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Efficacy and mucosal toxicity of concomitant chemo-radiotherapy in patients with locally-advanced squamous cell carcinoma of the head-and-neck in the light of a novel mathematical model

Lidia Strigari[a,*], Paola Pinnarò[b], Paolo Carlini[c], Francesco Torino[d], Silvia Strolin[a], Silvia Minosse[a], Giuseppe Sanguineti[b], Marcello Benassi[e]

[a] Laboratory of Medical Physics and Expert Systems, Regina Elena National Cancer Institute, Rome, Italy
[b] Department of Radiation Oncology, Regina Elena National Cancer Institute, Rome, Italy
[c] Department of Medical Oncology, Regina Elena National Cancer Institute, Rome, Italy
[d] Department of Systems Medicine, Chair of Medical Oncology, University of Rome Tor Vergata, Rome, Italy
[e] Medical Physics Unit, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola, FC, Italy

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ABSTRACT

Background: In the last several decades, combined radiotherapy (RT) and chemotherapy (CT) have been recognized as feasible in locally-advanced-squamous-cell-carcinoma of the head-and-neck (LA-HNSCC). Several meta-analyses identified concurrent RT + CT (CRT) most likely effective approach respect to RT-alone. However, radiobiological models comparing different chemotherapeutic schedules against delivered RT fractionation schedule for overall survival and toxicity are still needed.
Methods and materials: Based on 9 randomized trials (2785 patients), radiobiological models and multivariate logistic regression model were used to derive dose-response curves and estimate the 5-year-overall survival (OS) and ≥G3 acute mucositis rate of CRT or RT-alone.
Results: Equivalent dose at 2 Gy/fraction (EQD2) was calculated using the linear quadratic model. The effect of CRT schedules, considering the CT type and its administration schedule and the HPV status of tumors were estimated using the univariate/multivariate logistic regression. The multivariate logistic regression model for 5y-OS indicated EQD2 and the type of CT, the chemo-sensitization fraction and the HPV status significant prognostic factors, while for toxicity both EQD2 and the concomitant administration of 5-fluorouracil (5Fu) resulted as significant prognostic factors. Combined schedules cisplatin (DDP)+/−5Fu + RT produced the higher OS compared with combined carboplatin+/−5Fu + RT or RT-alone.

* Corresponding author at: Laboratory of Medical Physics and Expert Systems, Regina Elena National Cancer Institute, via E. Chianesi 53, 00144 Rome, Italy.
E-mail address: strigari@ifo.it (L. Strigari).

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The concomitant administration of Fu and schedule with high EQD2 increase the rate of observed ≥G3 acute mucositis.
Conclusion: Multivariate logistic regression models can be used to predict CRT effect in terms of OS and ≥G3-mucositis, contributing to the identification of novel treatment schedules.

1. Introduction

To improve the generally poor tumor control obtained with either surgery or radiation-therapy (RT) in patients affected by locally-advanced squamous-cell-carcinoma of the head-and-neck (LA-HNSCC), conventional modified fractionation regimens and combined RT + chemotherapy (CT), with or without surgery, have been used. The benefit of concomitant chemo-radiotherapy (CRT) has been widely investigated (Pignon et al., 2009; Blanchard et al., 2011). The majority of studies and meta-analyses found that CRT significantly improves both local control (LC) and overall survival (OS). Although, the advantage in term of OS is no longer significant in resectable tumors when salvage surgery is part of the treatment (Forastiere et al., 2013).

Currently, concurrent cisplatin (DDP) and RT is the standard treatment for fit patients with LA-HNSCC (NCCN: http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf). However, the improvements of CRT compared with RT-alone were in some cases obtained at the expense of a significant increase in toxicity. Unfortunately, because of the extreme heterogeneity of clinical studies regarding both RT (total doses, fractionation and treatment time) and CT (the drug(s) and schedule), tools helping clinicians in balancing the highest efficacy with the lowest toxicity are yet to be identified to obtain the optimal CRT regimen.

Herein, we investigated the possibility to use multivariate logistic regression models to predict the clinical outcome, and in particular, the 5-year-OS (5y-OS) and the ≥G3 acute mucositis rate, after CRT or RT-alone, based on data from published randomized clinical trials. We focused on 5-year efficacy outcomes because at this time a clinical benefit in terms of OS has been reported by previous meta-analyses (Pignon et al., 2009; Blanchard et al., 2011).

There are some indications that acute side effects of CRT are more severe compared with each single treatment (Zackrisson et al., 2003), thus requiring interventions for preventing mucositis, which are not yet definitively assessed (Worthington et al., 2011). In addition, even if acute local toxicity is considered widely manageable in clinical practice, it affects quality of life in the majority of patients. In some subgroups, such as older patients, it may hamper the delivery of the scheduled treatment and outcomes. Furthermore, in our investigation we included the timing of the drug administration, which would interfere with cell repair process, as well as the treatment-related acute toxicity.

2. Materials and methods

2.1. Data preparation

To identify study we did a broad search of 3 databases Medline, Scopus, and Cochrane Library, supplemented by hand searches of meeting abstracts (ASCO, ASTRO, ECCO, EMSO, ESTRO) and trial registry. To be eligible for inclusion in our analysis, study population has to meet the following inclusion/exclusion criteria: (1) untreated patients affected by non metastatic LA-HNSCC; trials including different groups of patients with HN tumors (*i.e.* the oral cavity, oropharynx, hypopharynx and larynx) were included, while those comprising only nasopharyngeal carcinoma were excluded; (2) radiotherapy and CRT; (3) randomized clinical trials; (4) trials published in the last 15 years, in the attempt to evaluate modern treatment schedules; (5) cohorts of patients with ≥5 years median follow-up; (6) all the efficacy endpoints (*i.e.* 5y-OS; loco-regional free survival, LRFS and distant metastases rate, DM) and the ≥G3 mucositis rate should be clearly reported; (7) post-surgery CRT and induction CT were both exclusion criteria.

Reviews were screened for additional papers. All data were checked for internal consistency and compared with data published in related papers. Each trial was analyzed individually. The full search strategy is detailed in the Appendix A-Supplementary data, as well as the paper selection process reported in a flow-chart, using the PRISMA statement.

Two independent researchers screened the title and abstract for potentially evaluable studies. We retrieved the full text of selected papers and extracted all the efficacy endpoints using the WinDig vers.1.0 software (http://life.bio.sunysb.edu/morph/windig.html).

Eleven randomized trials (Forastiere et al., 2013; Bourhis et al., 2012; Calais et al., 1998; Ang et al., 2010; Staar et al., 2001; Jeremic et al., 1997, 2004; Huguenin et al., 2004; Brizel et al., 1998; Budach et al., 2005) were identified reporting four clinical endpoints. Nine trials (2785 patients) were used to extract model parameters for mixed LA-HNSCC cohort. One study has been excluded because it tested the induction CT (Corvò et al., 2001), and another one because it was the only study investigating mithomycin-C as concomitant drug (Budach et al., 2005). Data were extracted by using Kaplan-Meyer curves for all the studies and were consistent with the text. Toxicity data were derived by tables/text. A dataset has been generated based on cancer type, RT schedules, the number of patients (Table 1), median follow-up, 5y-OS, 5y-LRFS, 5y-DM and the ≥G3 mucositis rate (Table 2). Of note, the decision of excluding the postoperative group is based on the fact that the number of clonogenic cells after surgery should be different than in non-operated patients. The expected 5y-OS should be higher when the number of clonogens is lowered by surgery.

Moreover, data on human papillomavirus (HPV) status have been extrapolated from the paper by Calais et al. (1998) and applied to the whole population, assuming the same percentage of HPV positive or negative according to type of tumor (oropharynx *versus* other types).

2.2. Radiobiological models

The biologically effective dose (*BED*) was calculated using the following formula:

$$BED = D\left[1 + \frac{d}{(\alpha/\beta)}\right] - K \cdot [OTT\,(days) - T_{del}] \quad (1)$$

where: D = total dose; d = dose/fraction and $\alpha/\beta = 10Gy$ for tumor control, the overall treatment time was calculated as OTT (days) = 7.OTT (weeks), the re-population daily dose equivalent per day was $k = 1\mathrm{n}(2)/\left(\alpha \cdot T_{pot}\right) = 0.6Gy_{10}/day$, $T_{del} = 25days$ and $T_{pot} = 3days$.