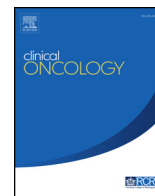




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Overview

Systematic Review and Meta-analysis of Conventionally Fractionated Concurrent Chemoradiotherapy versus Altered Fractionation Radiotherapy Alone in the Definitive Management of Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

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Abstract

Aims: Treatment intensification either by using concurrent chemoradiotherapy (CCRT) or altered fractionation radiotherapy (AFRT) improves outcomes of locoregionally advanced head and neck squamous cell carcinoma (HNSCC). The superiority of one approach over the other, however, remains to be firmly established. The aim of the present study was to compare outcomes of CCRT versus AFRT in the definitive non-surgical management of locoregionally advanced HNSCC for evidence-based decision making.

Materials and methods: An electronic search of Medline via PubMed was conducted with no language, year, or publication status restrictions. The Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effectiveness (DARE) were also searched electronically. Only randomised controlled trials assigning HNSCC patients randomly to conventionally fractionated CCRT or AFRT alone were included. Data were extracted independently by two reviewers and pooled using the Cochrane methodology for meta-analysis and expressed as a hazard ratio with 95% confidence intervals. Overall survival was the primary outcome of interest, whereas disease-free survival, locoregional control and toxicity were secondary end points.

Results: Five randomised controlled trials (involving 1117 patients and 627 deaths) directly comparing conventionally fractionated CCRT with AFRT alone were included. The risk of bias in included studies was low for efficacy outcomes, but high for toxicity outcomes. The overall pooled hazard ratio of death was 0.73 (95% confidence interval = 0.62–0.86), which significantly favoured conventionally fractionated CCRT over AFRT alone ($P < 0.0001$). Similarly, disease-free survival (hazard ratio = 0.79, 95% confidence interval = 0.68–0.92; $P = 0.002$) and locoregional control (hazard ratio = 0.71, 95% confidence interval = 0.59–0.84; $P < 0.0001$) were significantly improved with CCRT. There were no significant differences in the incidence of severe acute toxicity (dermatitis and mucositis) between the two approaches of treatment intensification. Late xerostomia was significantly increased with CCRT. Significant haematological toxicity and nephrotoxicity were seen exclusively with chemotherapy.

Conclusion: There is moderate quality evidence that conventionally fractionated CCRT improves survival outcomes compared with AFRT alone in the definitive radiotherapeutic management of locoregionally advanced HNSCC. No form of acceleration can potentially compensate fully for the lack of concurrent chemotherapy.

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Key words: Altered fractionation; chemoradiotherapy; concurrent; head and neck cancer; meta-analysis

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a common cause of cancer worldwide, more so in the developing countries where it constitutes almost one-

quarter of their cancer burden [1,2]. HNSCC largely remains a locoregional disease, making definitively locoregional therapy (either surgery or radiotherapy or both) the mainstay of treatment over the last few decades. Although distant metastases have increasingly been documented in

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recent times [3,4], locoregional recurrence still remains the predominant pattern of failure in HNSCC. Recent emphasis on preservation of organ form and function [5,6] with a potential favourable impact on quality of life has prompted more widespread use of definitive non-surgical approaches, particularly for cancers of the laryngo-pharynx. Traditionally, the most common non-surgical approach has been radical radiotherapy using conventional fractionation defined as radiotherapy given at a dose of 1.8–2 Gy per fraction, one fraction per day, five fractions per week to the prescribed total dose (generally 66–70 Gy in HNSCC) over 6.5–7 weeks [7,8].

It is now firmly established that the intensification of such treatment either by the addition of chemotherapy or by the alteration of the conventional fractionation schedule improves outcomes in the radiotherapeutic management of locoregionally advanced HNSCC [9]. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) provided robust and high-quality evidence for the benefit of adding chemotherapy [10] to locoregional treatment, which was later reconfirmed in a more recent and larger update [11]. Although the addition of any chemotherapy improved overall survival, maximal benefit (6.5% at 5 years) was seen with concurrent chemoradiotherapy (CCRT). In parallel, the Meta-Analysis of Radiotherapy in Carcinomas of the Head and neck (MARCH) also established the superiority of altered fractionation radiotherapy (AFRT) over conventional fractionation [12,13]. Any alteration of fractionation was associated with an overall survival benefit of 3.4%, with maximal benefit (8.2% at 5 years) from hyperfractionated radiotherapy (HFRT) compared with conventional fractionation [12,13]. Despite improving outcomes, AFRT has largely been ignored by the head and neck oncology community that has readily adopted conventionally fractionated CCRT as the contemporary standard of care in the radiotherapeutic management of locoregionally advanced HNSCC [14,15]. The evidence for the superiority of one approach of treatment intensification over the other remains to be established due to a relative lack of trials directly comparing the two, with the choice currently being dictated by personal and/or institutional biases. An indirect comparison meta-analysis [16] based on the MACH-NC and MARCH meta-analyses concluded that both CCRT and HFRT are significantly better than conventionally fractionated radiotherapy alone, but are comparable with one another for overall survival. It also concluded that accelerated radiotherapy (AXRT) alone with or without total dose reduction cannot compensate fully for the lack of chemotherapy.

Recently, randomised trials have directly compared both these approaches of treatment intensification. Although a couple of them have reported improved outcomes with conventionally fractionated CCRT compared with AFRT alone, others have failed to show a clear superiority of one approach over the other, possibly due to limitations of a small sample size and the associated low statistical power of individual studies. This provides an opportunity to pool the results of individual studies using modern meta-analytical methods to generate robust evidence for the

most optimal approach of treatment intensification in the radiotherapeutic management of locoregionally advanced HNSCC.

The primary aim of this analysis was to compare the outcomes of conventionally fractionated CCRT with AFRT alone in the definitive management of locoregionally advanced HNSCC for evidence-based decision making regarding the best form of treatment intensification.

Materials and Methods

This was a systematic review carried out in accordance with the Cochrane handbook [17] for systematic reviews of interventions. The quality of evidence was appraised and graded using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) [18] system. Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19] were used for preparation of the manuscript.

Literature Search Strategy

Eligible studies directly comparing conventionally fractionated CCRT with AFRT alone in the definitive management of locoregionally advanced HNSCC were identified through a systematic search of the medical literature using a validated search strategy. An electronic search of Medline via PubMed was conducted on 31 January 2014 with no language, year or publication status restrictions. The Cochrane Central Register of Controlled Trials (CENTRAL) and Database of Abstracts of Reviews of Effectiveness (DARE) were also searched electronically. Details of the search strategy are presented in [Appendix 1](#). The electronic search was further supplemented by hand-searching review articles, cross-references and conference proceedings.

Study Selection

For inclusion in the meta-analysis, trials had to be randomised controlled trials, include patients with locoregionally advanced but non-metastatic HNSCC, offer curative-intent treatment with primary non-surgical approaches, last accrual no later than January 2012 (enabling a minimum 2 year follow-up) and not be confounded by additional therapeutic differences between the two groups. Trials randomly assigning patients to platinum-based conventionally fractionated CCRT regimens or any form of altered fractionation were included. Trials comparing the two approaches in the postoperative adjuvant setting were excluded. Multi-arm trials were considered eligible, if they provided a direct comparison between CCRT and AFRT. Only the appropriate arms were included in the comparison from multi-arm trials. For trials with more mature data published or presented at a date later than the index publication, relevant data were also extracted from the update. Corresponding authors of the included studies were contacted for more information, clarifications, if any, and updated information whenever necessary.

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