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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Methods: We performed a search on bibliography databases, trials registries and meetings proceedings for published and unpublished randomized trials from January 1st 2000 to December 1st 2017.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.