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REVIEW ARTICLE

Comparison of different treatments for HPV+ oropharyngeal carcinoma: a network meta-analysis

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Abstract

Introduction Treatment of human papillomavirus (HPV)-related head and neck squamous cell carcinoma (HNSCC) is rapidly evolving. Despite either surgery or radiotherapy (RT), with or without chemotherapy (CT), being acceptable in intermediate and locally advanced diseases, there is uncertainty regarding the best treatment option for these patients. Therefore, we performed a network meta-analysis (NMA) to compare the relative efficacy of different treatments for HPV+ oropharyngeal carcinoma.

Material and methods Randomized clinical trials that enrolled adults with non-metastatic HPV+ oropharynx cancer and provided data about overall survival (OS) and/or progression-free survival (PFS) and/or locoregional control and distant metastases (LRC and DM) were included. Fixed- or random-effects models were fit using a Bayesian approach to NMA. Between-group comparisons were estimated using hazard ratios (HRs) with 95% credible intervals (CrIs). The primary outcome was OS.

Results A total of 844 citations were screened; 11 randomized clinical trials were included (HPV+ stage III–IV cancer, mainly oropharynx carcinomas). Nine treatment arms were compared. Radiotherapy (altered or standard fractionation) + tri-weekly cisplatin (HR 3.8; 95% CrIs 0.29–65 and 0.3; 95% CrIs 0.03–2.51) was superior to RT in term of OS (*P* score = 0.42 and 0.16). Radiotherapy with low and high cisplatin doses appeared similar (HR 1.57; 95% CrIs 0.19–12.72). Altered fractionation or standard RT + 3-weekly cisplatin are the 2 highest-ranked options in terms of PFS (*P* score = 0.35 and 0.34).

Conclusions This meta-analysis confirms the role of cisplatin added to RT as the best option for HPV+ oropharyngeal carcinoma. RT+ 3-weekly cisplatin is likely to be the best radical treatment in terms of OS and PFS.

Keywords Human papillomavirus · Oropharyngeal carcinoma · Chemoradiotherapy · Network · Meta-analysis

Introduction

Treatment of human papillomavirus (HPV)-related head and neck squamous cell carcinoma (HNSCC) is rapidly evolving. A subgroup of patients with HPV-related (HPV+) oropharyngeal squamous cell carcinomas (OPSCC) do not present traditional risk factors associated with HNSCC (e.g., smoking and alcohol consumption), with various prevalence according to the geographical area [1, 2]. Although the staging system and prognosis are different in HPV+ vs. HPV- unrelated cancers, the treatment of both virus-related and unrelated oropharyngeal cancer remains similar. Despite either surgery or radiotherapy (RT), with or without chemotherapy (CT), being acceptable in intermediate and locally advanced diseases, there is uncertainty regarding the best

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treatment option for these patients. Various systemic regimens associated with concomitant RT have, in fact, shown efficacy in unselected locally advanced HNSCC compared to RT alone (cisplatin, cetuximab, altered fractionation RT). However, there is no systematic evidence for comparing efficacy among different agents/schedules (e.g., weekly vs. 3-weekly cisplatin) in HPV + OPSCC. Therefore, we performed a network meta-analysis (NMA) to compare the relative efficacy of different treatments for HPV + OPSCC.

Materials and methods

The reporting of this study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMAs.

We performed searches on PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), using the terms "head and neck," "oropharyngeal," "oropharynx," "HPV," "p16," and "randomized" to find relevant studies published in the English language from inception to 1 January 2022. In addition, reference lists of the relevant articles were examined. We included published phase II/III RCTs assessing curative (radical) treatments in patients with HPV+/p16+ OPSCC. If a multi-arm trial compared more than two drugs or two different doses of one drug with another, we treated them as separate pairwise comparisons. Two investigators (PB and FP) independently screened the articles and abstracts according to the eligibility criteria. Disagreements were resolved by consensus.

The details of the studies (e.g., publication year, author, number of patients, type of study), patient characteristics (e.g., median age, sex), treatment arms, and outcomes (hazard ratios [HRs] and their 95% credible intervals [CrIs] for OS, progression-free survival [PFS], locoregional control [LRC] and distant metastases [DM]) were extracted into an Excel sheet. Survival data extracted were double-checked by a third reviewer (CG) to avoid potential assessment bias by investigators. Two independent reviewers (FP and PB) assessed the risk of bias for all included RCTs using the Cochrane Collaboration's tool. Any disagreements were resolved by consensus. Studies that included arms that cannot be estimated using NMA because they are not connected with others were excluded.

We conducted NMAs based on a Bayesian approach to calculate the pooled effect estimates and uncertainty for all interventions compared with the reference treatment. Comparative efficacy and safety are reported as HR for OS, PFS, DM, and LRC along with 95% CrI. Fixed-effect models were fitted if quantification of heterogeneity was not possible; otherwise, random-effects models were used. Statistical significance was set at a p value of 0.05. Heterogeneity and inconsistency were assessed by the between-study variance τ^2 value, Cochran Q with a p value, and I^2. Overall ranks of treatments were estimated using P scores, which were based solely on the point estimates and standard errors of the network estimates. Treatments with the highest and lowest P scores were considered the best and worst treatments, respectively. Network meta-analyses were performed under the Bayesian framework using the "gemtc" package (https://gemtc.drugis.org). Noninformative priors were set, and posterior distributions were obtained using 40,000 iterations after 20,000 burn-ins and a thinning interval of 10.

Results

Among 844 citations retrieved, 11 studies [3–13] were included in the quantitative synthesis and in NMA (Fig. 1). Characteristics of included studies are described in Table 1. Almost all patients analysed were HPV + OPSCC with stage III–IV at diagnosis. Five studies compared RT + cetuximab with CTRT or RT alone, 2 altered fractionated RT plus CT with conventional CTRT, 1 altered fractionated RT with standard RT, 1 RT + cisplatin plus or minus cetuximab, 1 RT + weekly cisplatin with RT alone, and 1 RT plus cisplatin plus or minus avelumab. Data was available in 10, 8, and 5 studies for NMA of OS, PFS, and LRC, respectively. Due to the paucity of data, a meta-analysis of DM was not feasible.

An NMA of 9 treatments was performed for OS. Compared with RT + 3-weekly cisplatin, RT alone (standard or altered fractionation) and RT + cetuximab were associated with a non-significant reduced OS among patients with HPV + OPSCC (Tables 2, 3; Fig. 2a, b). RT + 3-weekly cisplatin and weekly cisplatin were similar (HR = 1.57, 95% CrIs 0.19–12.72). Analysis of treatment ranking revealed that altered fractionation or standard RT + 3-weekly cisplatin had the highest likelihood of providing the maximal OS (P score: 0.42 and 0.16). RT alone or altered fractionation alone were most likely to be ranked last.

In PFS and LRC NMA, altered fractionation RT + 3-weekly cisplatin and RT + weekly cisplatin ranked as the best treatments, respectively (P score = 0.35 and 0.69; Tables 2, 3, 4, 5, 6, 7; Figs. 3a, b, 4a, b).

Discussion

This NMA shows that platinum-based concomitant treatment provides the maximal survival benefit for HPV + OPSCC. In particular, a 3-weekly cisplatin schedule proved to rank highest for OS benefit while overlapping with weekly cisplatin for PFS and LRC. Conversely, de-escalation strategies with RT alone, either conventional or altered fractionation, and the use of cetuximab resulted in poorer survival outcomes.

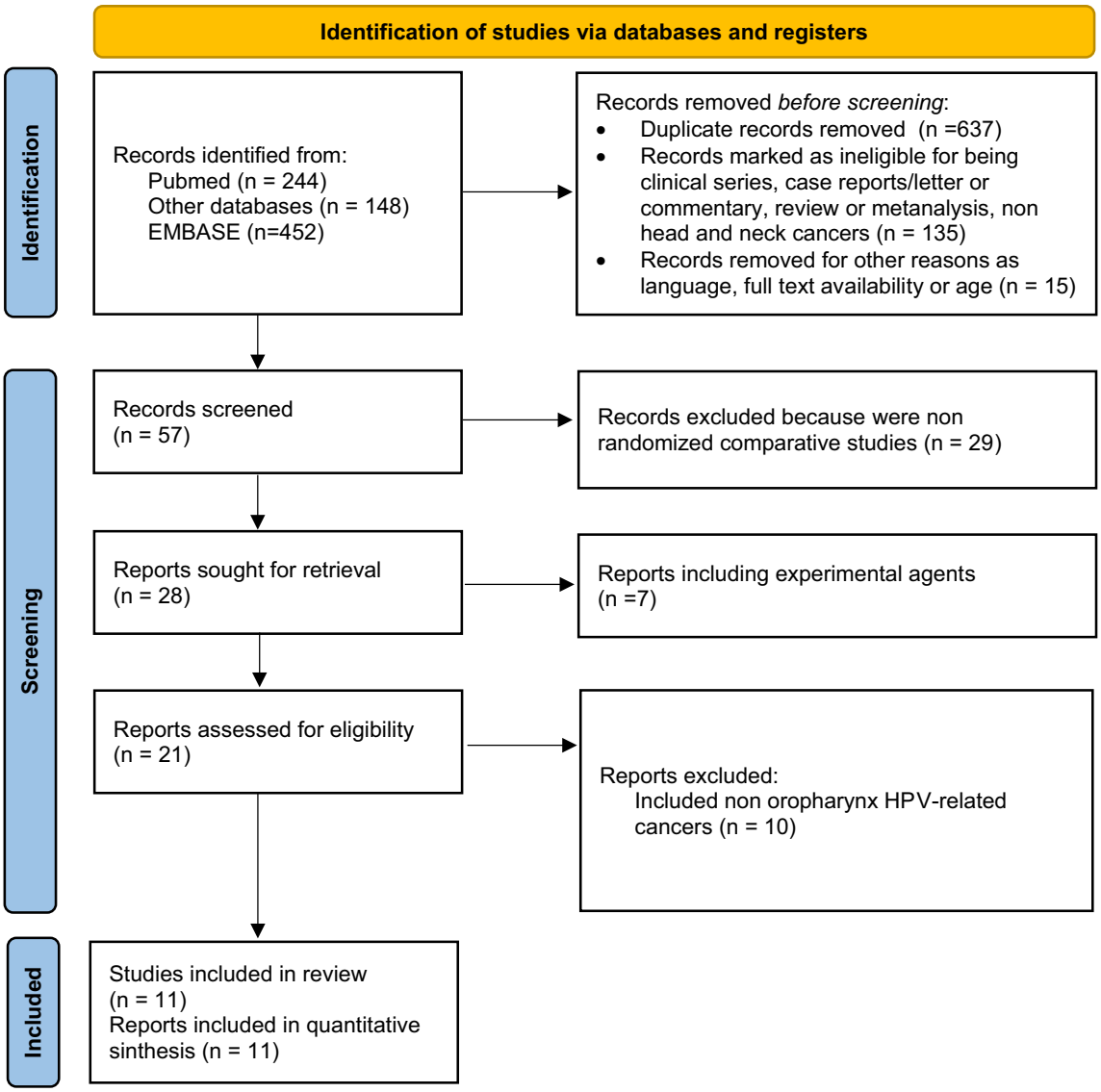

Fig. 1 flow diagram of included studies

Once again, platinum is confirmed to be the companion needed for definitive treatments in locally advanced HNSCC. However, there are still a few unanswered questions about the schedule and dose to be preferred [14]. A weekly schedule has recently been shown to be non-inferior to a 3-weekly schedule in the postoperative setting in a randomized trial, but the rate of p16 positivity was relatively low (10% of the patients) [15]. There is no evidence about platinum's more effective or less toxic schedule when given concurrently to RT with curative intent. The present NMA suggests that high-dose cisplatin could improve OS and obtain similar results for disease control, showing that the radiosensitizing effect is similar between the two schedules in HPV-positive cancers. We may argue whether there is a different impact on distant metastasis in favour of high-dose cisplatin and whether this could explain the increased OS identified.

Treatment de-escalation of systemic therapy seems not to be the most feasible strategy as of now. Whether RT could be de-intensified to provide a similar survival and better safety profile must be demonstrated. A recently published study by Tsai et al. [16] showed a favourable clinical outcome and quality-of-life profile for HPV + patients treated with a de-escalated RT strategy, both in the dose and target volume, while maintaining, in most cases, a high dose of cisplatin. Despite these results, it should be noted that half of the enrolled patients were never smokers, and among smokers, the large majority had a smoking history of fewer than 10 pack-years. Moreover, only a

Table 1 characteristics of included studies

Author/year	Type of study	N° patients	Site	Stage (%)	Control arm	Experimental arm	Dose/schedule systemic therapy	Median follow up (months)	Primary endpoint	Risk of bias
Kian Ang/2014	Phase III	891	Various	III/IV (100%)	RT (70 Gy) + CDDP	RT (70 Gy) + CDDP + CET	100 mg/m^2/3-weekly vs 400→250 mg/m^2/weekly	45.6	PFS failure	Low
Buglione/2016	Phase II	70	various	III (23%), IV (77%)	RT (70 Gy) + CDDP	RT (70 Gy) + CET	40 mg/m^2/weekly vs 400→250 mg/m^2/weekly	16	1 and 2 year LC	Moderate
Gillison/2019	Phase III	849	Oropharynx	III (7.5%), IV (92.5%)	RT (70 Gy) + CDDP	RT (70 Gy) + CET	100 mg/m^2/3weekly vs 400→250 mg/m^2/weekly	54	OS	Low
Fietkau/2019	Phase III	221	Various	III (16.2%), IV (83.8%)	RT (63.6 Gy) + paci-taxel + CDDP	RT (70.6 Gy) + 5FU + CDDP	20 mg/m^2/ weekly + 20 mg/ m2 × 4 days/4-weekly vs 600 mg/ m^2 + 20 mg/ m2 × 5 days/3 weekly	44	3y-DFS	Uncertain
Lee/2021	Phase III	697	Various	III/IV (100%)	RT (70 Gy) + CDDP	RT (70 Gy) + CDDP + Ave-lumab	100 mg/m^2/3weekly vs 100 mg/ m^2/3weekly + 10/ kg/2 weekly	14.6	PFS	Low
Mehanna/2018	Phase III	334	Oropharynx	III/IV (100%)	RT (70 Gy) + CDDP	RT (70 Gy) + CET	100 mg/m^2/3-weekly vs 400→250 mg/m^2/weekly	24	2y-severe (grade 3–5) toxicity	Low
Nguyen-Tan/2014	Phase III	721	Various	III/IV (100%)	RT (70 Gy) + CDDP	RT (72 Gy) in 42 fractions over 6 weeks + CDDP	100 mg/m2/3-weekly × 3 vs × 2 cycles	94.8	OS	Low
Rischin/2021	Phase III	189	Oropharynx	III/IV (100%)	RT (70 Gy) + CDDP	RT (70 Gy) + CET	40 mg/m^2/weekly vs 400→250 mg/m^2/weekly	49	Symptom severity from baseline to 13 weeks postcompletion of RT	Moderate
Rosenthal/2016	Phase III	182 (subgroup)	Oropharynx	III/IV (100%)	RT (70 Gy or twice-daily or concomitant boost)	RT (70 Gy or twice-daily or concomitant boost) + CET	400→250 mg/m^2/ weekly	NR	Locoregional control of disease duration	Low

Table 1 (continued)

Author/year	Type of study	N° patients	Site	Stage (%)	Control arm	Experimental arm	Dose/schedule systemic therapy	Median follow up (months)	Primary endpoint	Risk of bias
Yom/2021	Phase II	306	Oropharynx	T1–2 N1-N2b M0 or T3 N0-N2b M0 staging	RT (60 Gy of intensity-modulated RT)	RT (60 Gy of intensity-modulated RT) + CDDP	40 mg/m^2/weekly	31.2	2y-PFS & swallowing QOL was based on the mean of the composite MDADI scores at 1 year	Moderate
Zackrisson	Phase III	206 (subgroup)	Oropharynx	III/IV (83%)	RT standard fractionaqction (68 Gy)	RT accelerated fractionation (1.1 Gy + 2 Gy per day, 5 days/week for 4.5 weeks, total dose 68 Gy) and	–	109.2 for OS	2y LRC	Low

MDADI M. D. Anderson Dysphagia Inventory, *RT* radiotherapy, *CDDP* cisplatin, *5FU* 5Fluorouracil, *CET* cetuximab, *PFS* progression-free survival, *LC* local control, *LRC* locoregional control, *DFS* disease-free survival, *NR* not reported

minority of patients had a high disease burden, with only 31.5% T3–4 and 23.5% N2–3 disease.

Several studies are ongoing to evaluate different de-escalation strategies for HPV + OPSCC; however, phase 3 data are lacking, and it is currently not the proper time for a broad de-escalation of therapy outside of clinical trials [17]. A meta-analysis we published recently supports this concept [18]. This previous meta-analysis compared only standard vs. de-escalated treatments; conversely, the present paper adds new information and compares the entire treatment network indirectly, providing effect size data even if a direct comparison does not exist in the literature (for example, a randomized comparison between 3-weekly and weekly cisplatin both plus RT).

The results of this Bayesian comparison of various regimens for locally advanced HPV + OPSCC establish that CTRT with standard-dose cisplatin is the preferred and definitive approach, similar to those with non-HPV related OPSCC. We did not prove the superiority of high-dose cisplatin over lower weekly cisplatin doses, but we definitely confirmed the inferiority of RT alone or RT + cetuximab. Finally, we referred mainly to stage III–IV disease and not to T1–2 cancers, where single modalities may be endorsed (e.g., transoral surgery). Substantially, comparisons of various strategies confirm that locoregionally advanced HNSCC needs the same intensified treatment in both non-HPV and HPV + subtypes deserving more aggressive schedules (induction CT) for organ preservation aims or for severe bulky nodal disease likely in non-HPV cancers. For HPV + OPSCC, tailored induction chemotherapy has been studied only in nonrandomized trials, and induction chemotherapy may be conceived for the de-intensification of RT (sequential treatment for those unable to tolerate concomitant CTRT).

Some limitations of this study should be addressed. Firstly, we only generally compared the treatment strategies without considering intrinsic differences within each treatment strategy (e.g., disease sites, radiation techniques, radiation fractions, and total doses). Despite this bias, almost all studies included homogeneously patients with stage III–IV OPSCCs. Second, we did not perform an individual patient data meta-analysis, which may provide a higher evidence level than NMA. However, when there is a substantial amount of data, Tierney et al. showed that individual patient data meta-analysis may agree with those from aggregate data [19]. Finally, we excluded surgical trials for lack of significant and homogenous studies that may link the network.

In conclusion, cisplatin remains the sensitizing benchmark for definitive treatment of locally advanced (stage III–IV) HPV + OPSCCs, and the possibility of de-escalation strategies seems to pertain to companion therapies (RT or surgery). Findings from the many ongoing studies aim to provide data regarding the best selection of patient

Table 2 Comparison of the included interventions for OS: hazard ratio (95% CrI)

Alt fract RT	0.29 (0.01, 7.24)	1.1 (0.15, 7.95)	0.33 (0.01, 6.21)	0.49 (0.01, 16.23)	0.75 (0.06, 11.01)	0.53 (0.03, 6.91)
	Alt fract RT + 3wCDDP	3.82 (0.29, 65.27)	1.17 (0.26, 6.24)	1.71 (0.15, 21.61)	2.53 (0.37, 26.81)	1.85 (0.15, 27.47)
		RT	0.3 (0.03, 2.51)	0.44 (0.02, 8.03)	0.66 (0.13, 3.89)	0.48 (0.08, 2.46)
			RT + 3wCDDP	1.44 (0.21, 9.80)	2.17 (0.61, 10.26)	1.57 (0.19, 12.72)
				RT + 3wCDDP + CET	1.49 (0.15, 18.45)	1.09 (0.06, 18.18)
					RT + CET	0.7 (0.12, 3.07)
						RT + weekly platinum

Each cell gives the effect of the column-defining intervention relative to the row-defining intervention

Table 3 Ranking of various regimens by OS (rank 7 being the best, rank 1 being the worst)

Rank probabilities table							
	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Alt fract RT	0.32	0.21	0.12	0.10	0.07	0.06	0.08
Alt fract RT + 3wCDDP	0.03	0.04	0.05	0.08	0.15	0.21	**0.41**
RT	0.31	0.35	0.15	0.08	0.05	0.03	0.01
RT + 3wCDDP	0.01	0.02	0.05	0.10	0.25	0.38	0.16
RT + 3wCDDP + CET	0.14	0.08	0.11	0.14	0.21	0.14	0.16
RT + CET	0.11	0.18	0.30	0.26	0.10	0.02	0.01
RT + weekly platinum	0.06	0.09	0.19	0.21	0.16	0.12	0.14

The highest *P* score is highlighted in bold

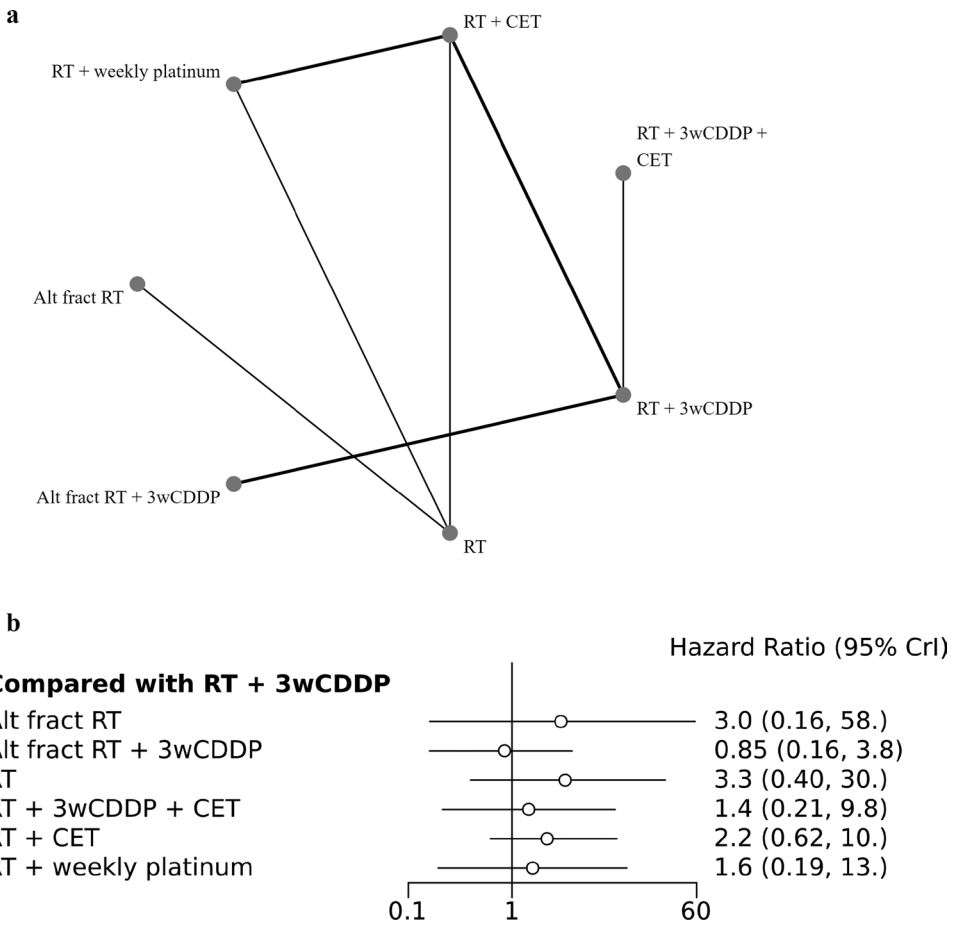

Fig. 2 **a**, **b** Forest plots showing the association of different treatments for HPV + cancers (overall survival)

Table 4 Comparison of the included interventions for PFS: hazard ratio (95% CrI)

Alt fract RT + 3wCDDP	2.24 (0.09, 52.23)	0.96 (0.08, 11.13)	1.5 (0.07, 29.32)	1.23 (0.05, 25.22)	2.24 (0.14, 33.66)	1.69 (0.07, 37.49)
	RT	0.44 (0.05, 3.16)	0.69 (0.04, 9.96)	0.56 (0.03, 7.69)	1.02 (0.2, 4.82)	0.77 (0.16, 3.31)
		RT + 3wCDDP	1.54 (0.26, 9.06)	1.27 (0.217, 7.6)	2.27 (0.67, 8.43)	1.73 (0.23, 12.31)
			RT + 3wCDDP + CET	0.8 (0.07, 10.47)	1.47 (0.18, 13.89)	1.12 (0.07, 16.28)
				RT + 3wCDDP + avelumab	1.8 (0.2, 16.04)	1.36 (0.1, 18.63)
					RT + CET	0.76 (0.156, 3.35)
						RT + weekly platinum

Each cell gives the effect of the column-defining intervention relative to the row-defining intervention

Table 5 Ranking of various regimens by progression-free (rank 7 being the best, rank 1 being the worst)

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7
Alt fract RT + 3wCDDP	0.15	0.08	0.07	0.10	0.10	0.12	**0.35**
RT	0.26	0.21	0.17	0.12	0.09	0.07	0.04
RT + 3wCDDP	0.01	0.02	0.06	0.14	0.27	0.34	0.14
RT + 3wCDDP + CET	0.16	0.12	0.12	0.16	0.15	0.13	0.12
RT + 3wCDDP + avelumab	0.11	0.10	0.10	0.14	0.16	0.17	0.19
RT + CET	0.18	0.27	0.27	0.15	0.07	0.02	0.01
RT + weekly platinum	0.12	0.17	0.18	0.16	0.12	0.11	0.11

The highest *P* score is highlighted in bold

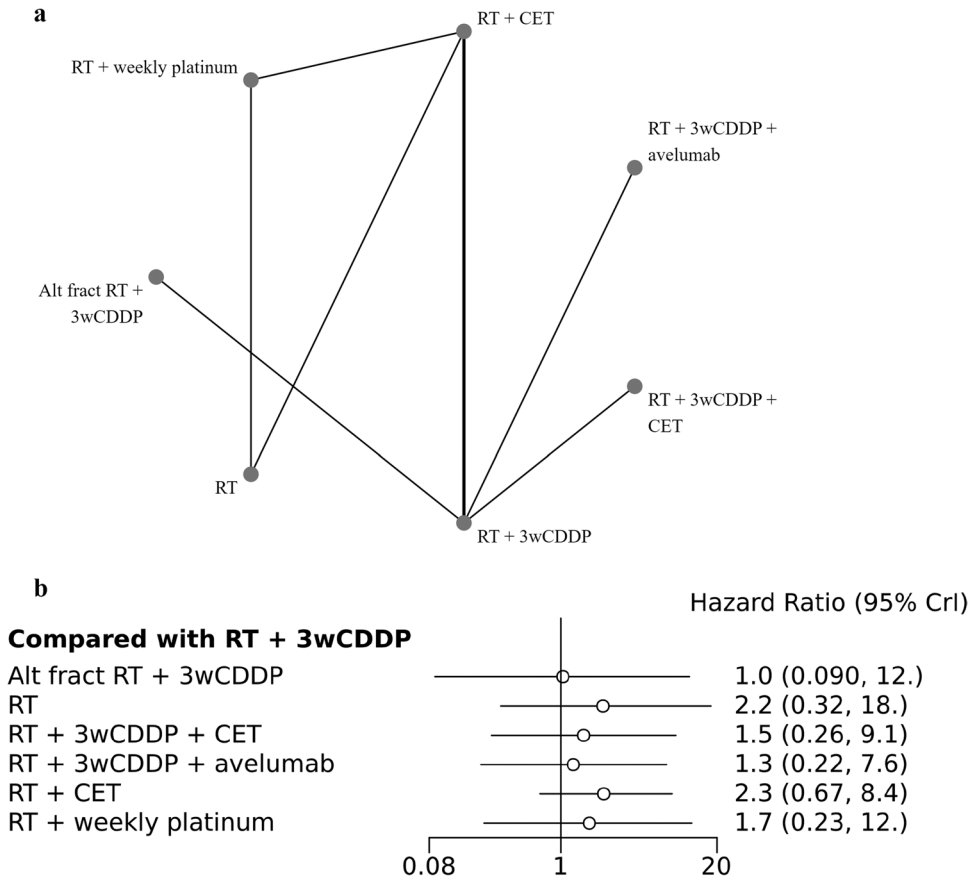

Fig. 3 **a**, **b** Forest plots showing the association of different treatments for HPV + cancers (progression-free survival)

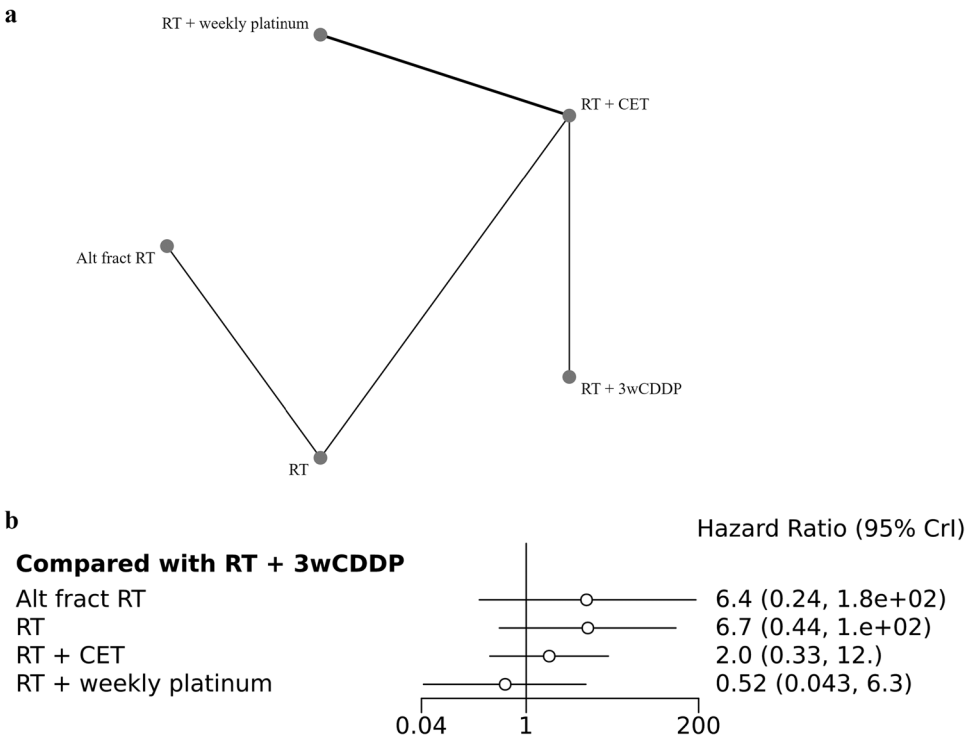

Fig. 4 **a**, **b** Forest plots showing the association of different treatments for HPV + cancers (locoregional control)

Table 6 Comparison of the included interventions for locoregional control (LRC): hazard ratio (95% CrI)

Alt fract RT	1.02 (0.14, 7.16)	0.15 (< 0.01, 4.22)	0.31 (0.01, 4.84)	0.08 (< 0.01, 2.12)
	RT	0.15 (0.01, 2.27)	0.30 (0.04, 2.25)	0.08 (< 0.01, 1.14)
		RT + 3wCDDP	2.03 (0.32, 12.47)	0.52 (0.04, 6.25)
			RT + CET	0.25 (0.04, 1.49)
				RT + weekly platinum

Each cell gives the effect of the column-defining intervention relative to the row-defining intervention

Table 7 Ranking of various regimens by locoregional control (rank 7 being the best, rank 1 being the worst)

	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
Alt fract RT	0.47	0.36	0.07	0.05	0.03
RT	0.43	0.47	0.05	0.02	0.01
RT + 3wCDDP	0.03	0.03	0.10	0.56	0.25
RT + CET	0.04	0.10	0.70	0.13	0.01
RT + weekly platinum	0.01	0.01	0.05	0.22	**0.69**

The highest *P* score is highlighted in bold

candidates for new de-intensification options capable of maintaining or improving survival and long-term quality of life.

Author contributions All authors contributed equally.

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Data availability Data are available from the corresponding author under reasonable request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics approval n/a.

Patient consent n/a.

Permission to reproduce material from other sources n/a.

Clinical trial registration n/a.

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