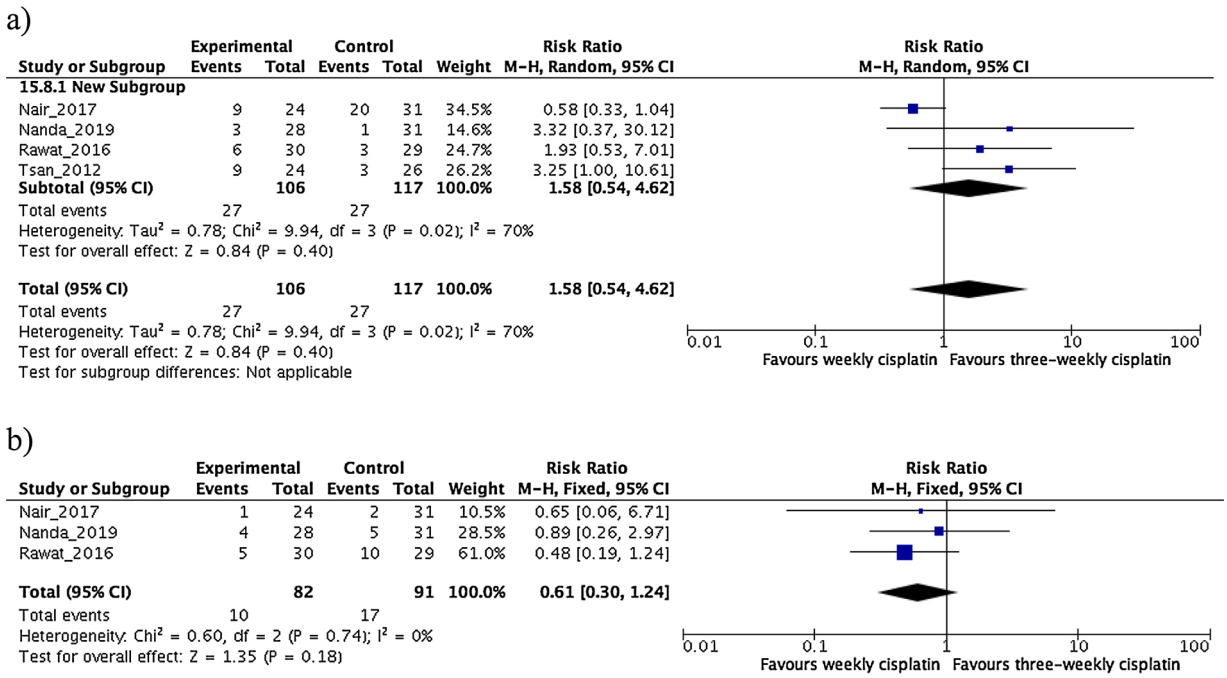

Fig. 5. Forest plot of treatment tolerability – compliance with concomitant chemotherapy (a) and radiotherapy (b).

3.4. Evidence to decision (EtD)

In essence, there was not a real benefit on survival outcomes, as well as on severe acute toxicity profile and treatment compliance, for the weekly cisplatin chemoradiotherapy regimen over the standard approach (three-weekly chemoradiotherapy). The certainty of evidence was graded as *very low*. There were concerns about the estimated risk of bias, inconsistency, indirectness and imprecision, mainly due to drop control for multiple comparisons, small sample size, modified intention-to-treat analysis and low quality of evidence.

3.5. Benefit/harm balance and final recommendation

The expert group panel suggests that weekly cisplatin should not be favoured in locally advanced SCCHN (conditional recommendation, very low confidence in estimates of effect) (Table 4), unless new evidence will be available.

4. Discussion

We performed a meta-analysis to compare the efficacy and toxicity of weekly cisplatin chemoradiotherapy versus three-weekly cisplatin chemoradiotherapy in patients with locally advanced head and neck squamous cell carcinoma. Results showed no significant clinical benefit for one of the groups over the other in term of OS (HR = 1.13, 95 %CI = 0.84–1.51), PFS (HR = 1.23, 95 %CI = 0.91–1.65; p = 0.17), acute toxicity (RR = 0.95, 95 %CI = 0.78–1.15) and treatment compliance.

These results are in agreement with previous meta-analyses (Szturz et al., 2017; Geiger et al., 2014). The strength of this meta-analysis is linked to its methodological accuracy. It is exclusively based on RCTs directly comparing weekly versus three-weekly cisplatin chemoradiotherapy in patients with locally advanced head and neck squamous cell carcinoma. RCTs have been identified from the medical literature using a validated search strategy. The limitations are mainly related to the restricted number of trials included and heterogeneity of the data: despite the study designs were similar among the included RCTs, different weekly cisplatin-based schedules were used – all but two up to a cisplatin minimal cumulative dose of 200 mg/m^2. Moreover, outdated external beam radiotherapy machine (Cobalt-60 teletherapy) or technique (three dimensional conformal radiotherapy) were used. Finally, they were powered for testing different primary end-points.

Whether weekly cisplatin chemoradiotherapy could be considered a standard for locally advanced head and neck squamous cell carcinoma cannot be defined by this meta-analysis. Weekly cisplatin was not associated with a difference in terms of outcomes, although overall a lower proportion of acute toxic events and radiotherapy interruption events were recorded. This assumption suggests that weekly cisplatin may achieve toxicity reduction while preserving survival outcomes. However, it should be noticed that in the study by Noronha et al. (2018) – the largest included study with 150 patients in each arm – almost all patients received postoperative chemoradiotherapy over 6 weeks, with a weekly cisplatin dose of 30 mg/m^2, far less than the 200 mg/m^2 considered effective. Thus, tit is likely that the less toxicity and worse tumor control in the low-dose arm might have resulted from insufficient total cisplatin dose, rather than the administration schedule itself.

Considering that patient's quality of life in this setting is crucial, several considerations should be made. Firstly, it should be highlighted that acute toxicity cases were described in different quantities (any grade versus severe toxicity) and profiles (overall versus each adverse event). An incomplete analysis of the acute nausea/vomiting profile, as well as nephrotoxicity profile, precluded any such estimation in the meta-analysis and, accordingly an adequate comparison between the two different schedules, Moreover data on late toxicity were estimated in only one trial (Szturz et al., 2017) and therefore it was not possible to perform a cumulative analysis. Because late toxicity is correlated to quality of life and there was no difference in treatment effect on survival outcomes, we believe that this missing analysis imposes caution upon

Table 4
Final recommendation.

Quality of evidence (GRADE)	Recommendation	Strength of recommendation
Very low	In patients with SCCHN treated with concomitant chemoradiotherapy, we suggest not offering weekly CDDP	Weak against intervention

SCCHN: squamous cell carcinoma of the head and neck; CDDP: cisplatin.

any specific assessment. Probably quality of care – mainly in term of technical progress in radiation techniques – might have influenced toxicity results. Nowadays, intensity modulated radiation therapy (IMRT) is the recommended technique in head and neck cancers management, due to its ability to reduce the high-medium doses delivered to the healthy tissues maintaining adequate target coverage (Jacinto et al., 2017). Therefore a plausible discordance between IMRT-related and no-IMRT-related toxicity should be considered. Another limitation is the absence of HPV data, limiting the ability to determine possible association between HPV status and treatment-related effects.

Because HPV-related disease is known to be associated with a better prognosis, both survival and toxicity analysis should be HPV-adjusted. Some studies comparing outcomes in patients treated with either weekly or three-weekly cisplatin have collected HPV status but in retrospective design and therefore were not included in the meta-analysis (Sahoo et al., 2017; Perez et al., 2017). Some studies showed that dose intensity of cisplatin could have a prognostic different impact in HPV negative versus positive diseases, without considering schedule of administration (Spreafico et al., 2016; Oliva et al., 2019). In this regard, one should tailor concomitant cisplatin considering the balance of activity and toxicity, the functional status of the patient and the characteristics of disease (HPV positive versus negative). Other major unanswered question relates to patient's age. Due to its supposed low toxicity profile, subgroup analysis and/or prospective trials focused on patients' age could identify a population who might benefit from a weekly cisplatin schedule in terms of better treatment compliance. In this context, with the same survival rates, cost-effectiveness as well as patient-friendly access should be prioritized. The aim is to reduce costs associated with treatment and its toxicity-related rehabilitation. Lastly, the power of the meta-analysis should be addressed. Despite we included only RCTs, the quality of evidence was graded as very low. Apart for Noronha et al. (2018), all the studies had small sample sizes, with 15–30 patients randomized to each arm. thus not enough powered to detect a significant difference even in the presence of a real difference between the groups. It implies that results from further RCTs would probably change the effect estimation confidence. A meta-analysis using individual patient data would probably overcome this weakness (Blanchard et al., 2019). Of note, the phase II/III Japan clinical oncology group study trial (JCOG1008) might provide new insights in the microscopically positive margin and/or extranodal extension post-operative setting. Preliminary results have been presented at 2020 American Society of Clinical Oncology (ASCO) meeting and showed a non-inferiority of weekly cisplatin compared to the three-weekly schedule with a favorable toxicity profile in these high-risk patients (Kiyota et al., 2020).

To conclude, although weekly cisplatin provides similar survival and acute toxicity results to three-weekly cisplatin, its role in the management of locally advanced head and neck squamous cell carcinoma remains to be defined. We hope to draw attention to the paucity of data on this topic and improve the quality of future research to create more robust evidence.

5. Conclusion

Without any support from large comparative phase III trials, three-weekly cisplatin chemoradiotherapy should remain the standard of care in locally advanced head and neck squamous cell carcinoma.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2021.103345.

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