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Locally advanced squamous cell carcinoma of the head and neck: A systematic review and bayesian network meta-analysis of the currently available treatment options

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ABSTRACT

Background: There are still many unresolved questions in the management of locally advanced Head and Neck Cancer (HNC). Many chemotherapeutic drugs and radiotherapy fractionation schemes are available and not all have been evaluated in head-to-head clinical trials. This systematic review and bayesian network meta-analysis aims to compare the available treatment strategies and chemotherapeutic options for locally advanced HNC.

Methods: We performed a search on bibliography databases, trials registries and meetings proceedings for published and unpublished randomized trials from January 1st 2000 to December 1st 2017. Trials had to compare systemic interventions and radiotherapy (RT) approaches for locally advanced, non-metastatic HNC. Trials recruiting patients whose surgery was the first treatment option, sample size less than 20 per arm or that did not use randomization for treatment allocation were excluded from the analysis. Summary estimates on Overall survival (OS), Progression-free survival (PFS) and toxicity outcomes (grade 3–4 mucositis and neutropenia) were extracted from the included studies on a predefined database sheet. Bias was assessed through the Chocrane risk of bias assessment tool. We performed a set of pair-wise meta-analyses using a random effect model. We also performed a random effect network meta-analysis under a bayesian framework.

Findings: From the 57 included trials, including 15,723 patients, was possible to conduct analysis on 26 treatments for OS, 22 treatments for PFS and 10 treatments for toxicity. In terms of OS Concurrent chemoradiotherapy (CCRT) with cisplatin (HR 0.70, 95% CrI [credible interval] 0.62–0.78) and cetuximab on top of CCRT (HR 0.7, 95% CrI 0.5–0.97) are clearly superior to conventional RT alone. Induction chemotherapy (IC) with cisplatin and fluorouracil (HR 0.74, 95% CrI 0.52–0.95), IC with docetaxel, cisplatin, fluorouracil (HR 0.55, 95% CrI 0.54–0.89) and IC with paclitaxel, cisplatin, fluorouracil (HR 0.55, 95% CrI 0.34–0.89) before CCRT are all superior to conventional RT. CCRT with cisplatin is also superior to altered fractionation RT (HR 0.74, 95% CrI 0.64–0.84). Altered fractionation RT is not superior to conventional RT (HR 0.95, 95% CrI 0.85–1.06). Regarding PFS, CCRT with cisplatin (HR 0.72, 95% CrI 0.63–0.83), cisplatin and fluorouracil (HR 0.67, 95% CrI 0.5–0.88), carboplatin (HR 0.63, 95% CrI 0.46–0.87), carboplatin and fluorouracil (HR 0.75, 95% CrI 0.56–1), IC with cisplatin and fluorouracil (HR 0.59, 95% CrI 0.45–0.78), IC with docetaxel, cisplatin and fluorouracil (HR 0.53, 95% CrI 0.41–0.68) and IC with paclitaxel, cisplatin and fluorouracil (HR 0.59, 95% CrI 0.35–0.99) are superior to conventional RT and altered fractionation RT. IC with docetaxel, cisplatin and fluorouracil shows a significant superiority against CCRT with cisplatin (HR 0.73 95% CrI 0.58–0.92). Altered fractionation RT is not superior to conventional RT (HR 0.91, 95% CrI 0.81–1.02).

Altered fractionation increases the risk of developing grade 3–4 mucositis compared to conventional RT (OR 3.74 95% 1.64–8.67)

Interpretation: CCRT with cisplatin remains the gold standard of treatment. Taxane based IC regimens may have a impact on locally advanced disease. Altered fractionation RT is inferior to CCRT and also does not seem to be

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meaningfully better than conventionally fractionated RT alone. Its role in locally advanced disease should be reevaluated.

Introduction

Head and neck cancer (HNC) is not uncommon, accounting for approximately 6% cancer cases and 2% of cancer related deaths worldwide. The vast majority of HNC are squamous cell carcinomas. Epidemiology trends have a wide variability depending on the geographic region examined. The annual incidence is estimated to be 43/100,000 in Europe and 16/100,000 in United States. Male to female ratio ranges from 2:1 to 4:1. Environmental factors, such as alcohol consumption, tobacco use and hpv virus infection play a major role in the pathogenesis of these cancers [1].

Most patients at diagnosis present with locally advanced HNC, whose management is challenging and generally relies on the involvement of a multidisciplinary team. Despite aggressive treatment, prognosis is poor and continuous research efforts are being made in order to improve the life expectancy of the affected patients.

Concurrent chemoradiotherapy (CCRT) with cisplatin is one of the most frequently used treatment options. On the other hand, there are still many unresolved questions on how to optimally manage locally advanced HNC [2]. Many chemotherapy drugs and schemes are available and multiple randomized trials have evaluated different treatment regimens between each other or against Radiotherapy (RT) alone. Moreover, new treatment options such as monoclonal antibodies targeting the EGFR receptor, new radiotherapy fractionation schedules and induction or adjuvant chemotherapy regimens have been developed and tested in phase II/III randomized trials. All this contributes to add more data to an already fragmented scenario. Traditional meta-analyses allow to gather the available evidence on a given topic and synthesize it to give an overall result favoring one treatment over another. When more than two treatment options are available and tested in multiple studies, a network meta-analysis allows to combine direct and indirect evidence to establish the likely best treatment [3]. In light of this, we decided to conduct a systematic review, a traditional pairwise meta-analysis and a bayesian network meta-analysis of phase II or III randomized clinical trials to compare and rank the available treatment strategies in patients with locally advanced head and neck cancer.

Methods

Search strategy and selection criteria

We performed a systematic review and network meta-analysis according to the PRISMA-NMA check-list [3]. We searched PubMed, Embase, Chocrane Central Register of Controlled trials, ClinicalTrials.gov, American Society of Clinical Oncology (ASCO) abstracts database from January 1st 2000 up to September 1st 2017. This choice has a solid base: the assumption of transitivity. Which means that similarity of the trials is of utmost importance to derive plausible indirect comparisons. In fact, transitivity can be impaired by including old studies, because old trials inconsistently report censoring, time-to-event data and randomization procedures. Also, the same treatments may have undergone radical changes in doses and treatment protocols (such as the introduction of intensity modulated radiotherapy in the 90s) which may further impair the validity of indirect comparisons.

Regarding inclusion criteria, only phase II or III randomized controlled trials comparing various systemic interventions and radiotherapy schemes for locally advanced, non-metastatic head and neck squamous cell carcinoma were searched to provide summary estimates on survival and toxicity outcomes. No language restriction was applied. We excluded articles recruiting participants with recurrent or metastatic disease, studies where surgery was the first treatment option or that compared different doses schedules of the same drug, sample sizes less than 20 patients and studies that did not use randomization for treatment allocation. Study authors were contacted when incomplete information was reported in the included articles.

Data extraction and assessment of risk of bias

Two investigators (OI and PDM) searched for studies independently and identification of studies was performed through screening of the titles and selecting the abstracts for full-text inclusion.

The reviewers screened all the abstracts and their suitability for the subsequent analysis according to the pre-specified inclusion and exclusion criteria. Inter-examiner (kappa) Cohen's test was conducted to evaluate the selection of titles, abstracts and complete reading with interpretation of the article, resulting in concordance test values of $k = 0.801$ for all the databases results retrieved. Any disagreement between the two reviewers was resolved by a third author (GS).

Data Extraction was done using a previously compiled database which consisted of study name, year of publication, list of treatments, years of follow-up, total number of randomized patients, survival and toxicity data including confidence intervals. Care was taken to identify and eliminate duplicate studies.

Risk of Bias was performed independently by two authors (OI and SPL) through the Chocrane risk of Bias tool.

Data synthesis and statistical analysis

Primary outcomes analyzed were Overall Survival and Progression Free Survival. Hazard Ratios (HR) were used as summary statistics. When HRs were not reported we estimated them from summary statistics with the methods described by Tierney and colleagues [4]. The secondary outcome was the acute/short term toxicity of the evaluated treatments. In this case we selected grade 3–4 Neutropenia and grade 3–4 Mucositis because they were the most consistently reported among the various studies. In this case Odds Ratios (OR) were the chosen measures for overall comparison, estimated from individual patients data.

Regarding the statistical analysis, we performed a series of traditional, pairwise meta-analyses, using a random effects model with RevMan 5.3. Overall Hazard Ratio with 95% confidence interval is presented for Overall Survival and Progression free survival, calculated through the inverse variance method. Sensitivity analysis was performed for the Induction Chemotherapy versus CCRT progression-free survival outcome, this was made because for this specific outcome the risk of confounding factors (studies analyzing just larynx or just oropharynx carcinoma) was considered higher than the other outcomes.

Overall Odds Ratio is presented for toxicity outcomes, calculated through the Mantel-Haenszel method.

We assessed statistical heterogeneity for each set of pair-wise meta-analyses with the I^2 method and p value.

We also performed a Bayesian Network meta-analysis in which the single treatment options were evaluated directly and indirectly. For OS and PFS we computed log hazard ratio and its standard error with respect to a baseline treatment, for each study. For toxicities, we computed the log odds ratio and its standard error. A continuity correction was used to incorporate zero-event studies for the mucositis and neutropenia endpoints, with a correction factor of 1. For each of the four endpoints we then evaluated the geometry of the network. We then computed both a random-effects and fixed-effects network meta-analysis within a Bayesian framework. Flat uniform priors for all parameters were used on the logHR and logOR scales, and on the standard

deviation scale for the heterogeneity parameters.

To ensure convergence, trace plots and the Brooks-Gelman-Rubin statistic were assessed, after Markov Chain Monte Carlo sampling of two parallel chains with different (random) initial values. In all cases we ended up using random-effects network meta-analysis models (see appendix table 38 for goodness of fit statistics and global heterogeneity). The pooled estimates are the posterior means and 95% credible intervals (CrI) after Markov Chain Monte Carlo sampling. We estimated the ranking probabilities for all treatments of being at each possible rank for each intervention. We then evaluated the posterior ranking probabilities of the first position, of all possible positions. The cumulative posterior ranking probabilities were also used, where we evaluated the cumulative ranking curve and its surface (SUCRA). Potential publication bias was evaluated through funnel plots and Egger's linear regression test. Inconsistency between direct and indirect sources of evidence was assessed both globally and locally method was finally used to report about inconsistency. This methods separates evidence on a particular comparison into direct and indirect evidence, and compares them for consistency. Sensitivity for OS and PFS was evaluated by removing one study at a time and repeating the analysis, only minor variations were observed for the pooled effect size estimates. All statistical analyses for the network meta-analysis were performed using the software R (version 3.3.3), R package GeMTC, and Jags (version 4.3.0).

Role of the funding source

There was no funding source for this study. The corresponding author is responsible for access to data and submission.

Results

Overall, 4828 citations were identified by the search on all the databases. Of these, 4724 were excluded on the basis of title and abstract, of the 104 selected for full text examination 57 [5–61] publications were included for data extraction and analysis (Fig. 1). Three of the included trials were unpublished in full text, one publication was not in English [17] and translation was performed by a certified professional. In total, 15,723 patients were randomized across the included trials. All the included publications (Table 1) reported HR for Overall Survival or reported data information from which HR could be extrapolated. 49 publications allowed extraction of data regarding Progression-free survival.

Around half of the studies reported sufficient data regarding toxicity (secondary outcome), 29 regarding grade 3–4 mucositis and 24 regarding grade 3–4 neutropenia.

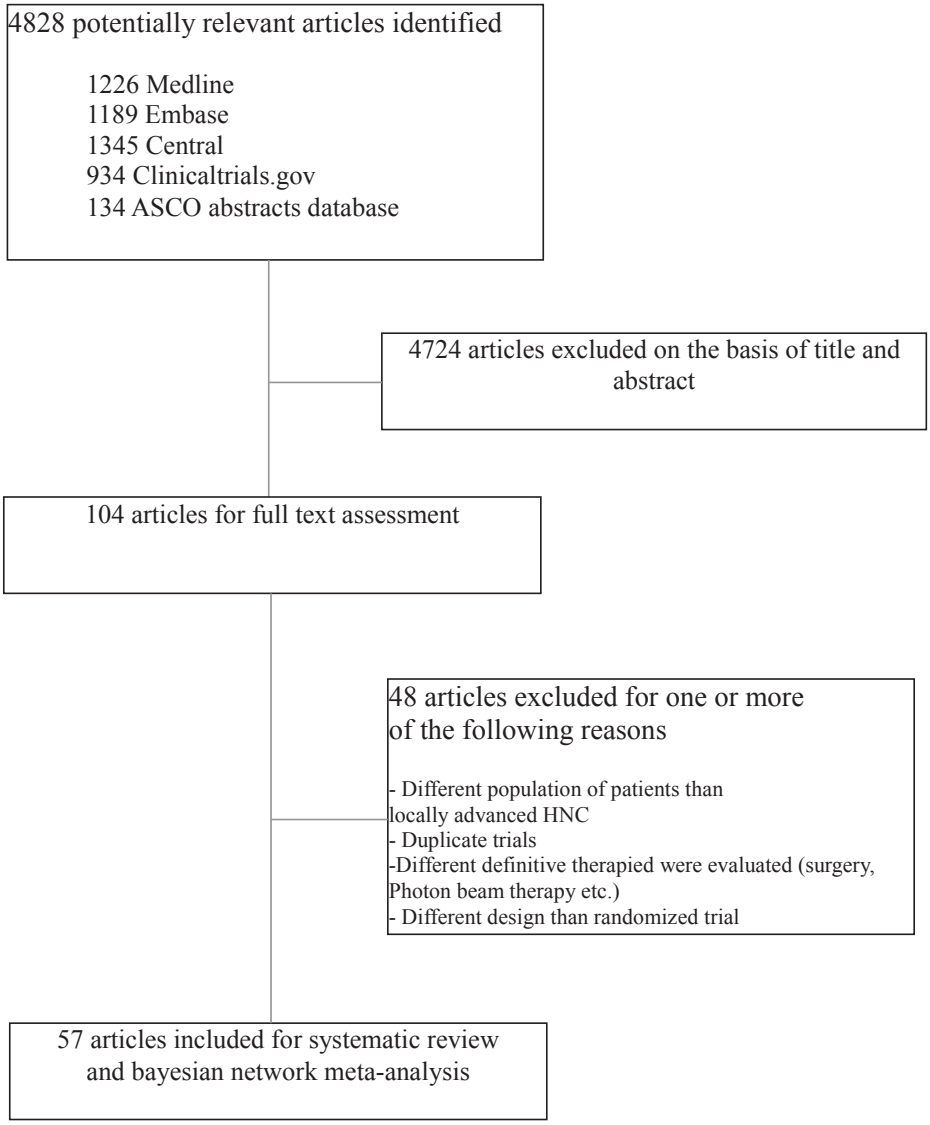

Fig. 1. Flowchart for the inclusion of studies.

Table 1
Description of the included Randomized Trials.

Author	Cancer sites (%)	Chemotherapy	Radiotherapy fractionation and dose to primary tumor
Adelstein, 2000	Oropharynx, hypopharynx, larynx (% not available)	5-fluorouracil 1000 mg/m^2/day and cisplatin 20 mg/m^2/day, both given as a continuous intravenous infusions over 4 days beginning on days 1 and 22	Conventional fractionation (66–72 Gy)
Adelstein, 2003	Oral cavity(14), oropharynx(59), hypopharynx(18), larynx(9)	Cisplatin 100 mg/m^2 on days 1, 22 and 43 3 cycles of a 4-day continuous infusion of fluorouracil 1000 mg/m^2/day and cisplatin 75 mg/m^2 on day 1, given every 4 weeks	Single daily fractionated radiation (70 Gy)
Ang, 2014	Oropharynx(70), hypopharynx (7), larynx(23)	Cisplatin 100 mg/m^2 on days 1 and 22, alone or in combination with cetuximab 400 mg/m^2 the week before radiotherapy and 250 mg/m^2 per week during radiotherapy	Accelerated RT (70–72 Gy over 6 weeks)
Bartelink, 2002	Oral cavity(40), oropharynx(40), hypopharynx(10), larynx(10)	10 mg/m^2 cisplatin, given daily between the first and the second session	Conventional fractionation (70 Gy) Accelerated fractionation Three fractions per day of 1.6 Gy (total 72 Gy)
Beitler, 2014	Oral cavity, oropharynx, hypopharynx, larynx (% not available)	N/A	Conventional RT 2 Gy/fraction/day to 70 Gy in 35 fractions over 7 weeks Accelerated fractionation with a Split (AFX-S) was delivered at 1.6 Gy/fraction, BID to 67.2 Gy over 6 weeks, with a 2 week break after 38.4 Gy
Bensadoun, 2006	oropharynx(60), hypopharynx (20)	Cisplatin 100 mg/m^2 on days 1, 22 and 43 and continuous infusion of 5-fluorouracil 750 mg/m^2/day cycle 1, 430 mg/m^2/day cycle 2 and 3	Conventional fractionation (80.4 Gy on oropharynx, 75.6 Gy on hypopharynx)
Bernier, 2004	Oral cavity(26), oropharynx(30), hypopharynx(20), larynx(24)	Cisplatin 100 mg/m^2 on days 1, 22 and 43	Conventional fractionation (66 Gy)
Bhouris, 2006	Oral cavity(14), oropharynx(77), hypopharynx(5), larynx(4)	N/A	accelerated radiotherapy 63 Gy (range, 61 to 70 Gy) Conventional radiotherapy 70 Gy (range, 68 to 74 Gy)
Bhouris, 2012	Oral cavity(11), oropharynx(66), hypopharynx(17), larynx(6)	Carboplatin 70 mg/m^2 per day plus fluorouracil 600 mg/m^2 per day from day 1 to 4, day 22 to 25, and day 43 to 46	conventional radiotherapy 70 Gy in 7 weeks accelerated radiotherapy accelerated radiotherapy chemotherapy received radiation doses of 70 Gy in 6 weeks
Bhouris, 2016	N/A	Cetuximab on days 1, 8, 15, 22, 29, 43, 50 Carboplatin 70 mg/m^2/day; 5FU 600 mg/m^2/day, at days 1–4, 22–25, 43–46	Conventional fractionation (70 Gy)
Bonner, 2010	oropharynx(60), hypopharynx (15), larynx(25)	Weekly cetuximab, initial dose 400 mg/m^2, followed by seven weekly doses at 250 mg/m^2	Conventional fractionation (70–72 Gy)
Budach, 2015	Oral cavity(8), oropharynx(60), hypopharynx(32)	5-FY 600 mg/m^2 continuous infusion days 1–5 on days 5 Mytomicin C injection 10 mg/m^2	Hyperfractionation (77.6 Gy)
Burtness, 2017	oropharynx 53/54%; hypopharynx 21/23%; larynx 18/12%; oral cavity 9/10%	Cisplatin 100 mg/m^2 on days 1, 22 and 43 or Carboplatin 70 mg per m^2 and per day for four days day 1; day 22; day 43	Conventional fractionation (66–72 Gy)
Chen, 2011	N/A	Paclitaxel 135–150 mg/m^2 day1, cisplatin 75–100 mg/m^2 day1 (every 3 weeks for 2 cycles)	Conventional fractionation (66–74 Gy)
Chitaparanux, 2013	Oral cavity(31), oropharynx(17), hypopharynx(4), larynx(48)	Carboplatin 70 mg per m^2 and per day for four days day 1; day 22; day 43 5 fluorouracil 600 mg per m^2 per day for four days. 3 cycles day 1; day 22; day 43	Conventional Fractionation (70 GY) or Accelerated Radiotherapy In the last two weeks, a boost volume (covering only the primary tumor site) was treated twice daily, 1.8 Gy per fraction in the morning and 1.2 Gy per fraction in the afternoon
Cohen, 2014	Oral cavity(14), oropharynx(66), hypopharynx(6), larynx(14)	CRT (docetaxel 30 mg/m^2, fluorouracil 600 mg/m^2 per day as a 24-h continuous infusion, hydroxyurea 500 mg PO × 11 doses 2 21-day cycles of IC (docetaxel 75 mg/m^2 on day 1, and fluorouracil 750 mg/m^2 on days 1 to 5) followed by CRT	Conventional fractionation (74–75 Gy)
Cooper, 2012	Oral cavity, oropharynx, hypopharynx, larynx (% not reported)	Cisplatin 100 mg/m^2 i.v. on days 1, 22 and 43	Conventional fractionation (60 Gy)
Corvò, 2001	Oral cavity(19), oropharynx(38), hypopharynx(22), larynx(13), nasopharynx (8)	Cisplatin 20 mg/m^2 per day 5-fluorouracil 200 mg/m^2 per day both given intravenously for 5 consecutive days	Alternating chemotherapy (4 courses during weeks 1, 4, 7, and 10) and radiotherapy (3 courses of 20 Gy each, given in fractions of 2 Gy per day, 5 times a week, during weeks 2–3, 5–6, and 8–9) for a total planned radiation dose of 60 Gy conventional radiotherapy course consisting in 30 fractions of 2 Gy per day, 5 times a week for 6 weeks, superimposed with a second course of 1.5 Gy, once a day, 5 times a week during the last 2 weeks for a total dose of 75 Gy
Cummings, 2007	Oropharynx(40), hypopharynx (20), larynx(40)	N/A	Conventional fractionation (50 Gy) Accelerated fractionation 58 Gy in 40 equal fractions
Denis, 2003	Oropharynx	Fluorouracil 600 mg/m^2 per day as a 24-h continuous infusion for 4 days and carboplatin given daily bolus 70 mg/m^2 per day for 4 days. The chemotherapy cycle was started on days 1, 22, 43	Conventional fractionation (70 Gy)
Dobrowsky, 2000	Oral cavity(28), oropharynx(38), hypopharynx(24), larynx(10)	20 mg/m^2 Mitomycin C on day 5 of therapy prior to one of the radiation fractions	Conventional fractionation with 70 Gy/7 weeks/35 fractions, a single dose of 2 Gy, 5 fractions per week hyperfractionated accelerated radiotherapy 1.6 Gy/fraction, BID to 67.2 Gy over 6 weeks
Ezzat, 2005	Oral cavity(25), oropharynx(23), hypopharynx(23), larynx(29)	Mitomycin C (15 mg/m^2) at the end of the first week of RT	Conventional fractionation (68 Gy)

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Table 1 (*continued*)

Author	Cancer sites (%)	Chemotherapy	Radiotherapy fractionation and dose to primary tumor
Fallai, 2006	Oropharynx	N/A	Conventional fractionation 66 to 70 Gy in 33 to 35 fractions Accelerated Fractionation 64 to 67.2 Gy in two fractions of 1.6 Gy every day, five days a week, with a planned two-week split at 38.4 Gy
Forastiere, 2013	Larynx	Up to 3 cycles of PF (cisplatin 100 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2 per day for 5 days) every 3 weeks Cisplatin 100 mg/m^2 on days 1, 22 and 43	Conventional fractionation (70 Gy)
Fountzilas, 2004	Oral cavity(15), oropharynx(33), hypopharynx(10), larynx (42)	Cisplatin (100 mg/m^2 on day 2, 22, 42) or Carboplatin (at an AUC of 7, on day 2, 22, 42)	Conventional Fractionation (70 Gy)
Geoffrois, 2016	N/A	Carboplatin 70 mg per m^2 and per day for four days day 1; day 22; day 43 5 fluorouracil 600 mg per m^2 per day for four days. 3 cycles day 1; day 22; day 43	Conventional fractionation (66–72 Gy)
Ghadjar, 2012	Oral cavity(9), oropharynx(53), hypopharynx(24), larynx(15)	2 cycles of cisplatin (20 mg/m^2 for 5 consecutive days during weeks 1 and 5)	Hyperfractionation (74.4 Gy)
Ghi, 2017	Oral cavity(24), oropharynx(55), hypopharynx(20), larynx(1)	CCRT (2 cycles of cisplatin 20 mg/m^2 from days 1 to 4, 5-fluorouracil 800 mg/m^2/day, 96 h continuous infusion, administered at weeks 1 and 6 of the radiation treatment) or CET/RT(cetuximab initiated one week before RT at 400 mg/m^2 loading dose and followed by 250 mg/m^2 weekly for 7 weeks)] or 3 cycles of TPF (docetaxel(75 mg/m^2 day 1/cisplatin 80 mg/m^2 day 1/5-fluorouracil 800 mg/m^2/day) 96 h of continuous infusion followed by CCRT or followed by CET/RT	Conventional fractionation (70 Gy)
Giralt, 2015	Oral cavity(12), oropharynx(48), hypopharynx(16), larynx(24)	2 cycles of cisplatin (100 mg/m^2) during radiotherapy or 3 cycles of panitumumab (9 mg/kg every 3 weeks) on day 1, 22, 43 of RT	Accelerated fractionation (70–72 Gy)
Gosh-Laskar, 2016	Oral cavity(5), oropharynx(56), hypopharynx(24), larynx(15)	Cisplatin 30 mg/m^2	Accelerated RT arm 66 to 70 Gy in 33–35 fractions,2 Gy per fraction, 6 fractions per week conventional RT arm 66 to 70 Gy in 7 weeks
Gupta, 2009	Oropharynx	2–3 cycles of cisplatin 75 mg/m^2 on day 1 and 5-fluorouracil 800 mg m^2 iv infusion for 9 h on days 1–3 followed by low-dose weekly cisplatin based chemoradiotherapy or chemoradiotherapy only	Conventional fractionation (66–70 Gy) in 6.5 to 7 weeks
Haddad, 2013	Oral cavity(18), oropharynx(55), hypopharynx(10), larynx(17)	Induction chemotherapy TPF: docetaxel 75 mg/m^2 day1, cisplatin 100 mg/m^2 day1, fluorouracil 1000 mg/m^2 day1–4. (every 3 weeks for 3 cycles) CCRT Arm 1: docetaxel 20 mg/m^2 (weekly for 4 weeks); Arm 2: weekly carboplatin area under the curve (AUC) 1.5 for 7 weeks. Cisplatin 100 mg/m^2 day 1, day 22	Conventional fractionation (70 Gy)
Harrington, 2015	Oral cavity(41), oropharynx(20), hypopharynx(13), larynx(23), multiple sites (3)	Adjuvant Lapatinib 1500 mg once daily for 3–7 days CCRT Cisplatin 100 mg/m^2 on days 1, 22, 43 and Lapatinib 1500 mg once per day for 1 year	Conventional fractionation (66 Gy)
Hitt, 2005	Oral cavity(13), oropharynx(35), hypopharynx(22), larynx(30)	Induction chemotherapy *Arm A* Cisplatin 100 mg/m^2 day 1, Fluoruracil 1000 mg/m^2/day over 120 h every 3 weeks *Arm B* TPF (Paclitaxel 175 mg/m^2 day 1, Cisplatin 100 mg/m^2 day 2, Fluorouracil 500 mg/m^2/day on days 2 to 6 every 3 weeks *CCRT* Cisplatin 100 mg/m^2 day 1, 22, 43 of RT	Conventional fractionation (70 Gy)
Hitt, 2013	Oral cavity(21), oropharynx(43), hypopharynx(18), larynx(18)	*Induction Chemotherapy* TPF: docetaxel 75 mg/m^2 day1, cisplatin 75 mg/m^2 day1, 5-fluorouracil 750 mg/m^2 day1–5. (every 3 weeks for 3 cycles) *PF*: cisplatin 100 mg/m^2 day1, 5-fluorouracil 1000 mg/m^2 day1–5. (every 3 weeks for 3 cycles) CCRT Cisplatin 100 mg/m^2 day 1, 22, 43 of RT	Conventional fractionation (70 Gy)
Huguenin, 2004	Oral cavity(8), oropharynx(53), hypopharynx(25), larynx(15)	Cisplatin 20 mg/m^2 5 consecutive days during weeks 1, 5, 6 of RT	Hyperfractionated RT (74.4 Gy)
Jeremic, 2000	Oral cavity(20), oropharynx(44), hypopharynx(16), larynx(10), nasopharynx(10)	Cisplatin 6 mg/m^2 on every treatment day of hyperfractionated RT	Hyperfractionated RT (77 Gy)
Lee, 2015	Oropharynx(84), hypopharynx (16)	Cetuximab 400 mg/m^2 first dose, then 250 mg/m^2 weekly for 9 weeks Docetaxel 75 mg/m^2, day 1 of every 3 weeks for 9 weeks (3 cycles) Cisplatin 75 mg/m^2, day 1 of every 3 weeks for 9 weeks (3 cycles)	Conventional fractionation
Lorch, 2011	Oral cavity(14), oropharynx(53), hypopharynx(15), larynx(18)	TPF (Docetaxel 75 mg/m^{2,} Cisplatin 100 mg/m^2, Fluoruroacil 1000 mg/m^2 24 h infusion for 4 days) PF (Cisplatin 100 mg/m^2, Fluoruroacil 1000 mg/m^2 24 h infusion for 5 days)	Conventional Fractionation (70–74 Gy)
Magrini, 2016	Oral cavity(14), oropharynx(48), hypopharynx(20), larynx(18)	Cetuximab 400 mg/m^2 *loading dose* followed by 250 mg/m^2 *once per week* CCRT (Cisplatin 40 mg/m^2 *once per week*)	Conventional Fractionation (70 Gy)

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Table 1 (*continued*)

Author	Cancer sites (%)	Chemotherapy	Radiotherapy fractionation and dose to primary tumor
Martins, 2013	Oral cavity(8), oropharynx(67), hypopharynx(6), larynx(18), nasopharynx (1)	Erlotinib 150 mg per day until completion of RT Cisplatin 100 mg/m^2 *days 1, 22, 43*	Conventional Fractionation (66–70 Gy)
Mesia, 2013	Oral cavity(55), oropharynx(45)	Adjuvant Cetuximab 200 mg/m^2 *weekly for 12 weeks* Cetuximab + RT 400 mg/m^2 *before* RT and 250 mg/m^2 *weekly during* RT	Conventional Fractionation (69.9 Gy)
Mesia, 2015	Oral cavity(9), oropharynx(53), hypopharynx(20), larynx(18)	CCRT (Cisplatin 100 mg/m^2 *days 1, 22, 43 of* RT) Panitumumab 75 mg/m^2 *days 1, 22, 43 of* RT Panitumumab 9 mg/kg *days 1, 22, 43 of* RT Cisplatin d*ays 1, 22, 43 of RT*	Conventional Fractionation (70 Gy)
Posner, 2007	Cancer sites Oral cavity (14), oropharynx (52), hyopharynx (16), larynx (18)	Chemotherapy Induction Chemotherapy TPF: docetaxel 75 mg/m2 day1, cisplatin 75 mg/m2 day1,5-fluorouracil 750 mg/m2 day 1–5. (every 3 weeks for 3 cycles) *PF*: cisplatin 100 mg/m2 day 1, 5-fluorouracil 1000 mg/m2 day 1–5. (every 3 weeks for 3 cycles) CCRT Carboplatin i.v. Infusion AUC 1.5 for maximum 7 weekly doses	Radiotherapy fractionation and dose to primary tumor Conventional Fractionation (70–74 Gy)
Poulsen, 2001	Oral cavity(10), oropharynx(67), hypopharynx(10), larynx(13)	N/A	Conventional fractionation with 70 Gy Accelerated Radiotherapy delivered in 1.8 Gy fractions twice/day to a dose of 39.6 Gy in 22 fractions over 16 days, with macroscopic disease receiving a dose of 59.4 Gy in 33 fractions over 24 days
Prades, 2010	Larynx	Concurrent chemoradiotherapy:Cisplatin 100 mg/m^2 on days 1, 22, and 43 Induction chemotherapy: Cisplatin 100 mg/m^2 day 1 fluorouracil 100 mg/m^2/day iv ondays 1–5 for two courses after 3 weeks	Conventional radiotherapy (total dose 70 Gy)
Quon, 2011	Oral cavity(30), oropharynx(27), hypopharynx(18), larynx(7) nasopharynx(13)	Cisplatin 20 mg/m^2 days 1, 8, 15, 22, 29, 36, 43	Conventional Fractionation (68–76 Gy)
Rischin, 2010	Oral cavity(13), oropharynx(55), hypopharynx(15), larynx(17)	Either Cisplatin 100 mg/m^2 *day 1 of weeks 1, 4, 7* of RT or Cisplatin 75 mg/m^2 + Tirapazamine 290 mg/m^2 *day 1 of weeks 1, 4, 7 or* Tirapazamine 160 mg/m^2 *3 times a week on weeks 2, 3*	Conventional Fractionation (70 Gy)
Rishi, 2013	Oropharynx	Cisplatin, 100 mg/m^2 intravenously was administered on days 1, 22 and 43 of the radiation schedule	40 Gy/20 fractions/4 weeks was given to the primary and draining lymph nodes (phase I) followed by 20 Gy/10 fractions/2 weeks after sparing the spinal cord (phase II), and final 6 Gy/3 fractions (phase III) 45 Gy/25 fractions/5 weeks as phase I was given to the primary tumor
Rodriguez, 2010	Oral cavity(88), oropharynx(4), hypopharynx(4), larynx(2)	Nimotuzumab 200 mg *weekly for 7 weeks*	Conventional Fractionation (60–66 Gy)
Ruo Redda, 2010	Oral cavity (19), oropharynx (56), hypopharynx(10), larynx (15)	Carboplatin 45 mg/m^2 *days 1–5, weeks 1, 3, 5, 7* (total dose 900 mg/m^2)	Conventional Fractionation (70 Gy)
Sanguineti, 2004	Oral cavity(20), oropharynx(18), hypopharynx(22), larynx(40)	N/A	Conventional fractionation was defined as delivery of 50 Gy at 2 Gy per fraction over 5 weeks to areas at low risk of containing microscopic disease and 60 Gy at 2 Gy per fraction over 6 weeks to areas at high risk The accelerated fractionation schedule was a biphasic concomitant boost schedule with a boost during the first week and last (5th) week of treatment
Semrau, 2006	Oropharynx (74), hypopharynx (26)	2 cycles 5-Fluorouracil 600 mg/m^2 *per day* and Carboplatin 70 mg/m^2 *per day, days 1–5 and 29–33*	Hyperfractionated or Accelerated (69.9 Gy *in 38 days*)
Takacsi-Nagy, 2015	Oral cavity (12), oropharynx (61), hypopharynx, (6) larynx (9)	2 cycles of TPF (Docetaxel 75 mg/m^2 *1 h infusion day 1,* Cisplatin 75 mg/m^2 *1 h infusion day 1*, Fluorouracil 750 mg/m^2 *continuous infusion day 1 to 5*)	Conventional Fractionation (50/70 Gy)
Tobias, 2010	Oral cavity(40), oropharynx(15), hypopharynx,(15) larynx(20), nasopharynx (7), other/unkown (3)	Fluorouracil 500 mg/m^2 and either Methotrexate 100 mg/m^2 or Vincristine max 2 mg, Bleomycine 30 mg/m^2	Conventional fractionation (50/60 Gy)
Vermorken, 2007	Oral cavity(18), oropharynx(46), hypopharynx(29), larynx(7)	TPF (Docetaxel 75 mg/m^2 *1 h infusion day 1,* Cisplatin 75 mg/m^2 *1 h infusion day 1*, Fluorouracil 750 mg/m^2 *continuous infusion day 1 to 5*) PF (Cisplatin 100 mg/m^2 *1 h infusion day 1*, Fluorouracil 1000 mg/m^2, *continuous infusion day 1 to 5*)	Conventional Fractionation (66/70 Gy)
Zorat, 2004	N/A	4-Cycles of Cisplatin 100 mg/m^2 *day 1,* 5- Fluorouracil 1000 mg/m^2 *day 5*	Conventional Fractionation (65/70 Gy)

About study quality, two trials were rated as high risk of bias according to the Chocrane risk of bias tool in terms of allocation concealment and randomization [26,42]. On the other hand, no study was rated as high risk regarding outcome data and selective reporting. In general terms, the overall quality of the studies included for this review can be considered high (see appendix Fig. 1).

Results of pair-wise meta-analyses

Results of random effects meta-analyses are shown in the appendix

Figs. 3–25 and the significant results are synthetically presented in Table 2.

Meta-analyses for overall survival showed that CCRT is significantly better than conventionally fractionated RT (HR 0.78 95% CI 0.70–0.87). This was independent by the administration of cetuximab or not. CCRT was also more effective when compared to altered fractionation radiotherapy (HR 0.74 95% CI 0.65–0.85).

A comparison between conventional fractionation RT versus altered fractionation RT (either accelerated or hyperfractionated) showed just a trend in favor of the alteration of fractionation schedules but no significant result came out from the analysis (HR 0.94 95% CI 0.87–1.01).

EGFR-targeting drugs failed to demonstrate an advantage in terms of Overall Survival against CCRT (HR 1.09 95%CI 0.90–1.32).

The role of induction chemotherapy was also evaluated against CCRT, it seemed to be a trend favoring the use of induction treatment although it was not statistically significant (HR 0.91 95%CI 0.79–1.15). Another comparison clearly showed a superiority of taxane based induction chemotherapy regimens versus induction without taxanes (HR 0.73 95%CI 0.64–0.83).

Adjuvant treatment comparisons were also possible, although on few studies. There seemed to be no benefit in adding a adjuvant drug after RT alone or CCRT.

Meta-analyses for progression-free survival significantly confirmed the superiority of CCRT versus RT alone (HR 0.78 95%CI 0.70–0.87). Also, CCRT is clearly superior to altered fractionation RT (HR 0.76 95%CI 0.70–0.83).

Induction chemotherapy seems to be superior in a significant way when compared to CCRT (HR 0.78 95%CI 0.65–0.94). Taxane-based are better than non taxane-based regimens (HR 0.76 95%CI 0.67–0.85). The sensitivity analysis further confirmed these results (see appendix Fig. 26).

The impact of adjuvant therapies on PFS after RT or CCRT are based on few studies and their role remains unclear.

Altered fractionation RT seems to confer a slight PFS advantage when compared to conventional fractionation RT (HR 0.91 95%CI 0.85–0.98).

Toxicity evaluation was based on reporting of grade 3–4 mucositis and neutropenia. Severe neutropenia is most likely to occur in patients treated with CCRT compared to any kind of RT (OR 16.01 95% CI5.48–46.81). Induction chemotherapy also increases this risk when compared to CCRT (OR 2.33 95% CI 1.58–3.44).

Regarding the risk of severe mucositis, CCRT increase the risk when compared to RT alone. The use of Induction Chemotherapy does not seem to confer more risk compared to CCRT alone.

Network meta-analysis

Network of eligible comparisons for Overall Survival is shown in Fig. 2. Network for Progression-free survival is shown in appendix Fig. 2. Results of network meta-analyses for primary outcomes are presented in Figs. 3 and 4 and significant results are synthetically presented in Table 2.

In terms of overall survival, CCRT with cisplatin (HR 0.70, 95% CrI 0.62–0.78) and cetuximab on top of CCRT (HR 0.7, 95% CrI 0.5–0.97) are clearly superior to conventional RT alone. IC with cisplatin and fluorouracil (HR 0.74, 95% CrI 0.52–0.95), IC with docetaxel, cisplatin, fluorouracil (HR 0.55, 95% CrI 0.54–0.89) and IC with paclitaxel, cisplatin, fluorouracil (HR 0.55, 95% CrI 0.34–0.89) before CCRT are all superior to conventional RT.

CCRT with cisplatin is also superior to altered fractionation RT (HR 0.74, 95% CrI 0.64–0.84). The analysis shows that cisplatin is superior to carboplatin (HR 0.63, 95% CrI 0.48–0.86). None of the IC drugs is significantly superior to CCRT although a trend in favor of IC is shown. Altered fractionation RT is not superior to conventional RT (HR 0.95, 95% CrI 0.85–1.06).

In terms of Progression-free survival, CCRT with cisplatin (HR 0.72, 95% CrI 0.63–0.83), cisplatin and fluorouracil (HR 0.67, 95% CrI 0.5–0.88), carboplatin (HR 0.63, 95% CrI 0.46–0.87), carboplatin and fluorouracil (HR 0.75, 95% CrI 0.56–1), IC with cisplatin and fluorouracil (HR 0.59, 95% CrI 0.45–0.78), IC with docetaxel, cisplatin and fluorouracil (HR 0.53, 95% CrI 0.41–0.68) and IC with paclitaxel, cisplatin and fluorouracil (HR 0.59, 95% CrI 0.35–0.99) are superior to conventional RT and altered fractionation RT. IC with docetaxel, cisplatin and fluorouracil shows a significant superiority against CCRT

Table 2
Synthesis of the significant comparisons in the network and the pairwise meta-analyses.

Comparison Overall Survival	Network meta-analysis HR (Random effects, 95% CrI)	Pairwise Meta-analysis HR (IV, Random effects, 95% CI)
CCRT cpt vs RT	0.70(0.62–0.78)	0.74(0.57–0.95)
CCRT carbopt vs RT	1.11(0.81–1.46)	0.67 (0.50–0.90)
CCRT cetuximab vs RT	0.69(0.5–0.97)	0.75(0.59–0.95)
CCRT cpt vs. altered fractionation RT	0.74(0.64–0.84)	0.74 (0.65–0.85)
CCRT cpt vs CCRT carbopt	0.63(0.48–0.86)	Not compared directly
IC docetaxel, cpt, FU vs IC cpt, FU	0.88(0.74–1.06)	0.72 (0.62–0.84)
IC paclitaxel, cpt, FU vs IC cpt, FU	0.74(0.48–1.14)	0.76(0.58–1.00)
IC docetaxel, cpt, FU vs CCRT cpt, fu	0.76(0.58–1.00)	0.73(0.55–0.97)
IC docetaxel, cpt, FU vs RT	0.74(0.59–0.92)	Not compared directly
IC paclitaxel, cpt, FU vs RT	0.65(0.52–0.82)	Not compared directly
IC docetaxel, cpt, cetuximab vs RT	0.55(0.34–0.89)	Not compared directly
Comparison Progression free-survival	Network meta-analysis HR (Random effects. 95% CrI)	Pairwise Meta-analysis HR (IV. Random effects. 95% CI)
CCRT cpt vs RT	0.72(0.63–0.83)	0.69(0.52–0.91)
CCRT cpt, FU vs RT	0.67(0.50–0.88)	0.55(0.25–1.19)
CCRT carbopt vs RT	0.63(0.46–0.87)	0.52 (0.32–0.69)
CCRT carbopt, FU vs RT	0.75(0.56–1.00)	0.77(0.62–0.95)
CCRT cetuximab vs RT	0.57(0.31–1.05)	0.75(0.59–0.95)
CCRT mytomicin, bleomycine, vincristine, FU vs RT	0.53(0.38–0.76)	0.72(0.53–0.98)
CCRT cpt vs. altered fractionation RT	0.79(0.69–0.92)	0.78 (0.67–0.91)
CCRT plus cetuximab vs IC TPF > RT plus cetuximab	0.93(0.47–1.82)	0.73 (0.54–0.99)
IC docetaxel, cpt, FU vs IC cpt, FU	0.89(0.74–1.07)	0.73 (0.64–0.83)
IC paclitaxel, cpt, FU vs IC cpt, FU	0.99(0.63–1.54)	0.76(0.58–1.00)
IC docetaxel, cpt, FU vs CCRT cpt, fu	0.58(0.45–0.56)	0.72(0.55–0.94)
Altered fractionation vs Conventional fractionation	0.91(0.81–1.02)	0.91(0.85–0.98)

HR, Hazard Ratio. CrI, Credible Interaval. IV, inverse variance. CI, Confidence Interval. CCRT, concurrent chemoradiotherapy. Cpt, cisplatin. RT, radiotherapy. Carbopt, carboplatin. IC, induction chemotherapy. FU, fluorouracil. TPF, taxane, cisplatin, fluorouracil.

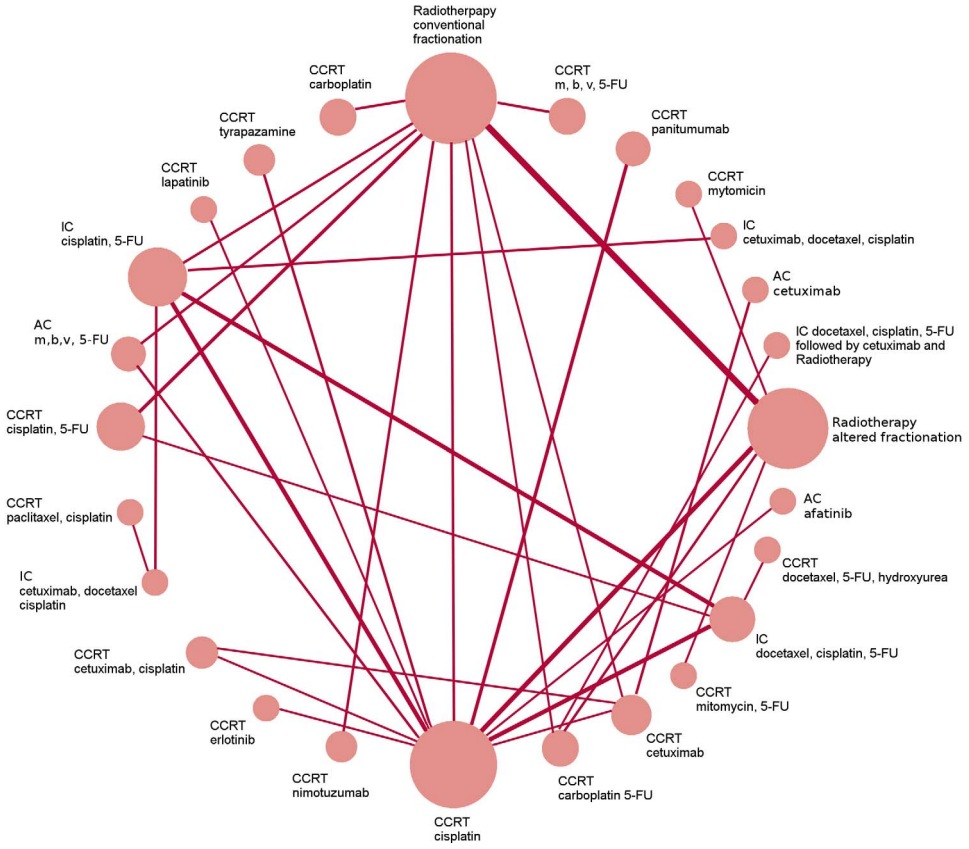

Fig. 2. Network of treatments available for comparison of Overall Survival. Dimensions of nodes and thickness of lines corresponds respectively to the number of studies evaluating a given treatment and the number of studies comparing the two connected treatments.

Fig. 3. Results of Network meta-analysis for overall comparison.

with cisplatin (HR 0.73 95% CrI 0.58–0.92). Altered fractionation RT is not superior to conventional RT (HR 0.91, 95% CrI 0.81–1.02), this contrasts with the results of the pair-wise meta-analysis.

Results for the secondary outcome of neutropenia put in evidence that all the chemotherapeutic agents significantly increase the risk of this complication when compared to conventional or altered fractionation RT (see appendix Fig. 36). CCRT with panitumumab increases the risk when compared to CCRT with cisplatin (OR 8.2, 95% CrI 1.18–71.5) or cisplatin plus cetuximab (OR 24.2, 95% CrI 4.2–502.9) but not compared to cetuximab alone (OR 18.69, 95% CrI 0.75–719.1).

Network meta-analysis showed that altered fractionation increases the risk of developing grade 3–4 mucositis compared to conventional RT (OR 3.74 95% 1.64–8.67), other comparisons gave no significant results (see appendix Fig. 37).

Treatments ranking based on cumulative probability plots and SUCRA was performed. SUCRA plots for single treatments are

Fig. 4. Results of network meta-analysis for progression-free survival.

represented in the appendix Figs. 32–35. What emerges clearly is that it is highly likely that conventional RT is the worst treatment option. On the other hand, absolute statements regarding single treatments ranking as the best are avoided in this sub-analysis. This is because rankograms inherently lack of reliability when there is little evidence available on a specific treatment, which can be spuriously positioned in the highest rank. In fact, none of the treatments has more than 50% probability to be ranked as either best, second best or third best. The same is true for PFS rankings.

Funnel plots for primary outcomes were not suggestive of any publication bias (see appendix Figs. 26–27). Global heterogeneity has been found to be very low in the network analysis, I^2 values were 2% for OS and 16% for PFS. The test for global inconsistency was not significant ($p > 0.05$) for all the comparisons in primary outcomes (see appendix Figs. 29–32). Finally, quality of evidence according to the risk of bias assessment tool can be considered high for the majority of the included studies (see appendix Fig. 1).

Discussion

Our study represents the most complete synthesis of data of the studies published since 2000 regarding chemotherapy and radiotherapy treatments for locally advanced head and neck cancer.

Although previous meta-analyses focused on this topic, we believe that our work adds a original contribution for many reasons. A recent network meta-analysis [62] focused on systemic therapies for locally advanced HNC but in our opinion it has some flaws that may impair its conclusions. It includes old and new studies for treatments comparison. It does not focus on single treatments options but instead on broad treatment categories (e.g. CCRT vs. RT), thus not exploiting the advantages of establishing treatments hierarchies for specific agents and treatments, which instead should be the strength of a network analysis. Moreover, the authors excluded trials evaluating altered fractionation schedules and considered Overall Survival as the sole end point.

The MACH-NC meta-analysis and its updates [63] are very important papers that helped to drive subsequent research and also the clinical approach to HNC patients. On the other hand, they were focused on head and neck cancer as whole and not specifically on locally advanced disease. Moreover, the original paper evaluated studies conducted between 1965 and 2000, when therapies could be much different than more modern ones. Also, the MACH-NC is a traditional pairwise analysis, and indirect comparisons using robust statistical methods were not performed, in this way it is difficult to understand if a therapeutic drug or schedule is better than the other. It also compared chemotherapy versus different radiotherapy schedules, not differentiating between conventional fractionation and altered fractionation.

In our analysis, we specifically take into consideration locally advanced HNC. We included only studies conducted after 1999 so that comparisons between treatments can be methodologically appropriate. In fact, a network meta-analysis requires the respect of the assumption of transitivity, which is a fundamental prerequisite of any indirect comparison.

Also, we considered as primary end-points both the overall survival and the progression-free survival. We think that this adds a broad perspective to the whole analysis because the OS is the gold standard to understand the impact of a therapy toward patient outcomes. On the other hand, the progression-free survival may be important to understand the impact of a given therapy on the disease and for this reason it may be a starting point to drive future studies and research.

Additionally, we also evaluated toxicity outcomes, choosing grade 3–4 mucositis and neutropenia as a reliable estimate of toxic effects. We found consistency in the networks for the primary and the secondary endpoints for almost all the comparisons. Moreover, global heterogeneity is very low for both outcomes and funnel plots do not show any risk of bias. This further strengthens our results.

We confirmed that concurrent chemoradiotherapy (CCRT) remains the best approach for patients affected by locally advanced head and neck cancer. We can conclude that CCRT is superior to both conventionally fractionated and altered fractionation Radiotherapy alone and Cisplatin should be the gold standard of care. This is the first time that a synthesis of the evidence is performed on altered fractionation versus CCRT in locally advanced HNC. Our results finally allow to understand that alteration of the fractionation schedules do not seem to improve the OS or the PFS in this population of patients and the choice of opting for a altered fractionation schedule needs to be reevaluated. This is important in light of the increased workload for the radiotherapists and also a greater commitment on the patient's side if altered schedules are implemented. Also, the results of the network meta-analysis do not show an advantage of altered fractionation RT in comparison to conventional RT. Anyway, the role of altered fractionation RT in patients who cannot undergo chemotherapy for any reason is worth further investigation in future studies.

We can state that Induction Chemotherapy (IC) followed by CCRT may be effective in the treatments of HNC patients. Although just a not

statistically significant trend in favor of IC was found for overall survival, the results regarding progression-free survival showed a statistically significant advantage of administering IC before CCRT, in particular IC with taxane based drugs. This was concordant both in the traditional and in the network meta-analyses. This means that IC has a impact on the disease and should at least be considered as a treatment option. This contrasts with the results of a previous meta-analysis [64], likely because we included more recent studies to our analysis. The sensitivity analysis performed on this specific outcome strengthened our results. It should be pointed out that increased toxicity of IC is confirmed by our analysis on severe neutropenia but not on severe mucositis when compared to CCRT alone.

The role of adjuvant chemotherapy remains unclear, mostly because few studies evaluated this approach, so further research is encouraged.

In the last decade, new treatment approaches with EGFR targeted therapies have been developed and studied. Cetuximab added to CCRT gives an advantage compared to conventional RT alone but both the pairwise and the network meta-analysis showed that none of the included EGFR-targeted drugs on top of CCRT give a significant advantage over traditional CCRT regimens for both OS and PFS. The most common toxic effects of these drugs have been reported to be acneiform rash and skin reactions which were not included in our analysis, on the other hand there seemed to be no increase in severe mucositis and neutropenia when EGFR therapies were used.

Limitations of this network meta-analysis are numerous. First, there is a lack of evaluation of quality of life related outcomes. This is due to the fact that they are scarcely reported on the published clinical trials. Second, it would be ideal to conduct a meta-analysis of this kind differentiating between tumor sites and tumor stage, but again not enough data is available on single anatomic locations or specific stage of the tumor to obtain high quality overall results. Third, it would be desirable that the trials would describe proper stratification in regard to HPV positivity, so to understand if a difference in outcomes exist between hpv positive or negative patients; we were not able to perform such analysis because only few studies reported hpv status stratification. Finally, results on toxicity should be taken with caution given that few studies reported details on overall occurrence of grade 3–4 toxic events. For this reason, we were forced to choose only the two most commonly reported toxic effects, but also in this case we were able to extract meaningful data from just around half of the included trials.

In conclusion, our systematic review and bayesian network meta-analysis confirm and further validates the results of previous analyses. It also adds some original insights in terms of previously unstudied outcomes. Further research and well designed randomized controlled studies, especially with proper stratification according to hpv status, tumor stage and anatomic locations will allow to get deeper insights in the optimal management of patients affected by locally advanced squamous cell carcinoma of the head and neck.

Conflict of interest

All the authors declare that there is no conflict of interest related to this article.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.oraloncology.2018.03.001.

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