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ORIGINAL RESEARCH

# Altered fractionation radiotherapy with or without chemotherapy in the treatment of head and neck cancer: a network meta-analysis

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**Objectives:** A Bayesian network meta-analysis (NMA) was conducted in patients with head and neck cancers (HNCs) to estimate the efficacy and safety of treatment with conventional fractionation radiotherapy (CF), conventional fractionation chemoradiotherapy (CF_CRT), hyperfractionated radiotherapy (HF), hyperfractionated chemoradiotherapy (HF_CRT), accelerated fractionation radiotherapy, accelerated fractionation chemoradiotherapy, accelerated hyperfractionated radiotherapy (HART) or accelerated hyperfractionated chemoradiotherapy (HACRT) to identify superior treatments to aid in clinical decisions.

**Methods:** PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for potentially eligible randomized controlled trials up to December 2016. Overall survival (OS), disease-free survival (DFS) and locoregional control (LRC) were considered efficacy outcomes, whereas acute toxicity and late toxicity on skin and mucosa were considered safety outcomes. The surface under the cumulative ranking curve (SUCRA) was calculated to rank each treatment in each index.

**Results:** Data from 72 trials with 21,868 participants were included in the analysis. Concerning OS, all treatments were associated with a significant advantage compared to CF alone, with HR effect sizes ranging from 0.64 to 0.83, and HACRT was significantly more effective than all the other treatments. The network comparisons of both HACRT vs HART and HF_CRT vs HF demonstrated a higher OS benefit, with an HR of 0.78 (95% credible interval [CrI]: 0.64–0.95) and 0.78 (95% CrI: 0.61–0.99), respectively. The results of SUCRA indicated that HACRT had the best ranking for OS and LRC, HF_CRT for DFS, HART for acute and late skin toxicity, CF_CRT for acute mucosal toxicity and HF_CRT for late mucosal toxicity.

**Conclusion:** The NMA results support the notion that HACRT is the preferable treatment modality for HNCs because it has better rankings in all three efficacy indexes, although it does present a high risk of acute mucosal toxicity.

**Keywords:** altered fractionation radiotherapy, head and neck cancer, randomized controlled trials, network meta-analysis

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## Introduction

Head and neck cancers (HNCs) represent the sixth most common carcinoma worldwide, with an estimated incidence of >500,000 new cases each year.[1–3] They are also a major oncologic burden in developing countries (age-standardized rate of incidence of 10–30/100,000).[4] There are various treatments for HNCs, including postoperative radiotherapy, chemoradiotherapy, radical radiotherapy and induction chemotherapy, followed by concurrent chemoradiotherapy and bio-radiotherapy which are developed recently.[5] Since X-rays were invented by WC Roentgen in 1895,

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radiation has been used for different malignancies and for benign conditions. However, the concept of fractionation was unknown. Thor Stenbeck used a treatment to cure skin cancer in which small doses of radiation were given each day, which was subsequently called "fractionation radiotherapy".[6] Later studies by Coutard showed that protracted fractionation in throat cancers resulted in tolerance of the skin and mucous membranes as well as improvement in the tumor response.[7] Conventional fractionation radiotherapy (CF) with 1.8–2.0 Gy per fraction was found to give good local control and lead to low normal tissue complication rates.[8] Different fractionation schedules came into practice with a better understanding of the "four Rs" of radiobiology and biologically effective doses. Since the 1980s, different radiotherapy methods have been developed, including altered fractionation radiotherapy, hyperfractionated radiotherapy (HF), accelerated fractionation radiotherapy (AF), accelerated hyperfractionated radiotherapy (HART), hypofractionation and combinations of these.[9] The differences between these unconventional fractionation radiotherapy methods depend on their doses and the amount of time. HF is delivered through a greater number of smaller treatment doses. In AF, radiotherapy is delivered in lesser amount of time, with greater number of treatments per day. In HART, the number of treatments per day and treatment doses are greater. In hypofractionation, the number of fractions that are delivered are decreased by increasing daily treatment doses.[10] Many modified fractionation schemes have shown an improvement in overall survival (OS) and locoregional control (LRC) compared to standard fractionation in randomized clinical trials.[11–18] Several meta-analyses have compared two different radiotherapy methods with or without chemotherapy.[19–23] However, randomized comparisons of all these strategies have not been carried out so far. This study adopted network meta-analysis (NMA) to conduct a comprehensive comparative analysis of the efficacy and safety of various altered fractionation radiotherapy strategies or their combinations with chemotherapy based on published original literature, aiming to provide evidence for clinical decision making.

# Methods

## Search strategies and study selection

PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for potentially eligible studies published from inception to December 2016. Search terms were the combination of subject words and free words of the keywords "head and neck cancer", "hyperfraction*", "accelerated fractionation*" and "Randomized Controlled Trial". The details of the search strategies for every database are provided in the Supplementary materials. In addition, we scanned the reference lists of the existing systematic reviews and meta-analyses relevant to this NMA for additional trials. We restricted the language to English.

The titles and abstracts were identified, and the full texts of potentially eligible studies were reviewed in duplicate by two reviewers (Yingyu Liu and Yangyu Zhang) independently. We conducted the meta-analysis and reported the results according to the PRISMA statement.

## Inclusion and exclusion criteria

To be eligible, trials were required to meet the following inclusion criteria:

1) Study objective: Patients with HNCs, which were defined according to the Medical Subject Headings categories, including oral cavity, oropharyngeal, hypopharyngeal, laryngeal, esophageal and nasopharyngeal carcinomas, were eligible.
2) Study intervention: Comparison between altered fractionation radiotherapy (accelerated or/and hyperfractionated) with or without chemotherapy and conventional radiotherapy (1.8–2.0 Gy/fraction per day for 5 days/week), or to be specific, comparison between CF, conventional fractionation chemoradiotherapy (CF_CRT), HF, hyperfractionated chemoradiotherapy (HF_CRT), AF, accelerated fractionation chemoradiotherapy (AF_CRT), HART or accelerated hyperfractionated chemoradiotherapy (HACRT) was eligible for analysis.
3) Outcome parameters: OS, disease-free survival (DFS) and LRC were the indexes used to evaluate the efficacy. The assessment of safety included acute and late toxicity on skin and mucosa. Radiotherapy-related toxicities were graded according to the Acute and Late Scoring Criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer,[24] and chemotherapy-related toxicities were scored using the WHO criteria.[25] Incidence of toxicities of grade $\geq$3 was recorded.
4) Study design: Randomized controlled trials were included for analysis. Trials were excluded if they were: conference papers or abstracts; duplicates, as confirmed by the trial number; confounded by additional therapeutic differences, such as a monoclonal antibody or sensitizer; or with incomplete outcome data, selective reporting or other obvious bias.

## Data extraction and quality assessment

Data extraction and quality assessment were performed independently by at least two of six reviewers (Yingyu Liu, Xinyu Liu, Wei Bai, Yueyue You, Yan Song and Lili Zhang). The data collected for all patients included age, sex, tumor site, stage or T and N classification, histology, performance status, allocated treatment details and outcomes. The primary end point of our NMA was OS, as defined from the time of randomization or the start of treatment to death from any cause. For OS, DFS and LRC, HRs and their 95% CIs were used to estimate treatment effects. If the reported data were insufficient, we estimated the HR and 95% CI or extracted data from OS curves of treatment effects with methods as described by Parmar et al[26] and Tierney et al[27] using Engauge Digitizer software version 4.1.

We assessed the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.0.0),[28] including the following items: generation of a randomization sequence, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias.

## Statistical analyses

To compare the relative effects and safety of altered fractionation radiotherapy with or without chemotherapy in the treatment of HNC, we conducted an NMA in a Bayesian framework. The random-effects model was adopted. Brooks–Gelman–Rubin and trace plots were used to diagnose and assess the convergence of models. Four chains were fit with 20,000 burn-ins and 5,000 iterations each. We used the HR and its 95% credible interval (CrI) to measure the relative efficacy size with log-transformed HRs from each trial and the corresponding standard errors, while for binary outcomes, the safety was assessed with risk ratio (RR) and 95% CrI. A significantly increased HR or RR (HR or RR $>1$) suggested that one therapy may be less efficacious and safer than another, and a 95% CrI in that range did not include 1, indicating a statistically significant difference and vice versa. CrIs can be interpreted as conventional CIs in the presence of minimally informative priors.

NMA also provided a ranking probability of each treatment if the probability of each arm achieving the best rank among all treatments was calculated. The surface under the cumulative ranking curve (SUCRA) was computed to help identify the most appropriate treatment for each outcome. A larger SUCRA value represented a better rank. In the forest plots, we ranked the effects of the treatment regimens according to SUCRA values. Furthermore, node-splitting models were adopted to test the inconsistency of each comparison, and a $P$-value $<0.05$ indicated the significance of the inconsistency. All the analyses were performed with the R 3.4.1 packages "Gemtc" and JAGS.

# Results

## Search results

The search strategy identified 2,082 studies, and through reviewing the reference lists of all eligible articles and relevant systematic reviews, we identified 24 additional studies. After excluding duplicate studies, screening titles and abstracts and reading full texts, 72 studies with 21,868 participants were included in the analysis. PRISMA flowcharts are shown in Figure 1. Within the included studies, 40 (55.6%) provided the details about randomization methods, and most studies did not describe the details of blinding and concealment. The details of all the 72 articles are described in Table S1.

## Network results

The networks of eligible comparisons on the primary outcome, OS, are shown in Figure 2. The size of the nodes reflects the number of corresponding trials. The lines link the direct comparisons, and the thickness of the lines represents the number of trials comparing the two therapies. The network plot indicated that CF was included in the largest number of comparisons and that AF was included in the second largest number of comparisons. Although comparisons of AF and CF were common, few comparisons of AF_CRT and HF_CRT were identified.

We created hierarchies of effect size based on SUCRA rankings for all outcomes. All outcomes were outlined in the form of forest plots with all therapies compared to CF using the value of HRs with 95% CrIs. The complete results were recorded in the accompanying tables.

## Efficacy outcomes

OS is the primary indicator of the efficacy. The Bayesian NMA demonstrated that all treatments were superior to CF alone, with HR effect sizes ranging from 0.64 to 0.83, and HACRT was significantly more effective than all the other treatments. Network comparisons of HACRT vs HART and HF_CRT vs HF showed a statistically significant OS benefit with an HR of 0.78 (95% CrI: 0.64–0.95) and 0.78 (95% CrI: 0.61–0.99), respectively (Table 1 and Figure 3A). The results of node-splitting analysis of inconsistency indicated that the direct and indirect treatment effects between AF_CRT and CF ($P$=0.02) were inconsistent.

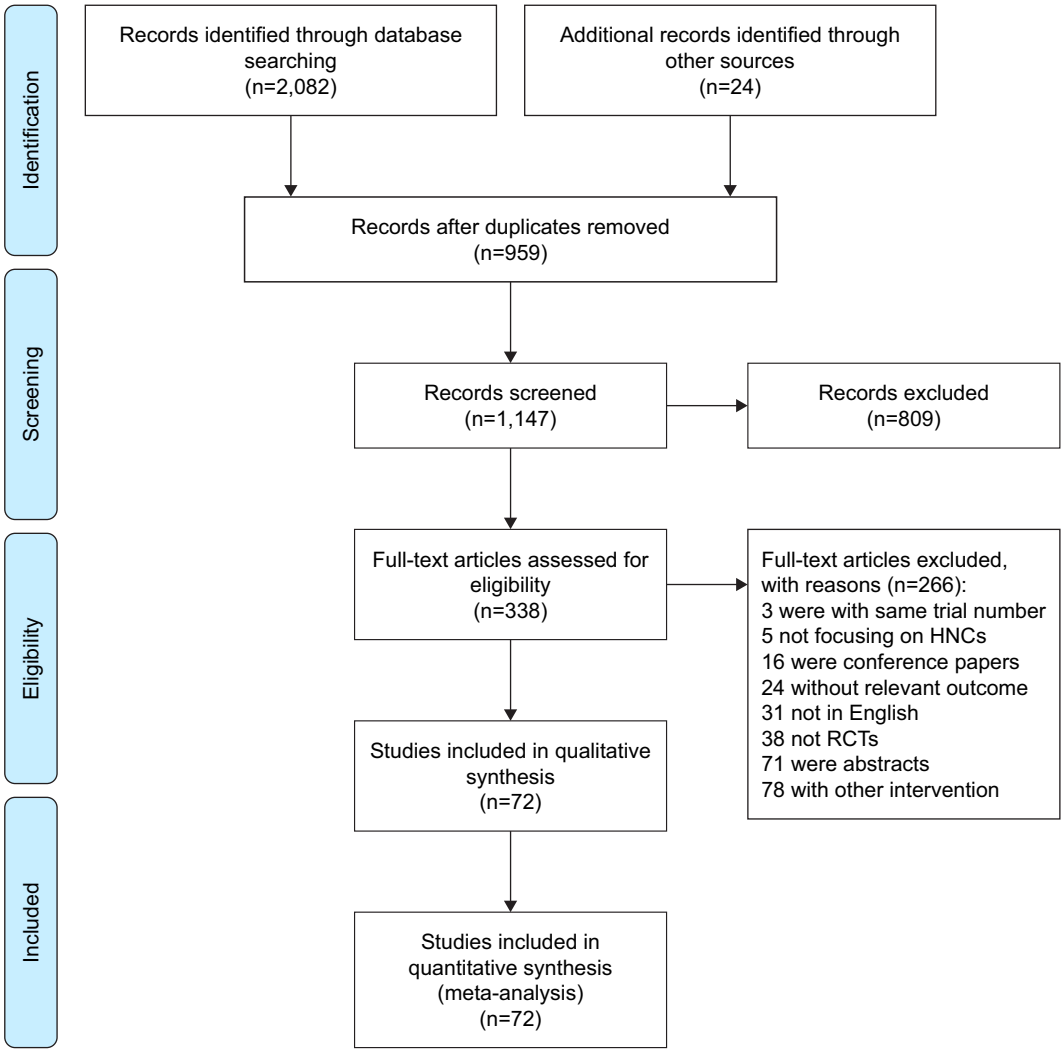


**Figure 1** PRISMA flow diagram.
**Abbreviations:** HNCs, head and neck cancers; RCTs, randomized controlled trials.

For DFS, HF_CRT, CF_CRT and AF conferred an advantage over CRT alone: the HRs (and corresponding 95% CrIs) were 0.56 (0.34–0.92), 0.76 (0.61–0.96) and 0.86 (0.76–0.97), respectively. The results also suggested a favorable DFS benefit of HF_CRT compared with HF (HR: 0.62, 95% CrI: 0.39–0.99). The SUCRA results depicted that the prognosis of HNC patients treated with HF_CRT was the best (SUCRA=89.3%) (Table 1 and Figure 3B). No evidence of significant differences between direct and indirect comparisons was detected ($P>0.05$).

Data on LRC were available for 43 trials. From the results, when compared with CF, HACRT, HART and AF demonstrated significantly higher LRC (HR: 0.53, 95% CrI: 0.37–0.74; HR: 0.75, 95% CrI: 0.58–0.96; and HR: 0.78, 95% CrI: 0.69–0.86, respectively). HART, AF, HF and CF_CRT were not significantly better than HACRT, with a range of significant mean HRs of 1.43–1.70. According to the rankings associated with the SUCRA values, HACRT was the most preferable treatment, with a SUCRA value of 91.3%, whereas AF_CRT and HF_CRT ranked second and third (SUCRA: 68.0% and 66.7%, respectively) (Table 2 and Figure 3C). Investigation of inconsistencies between direct and indirect evidence with node-splitting models detected that there were inconsistencies between AF and CF ($P=0.003$), AF and CF_CRT ($P=0.004$) and CF and CF_CRT ($P=0.002$).

## Safety outcomes

Acute toxicity and late toxicity could reflect the safety characteristics of the treatments. We assessed acute and late toxicity on skin and mucosa. With respect to serious (grade ≥3) acute skin toxicity, compared with CF, HF (RR: 1.60, 95% CrI: 1.06–2.40) and AF_CRT (RR: 1.62, 95% CrI: 1.11–2.51)

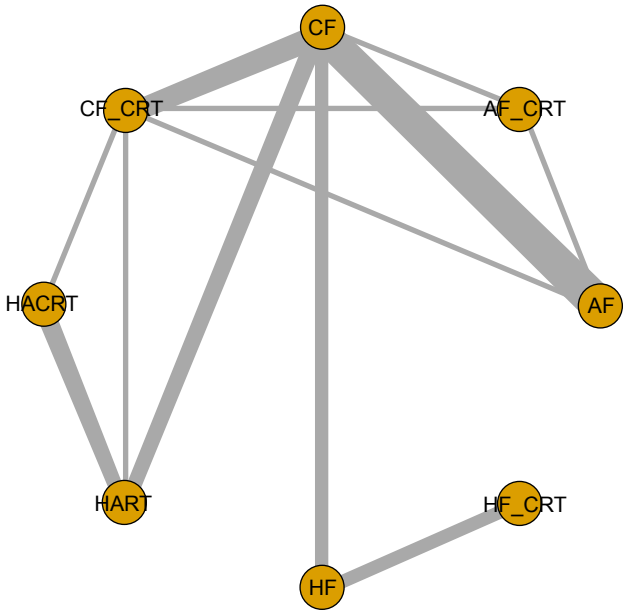


**Figure 2** Network plot for all the treatments included in the network meta-analysis.
**Abbreviations:** CF, conventional fractionation radiotherapy; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy.

were significantly associated with an increased risk, whereas AF_CRT yielded more acute skin toxicity than CF_CRT (RR: 1.47, 95% CrI: 1.05–2.26). For acute mucosal toxicity, CF showed a strong and favorable benefit compared with other treatments, with a mean RR effect size ranging from 0.38 to 0.94; HART and CF_CRT were not statistically significant (Table 3). The top three treatments ranked by their SUCRA values were HART (84.5%), HACRT (74.4%) and CF (67.5%) for acute skin toxicity, and CF (94.7%), CF_CRT (88.5%) and HART (54.1%) for acute mucosal toxicity. For late toxicity, only HF (RR: 3.26, 95% CrI: 1.38–8.31) was significantly associated with an increased risk for late mucosal toxicity compared with CF_CRT. No other significant difference was observed among other intervention comparison groups for late toxicity (Table 4). As shown in Figure 4, HF_CRT and HART had the highest probability of being the treatment approaches with the least amount of toxicity on skin and mucosa for HNCs, as their SUCRA values were 82.8% and 54.9%, respectively.

For acute skin toxicity, late skin toxicity and late mucosal toxicity, significant inconsistencies between direct and indirect evidence were not found among the various treatment comparisons. However, with respect to acute mucosal toxicity, the direct and indirect treatment effects between AF_CRT and AF ($P$=0.012) and CF_CRT and AF ($P$=0.032) seemed to be inconsistent.

## Discussion

Surgery is the mainstream treatment for patients with HNCs, but it leads to poor results. In attempts to improve patient outcomes, various forms of chemotherapy, radiotherapy, targeted therapy and immunotherapy have been introduced.

**Table 1** OS and DFS of treatments for head and neck cancer (HR [95% CrI])

| | **DFS** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **OS** | CF | 1.58 (0.85–2.98) | **1.79 (1.09–2.95)** | **1.31 (1.04–1.65)** | 1.29 (0.84–1.97) | **1.16 (1.03–1.32)** | 1.10 (0.95–1.32) | 1.06 (0.92–1.38) |
| | **0.64 (0.50–0.83)** | HACRT | 1.14 (0.51–2.46) | 0.83 (0.43–1.55) | 0.82 (0.39–1.66) | 0.74 (0.39–1.38) | 0.70 (0.37–1.33) | 0.68 (0.37–1.26) |
| | **0.64 (0.46–0.88)** | 0.99 (0.66–1.51) | HF_CRT | 0.74 (0.42–1.27) | 0.72 (0.37–1.37) | 0.65 (0.39–1.08) | **0.62 (0.39–0.99)** | 0.60 (0.36–1.06) |
| | **0.71 (0.60–0.83)** | 1.10 (0.83–1.46) | 1.11 (0.78–1.58) | CF_CRT | 0.98 (0.68–1.41) | 0.89 (0.70–1.14) | 0.84 (0.64–1.13) | 0.81 (0.63–1.14) |
| | **0.73 (0.58–0.90)** | 1.13 (0.81–1.57) | 1.14 (0.77–1.68) | 1.02 (0.82–1.28) | AF_CRT | 0.90 (0.59–1.41) | 0.86 (0.55–1.38) | 0.83 (0.55–1.39) |
| | **0.81 (0.72–0.91)** | 1.26 (0.96–1.67) | 1.27 (0.90–1.79) | 1.14 (0.96–1.36) | 1.12 (0.90–1.40) | AF | 0.95 (0.78–1.18) | 0.91 (0.76–1.22) |
| | **0.82 (0.66–1.02)** | 1.28 (0.92–1.80) | **1.29 (1.01–1.64)** | 1.16 (0.89–1.52) | 1.13 (0.83–1.55) | 1.01 (0.79–1.30) | HF | 0.96 (0.78–1.31) |
| | **0.83 (0.68–0.99)** | **1.28 (1.05–1.56)** | 1.30 (0.89–1.87) | 1.16 (0.93–1.45) | 1.14 (0.86–1.50) | 1.02 (0.82–1.26) | 1.01 (0.75–1.33) | HART |

**Notes:** Treatments are reported in the order of efficacy ranking. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the row-defining treatment and the column-defining treatment. Statistically significant results are in bold.
**Abbreviations:** OS, overall survival; DFS, disease-free survival; CrI, credible interval; CF, conventional fractionation radiotherapy; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy.

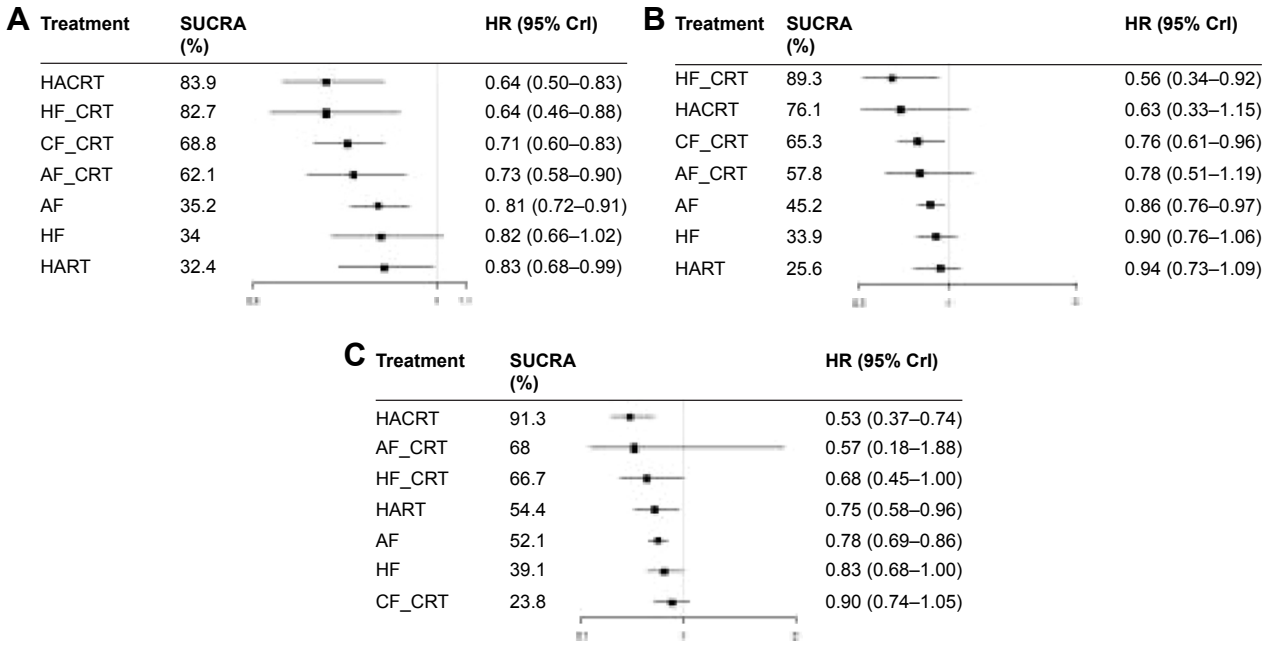


**Figure 3** Forest plots of efficacy of different treatments compared with conventional fractionation radiotherapy: (**A**) overall survival; (**B**) disease-free survival; and (**C**) locoregional control.

**Abbreviations:** CrI, credible interval; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy; SURCA, surface under the cumulative ranking curve.

Over the last several decades, a large body of high-quality evidence has shown that the addition of chemotherapy to radiotherapy[29,30] or altering the fractionation[31,32] consistently and convincingly improves outcomes in locoregionally advanced HNCs. However, there is no conclusion about which one among altered fractionation radiotherapy treatments has a better prognostic effect.

The main goal of our study was to verify the efficacy (OS, DFS and LRC) and safety (acute and late toxicity on skin and mucosa) of eight treatments (CF, CF_CRT, HF, HF_CRT, AF, AF_CRT, HART and HACRT). Seventy-two papers, which included a total of 21,868 patients with HNCs, were analyzed. We chose OS, which crucially depends on the observation time, as the primary outcome for our analysis.

**Table 2** LRC of treatments for head and neck cancer (HR [95% CrI])

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| CF | | | | | | | |
| **0.53 (0.37–0.74)** | HACRT | | | | | | |
| 0.57 (0.18–1.88) | 1.08 (0.33–3.78) | AF_CRT | | | | | |
| 0.68 (0.45–1.00) | 1.30 (0.82–1.99) | 1.19 (0.34–4.00) | HF_CRT | | | | |
| **0.75 (0.58–0.96)** | **1.43 (1.08–1.87)** | 1.32 (0.39–4.23) | 1.10 (0.78–1.57) | HART | | | |
| **0.78 (0.69–0.86)** | **1.48 (1.03–2.11)** | 1.36 (0.41–4.30) | 1.14 (0.77–1.73) | 1.03 (0.79–1.36) | AF | | |
| 0.83 (0.68–1.00) | **1.57 (1.07–2.32)** | 1.45 (0.43–4.64) | 1.21 (0.81–1.86) | 1.10 (0.81–1.51) | 1.06 (0.86–1.33) | HF | |
| 0.90 (0.74–1.05) | **1.70 (1.18–2.44)** | 1.56 (0.47–4.99) | 1.31 (0.87–2.02) | 1.19 (0.90–1.59) | 1.15 (0.96–1.37) | 1.09 (0.83–1.39) | CF_CRT |

**Notes:** Treatments are reported in the order of efficacy ranking. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the row-defining treatment and the column-defining treatment. Statistically significant results are in bold.

**Abbreviations:** LRC, locoregional control; CrI, credible interval; CF, conventional fractionation radiotherapy; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy.

**Table 3** Acute skin toxicity and acute mucosal toxicity of treatments for head and neck cancer (RR [95% CrI])

| | **Acute mucosal toxicity** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Acute skin toxicity** | CF | 0.66 (0.42–1.03) | **0.38 (0.19–0.72)** | 0.94 (0.73–1.22) | **0.59 (0.47–0.75)** | **0.63 (0.46–0.86)** | **0.54 (0.37–0.76)** | **0.58 (0.34–0.97)** |
| | 0.70 (0.28–1.58) | HART | 0.57 (0.31–1.01) | 1.42 (0.92–2.20) | 0.90 (0.56–1.45) | 0.94 (0.55–1.62) | 0.81 (0.47–1.37) | 0.87 (0.44–1.72) |
| | 0.76 (0.23–2.27) | 1.08 (0.50–2.32) | HACRT | **2.48 (1.35–4.84)** | 1.57 (0.82–3.17) | 1.66 (0.83–3.47) | 1.43 (0.71–2.93) | 1.52 (0.68–3.56) |
| | 1.11 (0.80–1.46) | 1.57 (0.71–3.82) | 1.46 (0.49–4.64) | CF_CRT | **0.63 (0.47–0.84)** | **0.67 (0.45–0.98)** | **0.57 (0.39–0.81)** | 0.61 (0.35–1.08) |
| | 1.14 (0.85–1.53) | 1.63 (0.71–4.14) | 1.51 (0.50–5.00) | 1.03 (0.76–1.45) | AF | 1.05 (0.75–1.48) | 0.91 (0.64–1.25) | 0.97 (0.56–1.66) |
| | **1.60 (1.06–2.40)** | 2.28 (0.93–6.06) | 2.12 (0.66–7.23) | 1.44 (0.93–2.32) | 1.40 (0.92–2.12) | HF | 0.86 (0.54–1.32) | 0.92 (0.60–1.40) |
| | **1.62 (1.11–2.51)** | 2.33 (1.00–6.15) | 2.15 (0.71–7.50) | **1.47 (1.05–2.26)** | 1.42 (1.00–2.16) | 1.02 (0.62–1.78) | AF_CRT | 1.07 (0.59–2.01) |
| | | | | | | | | HF_CRT |

**Notes:** Treatments are reported in the order of safety ranking. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the row-defining treatment and the column-defining treatment. Statistically significant results are in bold.

**Abbreviations:** RR, risk ratio; CrI, credible interval; CF, conventional fractionation radiotherapy; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy.

On the one hand, this measure is not biased by the outcome definition and assessment. On the other hand, it can comprehensively synthesize and cover nearly all deaths caused either by toxicity or by disease progression.

A mixed treatment comparison meta-analysis proved that among locoregional treatment, radiotherapy, chemotherapy, concomitant chemoradiotherapy, altered fractionation radiotherapy and altered fractionation concomitant chemoradiotherapy, the last one leads to the highest probability of survival in patients with nonmetastatic HNCs: 98% in a fixed effects model and ≥94% in a random effects model.[33]

Based on this study, we synthetically explored and compared each altered fractionation radiotherapy strategy or its combination with chemotherapy for the first time. Our results showed that each altered fractionation radiotherapy strategy was superior to conventional radiotherapy, which is consistent with the conclusions of previous research.[32]

In addition, the most important finding from our analysis was that HACRT was significantly more effective than all the other treatments. However, it may have been partially responsible for directing head and neck oncologists away from the altered fractionation radiotherapy,[34] whereas clinicians have

**Table 4** Late skin toxicity and late mucosal toxicity of treatments for head and neck cancer (RR [95% CrI])

| | **Late mucosal toxicity** | | | | | | |
|---|---|---|---|---|---|---|---|
| **Late skin toxicity** | CF | 1.01 (0.22–5.02) | 2.53 (0.84–9.50) | 0.69 (0.45–1.04) | 0.47 (0.16–1.29) | 1.54 (0.46–5.13) | 0.63 (0.43–0.86) |
| | 0.68 (0.08–4.22) | HART | 2.56 (0.36–19.0) | 0.67 (0.13–3.31) | 0.47 (0.09–2.04) | 1.54 (0.35–5.97) | 0.62 (0.12–2.91) |
| | 0.82 (0.21–2.86) | 1.22 (0.15–13.08) | HF_CRT | 0.27 (0.08–0.75) | 0.19 (0.03–0.81) | 0.60 (0.10–3.05) | 0.25 (0.06–074) |
| | 0.85 (0.49–1.41) | 1.24 (0.19–11.03) | 1.02 (0.32–3.55) | HF | 0.69 (0.23–1.99) | 2.25 (0.64–7.80) | 0.93 (0.58–1.37) |
| | 1.16 (0.25–4.43) | 1.69 (0.23–15.99) | 1.36 (0.21–9.49) | 1.37 (0.28–5.82) | AF_CRT | **3.26 (1.38–8.31)** | 1.34 (0.49–3.73) |
| | 1.23 (0.56–2.57) | 1.81 (0.35–13.12) | 1.47 (0.35–6.88) | 1.45 (0.59–3.51) | 1.07 (0.34–3.78) | CF_CRT | 0.41 (0.12–1.33) |
| | 1.32 (0.90–1.96) | 1.93 (0.31–16.60) | 1.61 (0.46–6.38) | 1.56 (0.93–2.74) | 1.15 (0.30–5.27) | 1.08 (0.52–2.38) | AF |

**Notes:** Treatments are reported in the order of safety ranking. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the row-defining treatment and the column-defining treatment. Statistically significant results are in bold.

**Abbreviations:** RR, risk ratio; CrI, credible interval; CF, conventional fractionation radiotherapy; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy.

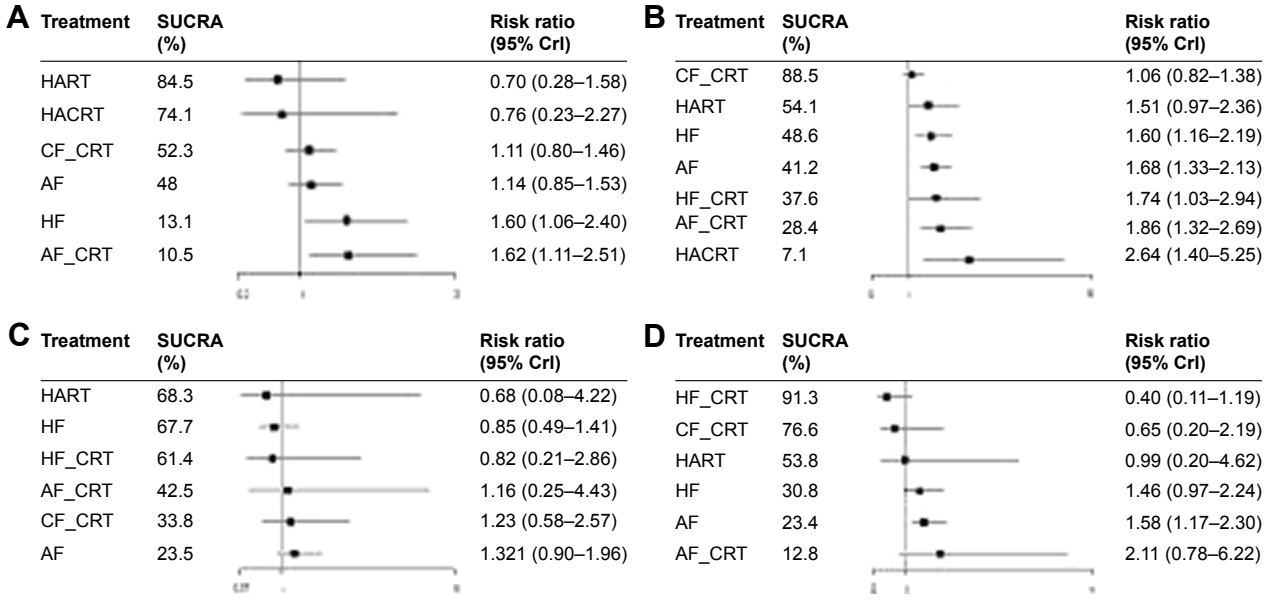


**Figure 4** Forest plots of safety of different treatments compared to conventional fractionation radiotherapy: (**A**) acute skin toxicity; (**B**) acute mucosal toxicity; (**C**) late skin toxicity; and (**D**) late mucosal toxicity.

**Abbreviations:** CrI, credible interval; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy; SUCRA, surface under the cumulative ranking curve.

readily adopted CF_CRT[35] as the contemporary standard of care in the radiotherapeutic management of locoregionally advanced HNCs. Most underdeveloped and developing countries (where HNC is a major burden) are lacking the radiotherapy infrastructure (equipment and human resources); therefore, patients must wait a long time for radiotherapy services.

Compared with traditional pairwise meta-analyses, NMA can present a comprehensive and transparent picture of hierarchies of combined direct and indirect evidence for all relative treatment effects and provide estimates with maximum power.[36–39] A pairwise meta-analysis directly comparing the efficacy of CF_CRT with altered fractionation radiotherapy alone in locoregionally advanced head and neck squamous cell carcinoma significantly favored CF_CRT for OS (HR: 0.73, 95% CI: 0.62–0.86), DFS (HR: 0.79, 95% CI: 0.68–0.92) and LRC (HR: 0.71, 95% CI: 0.59–0.84), and there were no significant differences in the incidence of severe acute toxicity (dermatitis and mucosa).[40] However, the results of an adjusted indirect overall comparison meta-analysis suggested no significant difference between them in OS,[41] which is in accordance with our NMA results. There were no significant differences between CF_CRT and other altered fractionation radiotherapy treatments in OS and DFS. CF_CRT, which had the lowest SUCRA value, exhibited the worst local control effect compared to the other treatments, but it showed the lowest risk of acute mucosal toxicity in its SUCRA ranking. In a meta-analysis, an OS benefit was also noted for patients treated with HF than with AF.[31] However, no significant differences were found.

In general, unconventional radiotherapy combined with chemotherapy has a better effect than unconventional radiotherapy alone, accompanied by the increased risk of acute toxicity; however, late toxicity was not significantly different. According to the recent evidence on both chemotherapy and radiotherapy, these schedules of altered fractionation radiotherapy are feasible and tolerable combined with concurrent chemotherapy.

The SUCRA results indicated that HACRT was the treatment with the best ranking in all three efficacy indexes but had a relatively acceptable risk of safety, which clinicians could adopt for curative treatment strategies through which patients may live for decades and be confident in its safety. Improvements in the understanding of tumor biology and advancement in radiotherapy planning and delivery may further enhance the utilization of altered fractionation radiotherapy.

This study is the most complete NMA to assess altered fractionation radiotherapy or its combination with chemotherapy in HNC compared with many treatments, which appeared to offer clearer results on their efficacy and safety. Furthermore, a comprehensive search strategy, strict selection criteria and a large amount of data (72 included studies with 21,868 patients) increased the reliability of

this analysis. However, there are several implicit limitations to our NMA. First, a few eligible studies reported data beyond 5 years with a limited follow-up period. The long-term relative efficacy and safety of these treatments have not been investigated in depth. Second, part of the included literature does not provide the corresponding outcome indicators directly. There will be some deviation in extracting the corresponding data from the survival curve. Third, the kind and dose of chemotherapy drugs and the timing of combination with chemotherapy (adjuvant, induction, alternating or concomitant) were not considered. There was a certain degree of difference between different drugs and the timing of chemotherapy in efficacy and safety, which may have a certain impact on our results. Fourth, we classified hybrid accelerated hyperfractionated, split- or late-course accelerated hyperfractionated and consecutive accelerated hyperfractionated as HART treatment. In future research, further advanced measures are compulsory for obtaining more accurate and appropriate results. Fifth, the results might be applied only to countries that have a well-developed medical infrastructure and an easily accessible healthcare system. Sixth, language restrictions on inclusion of the literature will lead to language selection bias. Exclusion of non-English studies may exclude studies that found a null effect and thus overestimate effectiveness.

## Conclusion

Our study presents a comprehensive and transparent picture of hierarchies of the efficacy and safety of altered fractionation radiotherapy with or without chemotherapy in the treatment of HNCs. The results of Bayesian analysis supported the role of HACRT as the preferable treatment modality for HNCs with high OS, DFS and LRC. However, its acute mucosal toxicity is relatively significant. Therefore, cautious and individualized treatment decisions are encouraged.

## Acknowledgments

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## Disclosure

The authors report no conflicts of interest in this work.

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# Supplementary materials

## Search strategies

### PubMed

**#1**

(("Head and Neck Neoplasms"[Mesh])) OR ((((((((((((((((((((((Head[Title/Abstract] AND Neck Neoplasms[Title/Abstract])) OR (Neoplasms, Head[Title/Abstract] AND Neck[Title/Abstract])) OR Head, Neck Neoplasms[Title/Abstract]) OR (Cancer of Head[Title/Abstract] AND Neck[Title/Abstract])) OR (Head[Title/Abstract] AND Neck Cancer[Title/Abstract])) OR (Cancer of the Head[Title/Abstract] AND Neck[Title/Abstract])) OR Upper Aerodigestive Tract Neoplasms[Title/Abstract]) OR UADT Neoplasms[Title/Abstract]) OR Neoplasm, UADT[Title/Abstract]) OR Neoplasms, UADT[Title/Abstract]) OR UADT Neoplasm[Title/Abstract]) OR Neoplasms, Upper Aerodigestive Tract[Title/Abstract]) OR Head Neoplasms[Title/Abstract]) OR Neoplasms, Head[Title/Abstract]) OR Neck Neoplasms[Title/Abstract]) OR Neoplasms, Neck[Title/Abstract]) OR Cancer of Head[Title/Abstract]) OR Head Cancer[Title/Abstract]) OR Cancer of the Head[Title/Abstract]) OR Cancer of Neck[Title/Abstract]) OR Neck Cancer[Title/Abstract]) OR Cancer of the Neck[Title/Abstract])

**#2**

((((cancer*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR tumor*[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinom*[Title/Abstract]

**#3**

(((((((head[Title/Abstract]) OR neck[Title/Abstract]) OR larynx[Title/Abstract]) OR pharnyx[Title/Abstract]) OR oropharyn*[Title/Abstract]) OR hypopharyn*[Title/Abstract]) OR laryn*[Title/Abstract]) OR oral cavity[Title/Abstract]

**#4**

#2 and #3

**#5**

#1 or #4

**#6**

((hyperfraction*[Title/Abstract]) OR accelerat*[Title/Abstract]) OR fractionat*[Title/Abstract]

**#7**

(Randomized Controlled Trial[Publication Type]) OR random*

**#8**

#5 and #6 and #7

### Embase

**#1**

'head and neck tumor'/exp

**#2**

cancer* OR neoplas* OR tumor* OR tumour* OR carcinom*:ti,ab

**#3**

'head'/exp OR head OR 'neck'/exp OR neck OR 'larynx'/exp OR larynx OR pharnyx OR oropharyn* OR hypopharyn* OR laryn* OR oral AND cavity:ti,ab

**#4**

#2 AND #3

**#5**

#1 OR #4

**#6**

hyperfraction* OR accelerat* OR fractionat*:ti,ab

**#7**

random*

**#8**

#5 AND #6 AND #7

### Cochrane Library

**#1**

MeSH descriptor: [Head and Neck Neoplasms] explode all trees

**#2**

cancer*:ti,ab,kw or neoplas*:ti,ab,kw or tumor*:ti,ab,kw or tumour*:ti,ab,kw or carcinom*:ti,ab,kw (Word variations have been searched)

**#3**

head:ti,ab,kw or neck:ti,ab,kw or larynx:ti,ab,kw or pharnyx:ti,ab,kw or oropharyn*:ti,ab,kw or hypopharyn*:ti,ab,kw or laryn*:ti,ab,kw or oral cavity:ti,ab,kw
(Word variations have been searched)

**#4**

#2 and #3

**#5**

#1 and #4

**#6**

hyperfraction*:ti,ab,kw or accelerat*:ti,ab,kw or fractionat*:ti,ab,kw (Word variations have been searched)

**#7**

random* (Word variations have been searched)

**#8**

#5 and #6 and #7

**Table S1** Description of included studies

| No | Reference | Subject | Age[a] | Gender (M/F) | Tumor site | Stage | Follow-up (median or mean) | Arm | Dose/ fraction (Gy) | Total dose (Gy) | Chemotherapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Marcial et al (1987)[1] | 187 | 64[b] | 134/53 | Oral cavity, pharynx, larynx and paranasal sinuses | III–IV | – | HF | 1.2 | 60 | |
| | | | | | | | | CF | 1.8–2.0 | 66.0–73.8 | |
| 2 | Sanchiz et al (1990)[2] | 859 | 56 (30–75) | 802/57 | – | T3–T4, N0–N3, M0 | – | AF | – | 70.4 | |
| | | | | | | | | AF_CRT | 2 | 60 | 5-fluorouracil 250 mg/m$^2$ |
| | | | | | | | | CF | 2 | 60 | |
| 3 | Pinto et al (1991)[3] | 98 | 39–70 | 84/14 | Oropharynx | III–IV | 22.5 months | HF | 1.1 | 70.4 | |
| | | | | | | | | CF | 2 | 66 | |
| 4 | Horiot et al (1992)[4] | 325 | – | – | Oropharynx | T2–T3 | ≥200 weeks | HF | 1.15 | 80.5 | |
| | | | | | | | | CF | 2 | 70 | |
| 5 | Bogaert et al (1995)[5] | 498 | – | 456/42 | – | – | – | CF | 2 | 75 | |
| | | | | | | | | HART | 1.6 | 67.2–72 | |
| 6 | Chan et al (1995)[6] | 77 | – | 69/8 | Nasopharynx and neck | N1–N3 | 28.5 months | CF_CRT | – | 58–66 | Cisplatin 100 mg/m$^2$ and 5-fluorouracil 1,000 mg/m$^2$ |
| | | | | | | | | CF | – | 58–66 | |
| 7 | Antognoni et al (1996)[7] | 69 | 60[b] (40–75) | 58/11 | Oral cavity and oropharynx | II–IV | 18 months | CF | 2 | 66 | |
| | | | | | | | | AF | 2 | 66 | |
| 8 | Merlano et al (1996)[8] | 157 | – | 131/26 | Pharynx, larynx or oral cavity | III–IV | – | CF_CRT | 2 | 60 | Cisplatin 20 mg/m$^2$ and fluorouracil 200 mg/m$^2$ |
| | | | | | | | | CF | 2 | 70 | |
| 9 | Corvo et al (1997)[9] | 40 | – | 35/5 | Oral cavity, oropharynx, larynx and nasopharynx | III–IV | 30 months | AF | 1.5 | 60 | |
| | | | | | | | | CF_CRT | 2 | – | Cis-platinum 20 mg/m$^2$/day and fluorouracil 200 mg/m$^2$/day |
| 10 | Dische et al (1997)[10] | 918 | – | 687/231 | Nasal sinus, nasopharynx, oral cavity, oropharynx, hypopharynx and larynx | T1–T4, N0–N3 | – | HART | 1.5 | 54 | |
| | | | | | | | | CF | 2 | 66 | |
| 11 | Horiot et al (1997)[11] | 500 | 57[b] | 450/50 | Hypopharynx excluded | T2–T4 | 4 years and 9 months | AF | 1.6 | 72 | |
| | | | | | | | | CF | 1.8–2.0 | 70 | |
| 12 | Brizel et al (1998)[12] | 116 | 59[b] | 96/20 | – | T2–T4, N0–N3 | 41 months | HF_CRT | 1.25 | 70 | Cisplatin 12 mg/m$^2$/day and fluorouracil 600 mg/m$^2$/day |
| | | | | | | | | HF | 1.25 | 75 | |
| 13 | Calais et al (1999)[13] | 222 | 55[b] (32–74) | 200/22 | Oropharynx | III–IV | 35 months | CF_CRT | 2 | 70 | Carboplatin 70 mg/m$^2$/day and 5-flourouracil 600 mg/m$^2$/day |
| | | | | | | | | CF | 2 | 70 | |
| 14 | Shi et al (1999)[14] | 85 | – | 50/30 | Esophagus | – | – | HART | 1.5 | 68.4 | |
| | | | | | | | | CF | 1.8 | 68.4 | |
| 15 | Dobrowsky and Naude (2000)[15] | 239 | 57 (31–77) | 203/36 | Oral cavity, oropharynx, larynx and hypopharynx | T1–T4, N0–N3 | 48 months | HART | 1.65 | 55.3 | |
| | | | | | | | | CF | 2 | 70 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 16 | Fu et al (2000)[16] | 1,073 | 30–90 | 854/219 | Oral cavity, oropharynx, supraglottic larynx, tongue or hypopharynx | II–IV | 23 months | HF<br>CF<br>AF<br>AF | 1.2<br>2<br>1.6<br>1.8 | 81.6<br>70<br>67.2<br>72 | |
| 17 | Jeremic et al (2000)[17] | 130 | – | – | Nasopharynx, oropharynx, hypopharynx, oral cavity or larynx | III–IV, M0 | 79 months | HF_CRT<br>HF | 1.1<br>1.1 | 77<br>77 | Cisplatin 6 mg/m$^2$/day |
| 18 | Skladowski et al (2000)[18] | 100 | 35–70 | – | Oral cavity, oropharynx, supraglottic larynx and hypopharynx | T2–T4, N0–N1, M0 | 37 months | AF<br>CF | –<br>1.8–2.0 | 64–76<br>60–74 | |
| 19 | Teo et al (2000)[19] | 159 | – | – | Nasopharynx | II–IV | 59.2 months | HART<br>CF | 1.6<br>2.5 | –<br>– | |
| 20 | Chua et al (2001)[20] | 136 | – | 121/15 | Oral cavity, pharynx and larynx | II–IV | 60 months | CF_CRT<br>AF | 2<br>1.5 | 60<br>75 | Cisplatin 20 mg/m$^2$/day and fluorouracil 200 mg/m$^2$/day |
| 21 | El-Weshi et al (2001)[21] | 50 | 39.9 (18–63) | 40/10 | Nasopharynx | III–IV | 55 months | HACRT<br>CF_CRT | 1.6<br>2 | 72<br>72 | Cisplatin 80 mg/m$^2$/day and 5-fluorouracil 750 mg/m$^2$/day |
| 22 | Poulsen et al (2001)[22] | 343 | 62 (34–82) | 279/64 | Oral cavity, oropharynx, hypopharynx or larynx | III–IV | 53 months | AF<br>CF | 1.8<br>2 | 59.4<br>70 | |
| 23 | Staar et al (2001)[23] | 240 | 57 (28–73) | 204/36 | Oropharynx and hypopharynx | III–IV | 22.3 months | HACRT<br>HART | 1.8<br>1.5 | 69.9<br>69.9 | 5-Fluorouracil 600 mg/m$^2$/day and carboplatinum 70 mg/m$^2$ |
| 24 | Awwad et al (2002)[24] | 70 | 50 (25–65) | 56/14 | Oral cavity, larynx and hypopharynx | T2–T4 | – | HART<br>CF | 1.4<br>2 | 46.2<br>60 | |
| 25 | Bartelink et al (2002)[25] | 59 | – | 38/11 | Oral cavity, oropharynx, larynx and hypopharynx | T2–T4 | – | HACRT<br>CF_CRT | 1.6<br>2 | –<br>– | Cisplatin 10 mg/m$^2$<br>Cisplatin 6 mg/m$^2$ |
| 26 | Gao et al (2002)[26] | 81 | 40–70 | 56/25 | – | – | – | HACRT<br>HART | 1.5–2<br>1.5–2 | –<br>– | Cisplatin 20 mg/day |
| 27 | Hliniak et al (2002)[27] | 395 | – | 339/56 | Glottis and supraglottic larynx | T1–T3, N0, M0 | 28 months | AF<br>CF | 2<br>2 | 66<br>66 | |
| 28 | Adelstein et al (2003)[28] | 182 | 57 (25–80) | 162/20 | Oral cavity, oropharynx, hypopharynx and larynx | III–IV | 41 months | CF_CRT<br>CF | 2<br>2 | 70<br>70 | Cisplatin |
| 29 | Olmi et al (2003)[29] | 192 | 56.1 (38–70) | 170/22 | Oropharynx | III–IV | – | CF<br>CF_CRT<br>HART | 2<br>2<br>1.6 | 66–70<br>66–70<br>64–67.2 | Carboplatin 75 mg/m$^2$ and 5-fluorouracil 1,000 mg/m$^2$ |
| 30 | Overgaard et al (2003)[30] | 1,476 | 62 (20–88) | 1,229/247 | Glottis, supraglottis, pharynx and oral cavity | T1–T4 | – | AF<br>CF | 2<br>2 | 62–68<br>62–68 | |
| 31 | Fountzilas et al (2004)[31] | 124 | 31–78 | 106/18 | Oral cavity, oropharynx, hypopharynx or larynx | III–IV | 5 years | CF_CRT<br>CF<br>CF_CRT | –<br>–<br>– | 70<br>70<br>70 | Cisplatin 100 mg/m$^2$<br><br>Carboplatin |

(*Continued*)

**Table S1** (*Continued*)

| No | Reference | Subject | Age[a] | Gender (M/F) | Tumor site | Stage | Follow-up (median or mean) | Arm | Dose/ fraction (Gy) | Total dose (Gy) | Chemotherapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 32 | Hehr et al (2004)[32] | 42 | 34–70 | 37/5 | – | III–IV | 44 months | HACRT | – | 69.0–72.0 | Mitomycin C 10 mg/m$^2$ and 5-fluorouracil 600 mg/m$^2$ |
| | | | | | | | | HART | – | 70.6–78.2 | |
| 33 | Huguenin et al (2004)[33] | 224 | 33–74 | 190/34 | Excluding nasopharynx and paranasal sinus | – | 39.5 months | HF_CRT | 1.2 | 74.4 | Cisplatin 20 mg/m$^2$ |
| | | | | | | | | HF | 1.2 | 74.4 | |
| 34 | Budach et al (2005)[34] | 384 | 54.5[b] (33–71) | 322/62 | Oropharynx, hypopharynx and oral cavity | III–IV | – | HACRT | 1.4–2 | 70.6 | Fluorouracil 600 mg/m$^2$ and mitomycin 10 mg/m$^2$ |
| | | | | | | | | HART | 1.4–2 | 77.6 | |
| 35 | Ezzat et al (2005)[35] | 60 | 52[b] | 20/40 | Oral cavity, oropharynx, hypopharynx and larynx | III–IV | 10.5 months | AF | – | 68 | |
| | | | | | | | | CF | – | 68 | |
| 36 | Lee et al (2005)[36] | 348 | 46.5[b] | 263/85 | Nasopharynx | N2–N3 | 2.3 years | CF_CRT | 2 | – | Cisplatin 100 mg/m$^2$ and fluorouracil 1,000 mg/m$^2$/day |
| | | | | | | | | CF | 2 | – | |
| 37 | Sanguineti et al (2005)[37] | 226 | 61.5[b] (30–82) | 209/17 | Oral cavity, oropharynx, hypopharynx or larynx | – | 30.6 months | AF | 2 | 60 | |
| | | | | | | | | CF | 2 | 50 | |
| 38 | Zhao et al (2005)[38] | 111 | 39–74 | 78/33 | Esophagus | T1–T4, N0–N1, M0 | – | HACRT | 1.5–1.8 | 68.4 | Cisplatin 25 mg/m$^2$/day and 5-fluorouracil 600 mg/m$^2$/day |
| | | | | | | | | HART | 1.5–1.8 | 68.4 | |
| 39 | Bensadoun et al (2006)[39] | 163 | 54 (38–76) | 144/19 | Oropharynx or hypopharynx | IV | – | HF_CRT | 1.2 | – | Cisplatin 100 mg/m$^2$ and 5-fluorouracil 750 mg/m$^2$/day |
| | | | | | | | | HF | 1.2 | – | |
| 40 | Bourhis et al (2006)[40] | 266 | – | – | Oropharynx, oral cavity, hypopharynx or larynx | T3–T4, N0–N3 | >6 years | AF | 2 | 63 | |
| | | | | | | | | CF | 2 | 70 | |
| 41 | Fallai et al (2006)[41] | 192 | – | 170/22 | Oropharynx | III–IV | 8.35 years | HART | 1.6 | 64–67.2 | |
| | | | | | | | | CF_CRT | – | 66–70 | Carboplatin 75 mg/m$^2$ and 5-fluorouracil 1,000 mg/m$^2$ |
| | | | | | | | | CF | – | 66–70 | |
| 42 | Semrau et al (2006)[42] | 240 | 57 (28–73) | 204/36 | Oropharynx and hypopharynx | III–IV | 57 months | HACRT | 1.5–1.8 | – | Carboplatin 70 mg/m$^2$/day and 5-fluorouracil 600 mg/m$^2$/day |
| | | | | | | | | HART | 1.5–1.8 | – | |
| 43 | Skladowski et al (2006)[43] | 100 | 35–70 | – | Oral cavity, oropharynx, hypopharynx and supraglottic larynx | T2–T4, N0–N1, M0 | 96 months | AF | – | 66–70 | |
| | | | | | | | | CF | – | 66–70 | |
| 44 | Cummings et al (2007)[44] | 331 | 31–75 | 271/60 | Oropharynx, hypopharynx or larynx | T3–T4 | 6.9 years | HF | – | 58 | |
| | | | | | | | | CF | – | 51 | |
| 45 | Daoud et al (2007)[45] | 154 | 42.8 (10–62) | 104/50 | Nasopharynx | – | 56 months | CF | 2 | 50–70 | |
| | | | | | | | | HF | 1.6 | 21.2–70.4 | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 46 | Katori et al (2007)[46] | 50 | 58.1[b] (48–74) | 43/7 | Nasopharynx, mesopharynx, hypopharynx, larynx, oral cavity or paranasal sinus | III–IV | 42 months | HF<br>CF | 1.2<br>2 | 76.8<br>70 | |
| 47 | Ghoshal et al (2008)[47] | 285 | 53[b] (28–78) | 252/33 | Oropharynx, larynx and hypopharynx | III–IV, M0 | 24 months | AF<br>CF | –<br>2 | 67.5<br>66 | |
| 48 | Overgaard et al (2010)[48] | 900 | 58 (22–85) | 723/177 | Larynx, pharynx and oral cavity | I–IV | 99 months | AF<br>CF | | 66–70<br>66–70 | |
| 49 | Saunders et al (2010)[49] | 918 | – | – | – | T2–T4, N0–N1, M0 | – | HART<br>CF | 1.5<br>2 | 54<br>66 | |
| 50 | Bourhis et al (2011)[50] | 109 | 55[b] | 99/10 | – | – | 11.9 years | AF_CRT<br>AF | 2<br>2 | 62–64<br>64 | Cisplatin 100 mg/m$^2$ and 5-fluorouracil 1 g/m$^2$/day |
| 51 | Lee et al (2011)[51] | 189 | 48[b] (25–68) | 147/42 | Nasopharynx | T3–T4, N0–N1 | 6.3 years | AF<br>CF<br>CF_CRT<br>AF_CRT | 2<br>2<br>2<br>2 | 69±5<br>69±3<br>68±7<br>69±3 | <br><br>Cisplatin 80–100 mg/m$^2$ and fluorouracil 1,000 mg/m$^2$/day<br>Cisplatin 80–100 mg/m$^2$ and fluorouracil 1,000 mg/m$^2$/day |
| 52 | Zackrisson et al (2011)[52] | 733 | 26–91 | 548/185 | Oral cavity, oropharynx, larynx and hypopharynx | I–IV | 5.1 years | AF<br>CF | 1.1+2.0<br>2 | 68<br>68 | |
| 53 | Bourhis et al (2012)[53] | 840 | 57[b] (34–75) | 731/109 | Oropharynx, oral cavity, hypopharynx and larynx | III–IV | 5.2 years | AF_CRT<br>AF<br>CF_CRT | 1.5–2<br>1.8<br>2 | 70<br>64.8<br>70 | Carboplatin 70 mg/m$^2$/day and fluorouracil 600 mg/m$^2$/day<br><br>Carboplatin 70 mg/m$^2$/day and fluorouracil 600 mg/m$^2$/day |
| 54 | Ghadjar et al (2012)[54] | 224 | 33–74 | 190/34 | Oral cavity, oro- or hypopharynx or larynx | II–IV | 9.5 years | HF<br>HF_CRT | 1.2<br>1.2 | 74.4<br>74.4 | <br>Cisplatin 20 mg/m$^2$ |
| 55 | Liu et al (2012)[55] | 111 | 39–74 | 78/33 | Esophagus | – | 24 months | HACRT<br>HART | 1.5–1.8<br>1.5–1.8 | 68.4<br>68.4 | Cis-platinum 25 mg/m$^2$ daily and 5-fluorouracil 600 mg/m$^2$ |
| 56 | Pan et al (2012)[56] | 200 | 49 (18–70) | 150/50 | nasopharynx | I–IV | 6.9 years | HART<br>CF | 1.2–1.5<br>2 | 78<br>70 | |
| 57 | Wang et al (2012)[57] | 98 | 55–74 | 63/35 | Esophagus | – | 45 months | HART<br>CF | 1.5<br>2 | 61–67<br>60–68 | |
| 58 | Chitapanarux et al (2013)[58] | 85 | 28–77 | 64/21 | Head and neck (except nasopharynx, nasal cavity and paranasal sinus and salivary gland) | III–IV | 43 months | CF_CRT<br>HART | 2<br>1.2–2.0 | 66<br>70 | Carboplatin 70 mg/m$^2$/day and 5-fluorouracil 600 mg/m$^2$/day |
| 59 | Ghadjar et al (2013)[59] | 224 | – | – | Oral cavity, oro- or hypopharynx or larynx | – | – | HF<br>HF_CRT | 1.2<br>1.2 | 74.4<br>74.4 | <br>Cisplatin 20 mg/m$^2$ |

(*Continued*)

**Table S1** (*Continued*)

| No | Reference | Subject | Age[a] | Gender (M/F) | Tumor site | Stage | Follow-up (median or mean) | Arm | Dose/ fraction (Gy) | Total dose (Gy) | Chemotherapy |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 60 | Majumder et al (2013)[60] | 64 | 42–72 | 50/14 | – | III–IV | – | CF_CRT | | 66 | Cisplatin 30 mg/m$^2$ |
| | | | | | | | | HF | 1.4 | 72 | |
| | | | | | | | | AF | | 66 | |
| 61 | Beitler et al (2014)[61] | 1,076 | – | – | Oral cavity, oropharynx, larynx and hypopharynx | III–IV | 14.1 years | HF | 1.2 | 81.6 | |
| | | | | | | | | AF | 1.6 | 67.2 | |
| | | | | | | | | AF | 1.8 | 72 | |
| | | | | | | | | CF | 2 | 70 | |
| 62 | Miszczyk et al (2014)[62] | 101 | 57 (42–73) | 78/23 | Excluding nasopharynx | T2N3, T3N03 and T4N0–N3 | – | HART | 1.6 | 64 | |
| | | | | | | | | CF | 2 | 72–74 | |
| 63 | Nguyen-Tan et al (2014)[63] | 721 | 26–82 | 597/124 | Oral cavity, oropharynx, hypopharynx or larynx | III–IV (excludingT1N or T2N1) | 7.9 years | AF_CRT | – | 72 | Cisplatin 100 mg/m$^2$ |
| | | | | | | | | CF_CRT | – | 70 | |
| 64 | Trotti et al (2014)[64] | 239 | 28–91 | 224/15 | Vocal cord | T2 | 7.9 years | CF | 2 | 70 | |
| | | | | | | | | HF | 1.2 | 79.2 | |
| 65 | Budach et al (2015)[65] | 384 | 33–71 | 322/62 | Oropharynx, hypopharynx and oral cavity | III–IV | 8.7 years | HACRT | 1.4–2.0 | 70.6 | 5-fluorouracil 600 mg/m$^2$ and mitomycin C 10 mg/m$^2$ |
| | | | | | | | | HART | 1.4–2.0 | 77.6 | |
| 66 | Gupta et al (2015)[66] | 109 | 56 (22–78) | 96/13 | Larynx, oropharynx and hypopharynx | T1–T4, N0–N3, M0 | 43 months | CF | – | 66 | |
| | | | | | | | | AF | – | 66 | |
| 67 | Kong et al (2015)[67] | 200 | 51[b] | 124/76 | Nasopharynx | III–IV | – | CF_CRT | 1.8–2.0 | – | Cisplatin 20 mg/m$^2$ and 5-fluorouracil 750 mg/m$^2$ |
| | | | | | | | | CF | 1.8–2.0 | – | |
| 68 | Lee et al (2015)[68] | 706 | – | – | Nasopharynx | III–IVB | 3.3 years | AF_CRT | – | – | Cisplatin 100 mg/m$^2$ |
| | | | | | | | | CF_CRT | – | – | Cisplatin 100 mg/m$^2$ |
| 69 | Lyhne et al (2015)[69] | 690 | 64.5 (25–87) | 637/53 | Glottic larynx | I–IV | 14.5 years | AF | – | 68 | |
| | | | | | | | | CF | – | 68 | |
| 70 | Zackrisson et al (2015)[70] | 733 | 62 (26–91) | 548/185 | Oral cavity, oropharynx, larynx and hypopharynx | I–IV | 9.1 years | AF | 1.1+2 | 68 | |
| | | | | | | | | CF | 2 | 68 | |
| 71 | Alam et al (2016)[71] | 60 | – | – | Oral cavity, oropharynx, larynx and hypopharynx | III–IV | 18 months | CF_CRT | – | 70 | Cisplatin 30 mg/m$^2$ |
| | | | | | | | | AF_CRT | – | 70 | Cisplatin 30 mg/m$^2$ |
| 72 | Ghosh Laskar et al (2016)[72] | 186 | 24–76 | 176/10 | Non-nasopharynx | II–IV | 54 months | CF_CRT | 2 | 66–70 | Cisplatin 30 mg/m$^2$ |
| | | | | | | | | AF | 2 | 66–70 | |
| | | | | | | | | CF | 2 | 66–70 | |

**Notes:** [a]Age was presented as median (range from min to max). [b]Age was presented as mean.

**Abbreviations:** CF, conventional fractionation radiotherapy; CF_CRT, conventional fractionation chemoradiotherapy; HF, hyperfractionated radiotherapy; HF_CRT, hyperfractionated chemoradiotherapy; AF, accelerated fractionation radiotherapy; AF_CRT, accelerated fractionation chemoradiotherapy; HART, accelerated hyperfractionated radiotherapy; HACRT, accelerated hyperfractionated chemoradiotherapy.

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