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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

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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.

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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 $T_{pot} = 3days$.

Table 1
Details on analyzed studies including the number of patients (# Pts), percentage of patients with oropharynx tumors (OP%), type and cycles of chemotherapy (CT), dose/fraction (d1/fr or d2/fr), number of fractions (N1 or N2), the overall treatment time (OTT), equivalent dose at 2 Gy/fraction (EQD_2), correct number cycles received (%) and chemo-sensitization fraction (FCS).

Reference	Trial identification number	RT course	# Pts	OP (%)	CT	Type of CT	Cycles	Correct number cycles received (%)	FCS	d1/fr (Gy)	N1	d2/fr (Gy)	N2	OTT (wks)
(Worthington et al., 2011)	GORTEC(§) 99-02	VeryART	281	65	No				0	1.8 × 2	18	0	0	3.7
		Conv	279	66	Yes	Carbo-Fu	3	71	29	2	35	0	0	6.9
		Hfx-ART	280	67	Yes	Carbo-Fu	2	92	67	2	20	1.5 × 2	10	6
(Bourhis et al., 2012)	GORTEC(§) 94-01	Conv	112	100	No				0	2	35	0	0	7.1
		Conv	108	100	Yes	Carbo-Fu	3	66	34	2	35	0	0	7.3
(Calais et al., 1998)	RTOG(#) 0129	Conv	361	60	Yes	DDP	3	69	9	2	35	0	0	7
		Hfx-ART	360	60	Yes	DDP	2	88	7	1.8	18	1.65 × 2	12	6
(Ang et al., 2010)	Cologne 95	Hfx-ART	127	69	No				0	1.8	15	1.8 + 1.5	13	6
		Hfx-ART	113	81	Yes	Carbo-Fu	2	90	36	1.8	15	1.8 + 1.5	13	6
(Staar et al., 2001)	Kragujevac1	Hfx	65	35	No				0	1.1 × 2	35	0	0	6.7
		Hfx	65	38	Yes	DDP	1	100	97	1.1 × 2	35	0	0	6.7
(Jeremic et al., 1997)	Kragujevac2	Conv	53	40	No				0	2	35	0	0	7.3
		Conv	53	36	Yes	DDP	35	91	100	2	35	0	0	7.3
		Conv	53	38	Yes	Carbo	35	92	100	2	35	0	0	7.3
(Jeremic et al., 2004)	SAKK(*) 10/94	Hfx	111	53	No				0	1.2 × 2	31	0	0	6.3
		Hfx	112	53	Yes	DDP	2	71	48	1.2 × 2	31	0	0	6.1
(Huguenin et al., 2004)	Duke 90040	Hfx	60	48	No				0	1.25 × 2	30	0	0	6
		Hfx	56	41	Yes	DDP-Fu	2	98	36	1.25 × 2	28	0	0	6.7
(Brizel et al., 1998)	INR C-HN-9 (°)	Hfx	66	36	No				0	1.875	40	0	0	6
		Conv	70	40	Yes	DDP-Fu	4	54	67	2	30	0	0	6

Abbreviations: DDP = cisplatin; MMC = mitomycin; Carbo = carboplatin; Fu = concurrent 5-Fluorouracil; Conv = Conventional RTfractionation; Hfx = hyper-fractionated (*e.g.* x2 = twice daily); ART = accelerated RT reducing the OTT; wks = weeks; Legend: (§) GORTEC = Grouped'OncologieRadiothérapie Tête Et Cou; (#) RTOG = Radiation Therapy Oncology Group; (*) SAKK = Swiss Group for Clinical Cancer Research; (°) INR C-HN = IstitutoNazionale per la RicercasulCancro—Head and neck.

Table 2
Details on analyzed studies including the median follow-up and the different evaluated endpoints.

Reference	Trial	Enrollement years	RT course	CT	Type of CT	F-up (yrs)	EQD_2 (Gy)	5y-OS (%)	5y-LRFS (%)	5y-DM (%)	≥G3 tox (%)
(Worthington et al., 2011)	GORTEC 99-02	2000–2007	VeryART	No		5.2	73.0	31.5	47	22.5	89
			Conv	Yes	Carbo-Fu	5.2	58.4	30	53	22.7	78.0
			Hfx-ART	Yes	Carbo-Fu	5.2	64.0	35	56	19.3	85
(Bourhis et al., 2012)	GORTEC 94-01	1994–1997	Conv	No		5.5	57.7	15.8	24.7	23	30
			Conv	Yes	Carbo-Fu	5.5	57.0	22.4	47.6	32	56
(Calais et al., 1998)	RTOG 0129	2002–2005	Conv	Yes	DDP	7.9	58.0	57	69	14.6	39.6
			Hfx-ART	Yes	DDP	7.9	67.3	60	66	12	33.1
(Ang et al., 2010)	Cologne 95	1995–1997	Hfx-ART	No		4.7	65.6	16	12	7.7	52
			Hfx-ART	Yes	Carbo-Fu	4.7	65.6	25	22	18.5	68
(Staar et al., 2001)	Kragujevac1	1991–1993	Hfx	No		4.6	67.3	25	36	43	42
			Hfx	Yes	DDP	4.6	67.3	46	50	14	49
(Jeremic et al., 1997)	Kragujevac2	1988–1990	Conv	No		5.6	57.0	15	27	11.3	4
			Conv	Yes	DDP	5.6	57.0	29	52	7.5	11
			Conv	Yes	Carbo	5.6	57.0	32	48	7.5	8
(Jeremic et al., 2004)	SAKK 10/94	1994–2000	Hfx	No		9.5	67.3	32	36	5.35	62
			Hfx	Yes	DDP	9.5	68.0	46	51	6.25	60
(Huguenin et al., 2004)	Duke 90040	1990–1995	Hfx	No		3.4 (§); 5*	69.6	25	43	18	77
			Hfx	Yes	DDP-Fu	3.4 (§); 5*	62.0	48.5	70	27	77
(Brizel et al., 1998)	INR C-HN-9	1992–1998	Hfx	No		5	65.7	19.4	21	21	63.0
			Conv	Yes	DDP-Fu	5	51.5	33.3	20	20	33.0

Abbreviations: CT = chemotherapy; DDP = cisplatin; MMC = mitomycin; Carbo = carboplatin; Fu = concurrent 5-Fluorouracil; OTT = overall treatment time; Conv = conventional RT fractionation; Hfx = hyper-fractionated (*e.g.* x2 = twice daily); ART = accelerated RT reducing OTT; yrs = years; F-up = median follow-up; OS = overall survival; LRFS = loco-regional free survival; DM = distant metastases rate; 5y = at 5 years; ≥G3 tox = G3 or more acute mucositis rate.Legend: (§) for patient alive; (*) Based on the randomization date and published papers. EQD_2 = equivalent dose at 2 Gy fraction calculated using the Eq. (2).

The equivalent dose at 2 Gy/fraction EQD_2 was calculated using the following formula:

$$EQD_2 = \frac{BED}{1 + \frac{2}{(\alpha/\beta)}} \quad (2)$$

and reported in Table 1. In Eqs. (1) and (2), the incomplete repair has not been included because it modifies BED/EQD_2 by a few percentage points (Strigari et al., 2012).

The conversion based on Eqs. (1) and (2) was applied to the prescribed dose to high level planning target volume (PTV), including primary and involved nodes. Furthermore, we assumed that the dose delivered to the mucosa was uniform and equal to the prescribed dose to the target, because we did not have any access to patients' dose volume histograms (DVHs).

2.3. Chemo-sensitization fraction

The chemo-sensitization fraction (CSF) defined as the ratio between the number of CT administrations and the total number of RT fractions (*i.e.* N1 + N2 of Table 1) is also reported in Table 1.

2.4. Data analysis and statistics

The odd ratio (OR) has been calculated for the investigated studies to evaluate the homogeneity of investigated cohorts (Mantel and Haenszel, 1959).

The multivariate logistic regression analysis (MVA) was used to derive dose-response curves from clinical data (*i.e.* 5y-OS) as a function of EQD_2 (continuous variable), CT administration (yes/no), CT type (Carbo/DDP), CSF (continuous variable), CT treatment with/without concurrent 5-Fluorouracil (5-Fu), cumulated dose of 5-Fu in mg (continuous variable) and HPV status (positive/negative). The MVA of ≥G3-mucositis included EQD_2 (continuous variable), CT administration (yes/no), CT type (Carbo/DDP), CT treatment with/without concurrent 5-Fu, cumulated dose of 5-Fu in mg (continuous variable) and CSF (continuous variable).

The Bayesian information criterion (BIC) has been used to introduce a penalty term for the number of parameters in the model and assess the best model.

The bootstrap approach was used to validate the model using B = 1000. Optimism of model and the bias-corrected Area Under the Curve (AUC) were calculated. The calibration curve was calculated using re-sampling and the mean absolute error and the mean squared error was derived. The correlation between predicted and observed values was assessed by Pearson *t*-test. P-values lower than 0.05 were considered statistically significant.

3. Results

Investigated trials regard studies considering an EQD2 ranging from 50 to 63 Gy and different schedules of carboplatin or cisplatin using a median value of CSF of 42% (range 7–100%).

Overall CRT statistically improves the 5y-OS rate in patients with LA-HNSCC when compared with RT-alone (p = 0.001), while it seems that it does not increase the ≥G3 mucositis rate (p = 0.963).

The analysis of OR comparing the number of reported deaths revealed that there is not significant heterogeneity within the investigated groups with an OR of 0.45 (0.33–0.62) for DDP-based CRT *versus* RT alone (Fig. 1a) and of 0.81 (0.65–1.00) for carbo-based CRT *versus* RT alone (Fig. 1b). Moreover, different schedules of radiotherapy need to be taken into consideration to correctly address the advantage or not of CRT.

The MVA for 5y-OS indicated EQD_2 and the type of CT, the CSF and the HPV status as significant prognostic factors (Table 3). In particular, the 5y-OS increases when the EQD_2 increases, thanks to the use of accelerated and/or hyper-fractionated schedules. The lower values of chemo-sensitization fraction were associated to higher values of OS, suggesting that the effect of CT should be referred to mechanisms different from the chemo-sensitization alone, which it is out of the scope of this paper. AUC was 0.76, and it was confirmed during the validation procedure while a mean squared error = 0.00336 was obtained by the calibration phase. The Pearson correlation test was 0.807 (p < 0.0001).

Table 3
Multivariate logistic regression model for 5y-OS indicated EQD_2 and the type of CT and the CSF significant prognostic factors.

Parameters	Coefficient	Standard Error	Wald Z	p-value
Intercept	−5.0631	0.6255	−8.09	<0.0001
EQD2	0.0453	0.0091	4.99	<0.0001
CT_type 1	0.6953	0.1596	4.36	<0.0001
CT_type 2	1.9080	0.1327	14.37	<0.0001
FCS	−0.0044	0.0019	−2.28	0.0225
HPVp = 1	1.8321	0.0954	19.21	<0.0001

Null model-2 Log Likelihood = 3675.2; Full model-2 Log Likelihood = 3233; P < 0.0001. Abbreviations: CT_type 1 = carboplatin; CT_type 2 = cisplatin; CSF = chemo-sensitization fraction.

Table 4
Multivariate logistic regression model for ≥G3-mucositis rate indicated EQD_2 and the concomitant administration of 5-Fu significant prognostic factors.

Parameters	Coefficient	Standard Error	Wald Z	p-value
Intercept	−8.0396	0.4928	−16.31	<0.0001
EQD2	0.1259	0.0077	16.29	<0.0001
Fu = 1	1.7282	0.1023	16.89	<0.0001

Null model-2 Log Likelihood = 5151; Full model-2 Log Likelihood = 4721; P < 0.0001. Abbreviations: Fu = concurrent 5-Fluorouracil.

In Fig. 2 the 5y-OS against the EQD2 is also reported for both carbo- or DDP-based CRT data, the size of symbols represents the logarithm of the chemo-sensitization, the solid lines show the predicted model based on the above described multivariate logistic regression approach, the dashed lines represent the lowest (*i.e.* 7) and highest value (*i.e.* 100) of CFS. In this plot the lower values of chemo-sensitization fraction were associated to higher values of OS, suggesting that the effect of CT should be referred to mechanisms different from the chemo-sensitization alone. Of note, in our dataset there was one trial using low dose carbo- and cisplatin (Fig. 2).

At the univariate analysis, the ≥G3-mucositis rate was higher (13% *versus* 8%) in schedules with the concomitant administration of 5-Fu, although the difference was not statistically significant (p = 0.15).

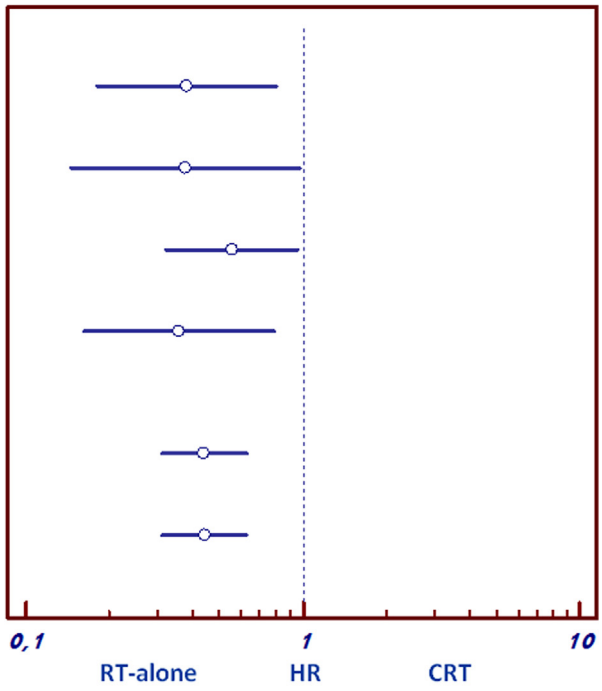
At the multivariate analysis, the EQD_2 and the concomitant administration of 5-Fu resulted as a significant prognostic factors of toxicity. Fig. 3 shows the experimental ≥G3-mucositis rate *versus* EQD2 for combined CRT with/without 5-Fu and the solid line indicates the predicted model (see Table 4) for the two groups (*i.e.* CRT with/without 5-Fu). AUC was 0.73 and it was confirmed during in the validation procedure, with a mean squared error = 0.0002 obtained based on the calibration phase. The Pearson correlation test was 0.882 (p < 0.0001). In the analyzed studies, 18% (range: 0%–46%) of patients did not complete the CRT treatment due to treatment-induced toxicity. Moreover, the compliance to the CRT schedule was lower when 5-Fu was co-administered (78% *versus* 85%, respectively) although the difference was not statistically significant.

The 5y-LRFS/DM rates show a large overlap in our cohort. The different rates of 5y-LRFS could also be affected by the different doses received by non-elective nodes, resulting very heterogeneous between studies (as indicated in Table 1). The increment

a.

TRIAL	CRT	RT-alone	OR	95% CI
Kragujevac1	35/65	49/65	0.381	0.181-0.803
Kragujevac2	36/53	45/53	0.376	0.146-0.971
SAKK 10/94	60/112	75/111	0.554	0.321-0.954
Duke 90040	29/56	45/60	0.358	0.163-0.785
Tot.(fixed effects)	160/286	214/289	0.44	0.309-0-627
Tot.(random effects)	160/286	214/289	0.441	0.309-0.629

Test for heterogeneity
Q = 1.2, DF = 3, P = 0.7530



b.

TRIAL	CRT	RT-alone	OR	95% CI
GORTEC 94-01	84/108	94/112	0.67	0.340-1.321
Cologne 95	85/113	107/127	0.567	0.299-1.077
Kragujevac2	36/53	45/53	0.376	0.146-0.971
GORTEC 99-02 (*)	195/279	194/281	1.041	0.727-1.492
GORTEC 99-02 (**)	182/280	194/281	0.833	0.585-1.185
Tot.(fixed effects)	582/833	634/854	0.809	0.653-1.003
Tot.(random effects)	582/833	634/854	0.77	0.580-1.021

(*) = Conventional RT course (**) = Hyper-fractioned accelerated RT course

Test for heterogeneity
Q = 5.8903, DF = 4, P = 0.2075

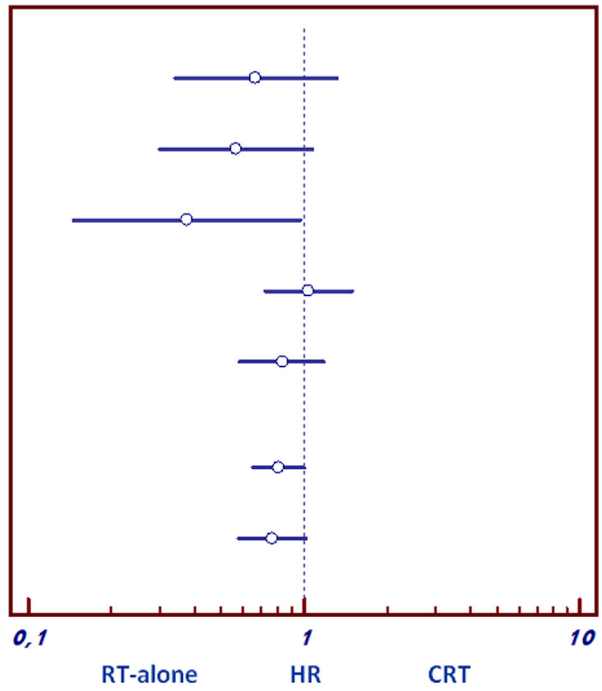


Fig. 1. Odd ratio (OR) based on 5-year overall survival (5y-OS) for randomized trials comparing cisplatin- (*i.e.* DDP) (a) and carboplatin- (carbo) based (b) concomitant radio-chemotherapy to radiotherapy alone. For trial identification see Tables 1 and 2. Columns CRT and RT-alone indicate the number of death/number of patients for the corresponding treatment arm. Abbreviations: Q = the weighted sum of squares on a standardized scale; DF = the degree of freedom; 95% CI = indicates the 95% confidence interval; P = the p-value.

of 5y-DM rates (solid lines) was higher for RT-alone than for CRT. This could be probably obtained because the 5y-OS increases when the EQD2 increases and thus DMs could be registered. In these cases, the rates of DMs were lower in patients who undergone concomitant CT, due to the effect of CT on microscopic disease distant from irradiation fields.

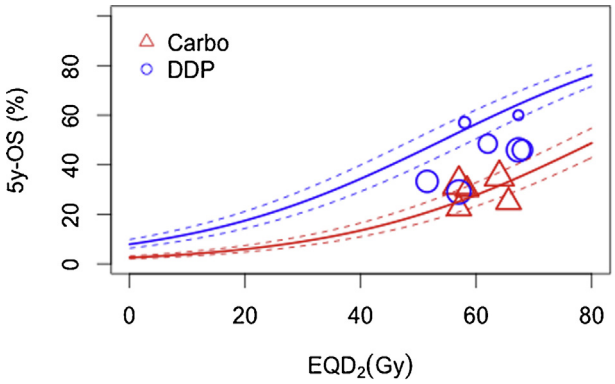


Fig. 2. The 5-year overall survival (5y-OS) against equivalent dose at 2 Gy/fraction (EQD_2) curve for cisplatin- (DDP-) and carboplatin- (carbo-) based chemotherapy. The size of the symbols represents the logarithm of chemo-sensitization fraction (CSF). The solid lines shows the multivariate logistic model prediction reported in Table 3, while the dashed lines are the lowest/highest values of CSF (*i.e.* 7 and 100%, respectively).

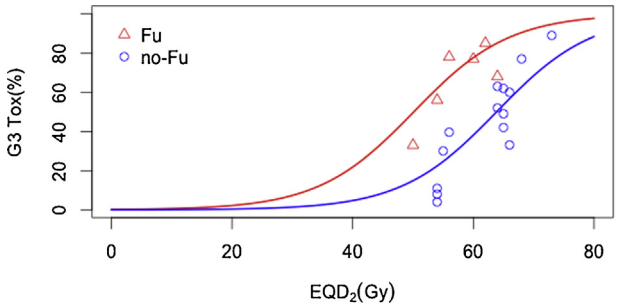


Fig. 3. The ≥G3-mucositis rate against the equivalent dose at 2 Gy/fraction (EQD_2) distinguishing chemotherapy with/without concurrent 5-Fluorouracil (Fu). The solid lines show the multivariate logistic model prediction reported in Table 4.

4. Discussion

CRT is a recommended treatment for patients affected by LA-HNSCC and it is now the standard of care as an organ-sparing approach in the treatment of stage III–IV squamous-cell-carcinoma (SCCs) of the larynx and the hypopharynx (Zbaren et al., 2008).

Given the complexity of managing LA-HNSCC patients, a multidisciplinary team approach is essential to fully understand the effect of combined strategies. In fact, various therapeutic issues remain to be resolved yet, including the optimal platinum-based regimen to be administered concurrently with RT, the type of platinum agent to be used (DDP *versus* carboplatin), the total dose of the platinum compound, the number of cycles, the best schedule of administration (daily, weekly, every 3 weeks, *etc.*), and whether to use it as a monotherapy or in combination with other cytotoxic agents. Moreover, as the optimal schedule that eventually could increase the rates of LC and/or OS, limiting at the minimum radiation-induced side effects, remains to be determined yet, the need of additional investigations is of utmost importance. Indeed, considering the limited number of randomized trials that evaluated not-platinum containing regimens, we focused our study on results obtained by DDP- and Carboplatin-based CRT trials.

To deeply investigate CRT effects, nine randomized trials have been selected from literature and we focused on the possibility of using radiobiological and logistic regression model to assess the impact of different fractionation schedules of RT and concurrent CT.

The novelty of our work resides in the estimation of the benefit of CRT in terms of 5y-OS or toxicity by using EQD_2, a formula including the RT treatment schedule, which is frequently different between compared arms. In fact, some randomized trials tested both the reduction of the overall treatment time (OTT) together with the change of type/duration of CT, not considering that in particular for head and neck cancers, the repopulation time is a crucial parameter (Bourhis et al., 2006). The striking radiobiological reason for the use of hyper-fractionated and/or accelerated RT protocols is the reduction of tumor cell repopulation, mostly seen in the second half of RT-course, while sparing normal tissues. A model has been proposed by Fenwick and colleagues (Fenwick et al., 2012) for evaluation of LC in LA-HNSCC for RT alone trials *versus* the EQD_2 (see cohort C), further highlighting the relevance of OTT and fractionation schemes. Another model explains toxicity only based on dose, dose-fraction and OTT (Mantel and Haenszel, 1959). Unfortunately, these models are not available for CRT schedules. Hartley and colleagues (Hartley et al., 2010) reported a linear increase on the toxicity rates for each EQD_2 increment as well as on local control (Meade et al., 2013). Unfortunately, this model does not take into consideration the type of CT.

Furthermore, the meta-analysis by Bourhis et al. (2012) underlined the importance of increasing total RT-dose in order to improve LC and OS, but comparing different schedules with or without CT could introduce additional confounding variables.

In our evaluation, we quantified the increase of 5y-OS obtained by the reduction in OTT and/or the concomitant administration of CT, taking into account the number of delivered CT cycles.

Logistic regression model was able to explain the 5y-OS of investigated trials, confirming the superiority of CRT compared with RT-alone in terms of OS in patients with LA-HNSCC, in particular when DDP-based CT-schedules are used. Lower DDP-doses or carbo-CRT may be better tolerated, but the survival outcomes are still controversial (Go and Adjei, 1999). In fact, 5y-OS rates were similar for concomitant low doses DDP- *versus* carbo-based CRT (Ghi and Floriani, 2011), but a statistically higher 5y-OS was observed when few administrations and the high DDP doses were used. Indeed, this treatment strategy currently represents the gold standard CRT for LA-HNSCC patients (Meade et al., 2013). Of note, our analysis includes a single trial with low doses DDP- or Carbo-based CRT. Furthermore, MVA allows investigating simultaneously different potential prognostic factors on a larger cohort based on nine randomized clinical trials.

In this regard, although the key mechanism of the RT/DDP interaction is considered to lethally affect damage repair (Orrecchia et al., 1994), inhibition of sub-lethal damage repair, selective radiosensitization of hypoxic cells and other mechanisms may also play important roles (Pajak et al., 1991). Laboratory data showed that the DDP-enhanced RT-effect is more pronounced when drug is present in target cells during irradiation (Schaake-Konig et al., 1992), especially when fractionated schedules are used (Schwachofer et al., 1991). However, this effect seems to be not supported from clinical data, as confirmed in present study. Of relevance, Fig. 2 suggests the intriguing issue whether high-dose carboplatin should be equal to low dose cisplatin in CRT treatment in the investigated patient population. However, this issue requires further prospective investigations to be clarified.

Moreover, in this study 5-Fu was more frequently associated to carbo-based (5/7 trials) than to DDP-based treatments (2/7 trials). As 5-Fu typically induces mucositis, this might explain the higher rates of mucositis reported in the selected trials (Table 2 and Fig. 3).

Of note, we considered the additional effect of CT in the entire spectrum of the adopted doses, not assuming the same slope at any dose, in particular for ≥G3 toxicity. This allows appreciating the different improvements of CT also when OS/toxicity rates are far from 50%. Furthermore, because ≥G3-mucositis is largely reversible and most patients recover over time, the overall therapeutic gain of

CRT could remain high when considering the long-term side-effect, such as fibrosis which is observed in few patients.

Our study present some limits. Firstly, it involves different patient populations as included in the selected studies. We tried to overcome this limitation calculating ORs within each randomized study according to the type of CT. The direct comparison between DDP- or carbo-based CT *versus* RT alone resulted significant, but not the indirect comparison between CT types. This could be probably due to the different RT schedules adopted within each arm in several of the investigated studies, suggesting that the assessment of EQD_2 could be crucial to more appropriately compare treatment results as pointed out by multivariate logistic regression.

The second limit consists in the fact that all comparisons are based on intention-to-treat analyses, although in the analyzed studies 18% (range: 0%-:46%) of patients did not complete the CRT treatment due to treatment-induced toxicity. For the CRT schedules, the treatment compliance of schedules with 5-Fu was lower (78% *versus* 85%, respectively) but the difference between schedules was not statistically significant. CRT potential advantage could out-weight in certain patients if treatment-derived complications would be reduced. In particular, intensive schedules may not be appropriate in LA-HNSCC patients with co-morbidity or poor performance status. Indeed, reduced compliance is observed in about one third of patients treated with intensive CRT (DDP:100 mg/m^2 every 3 weeks for 3 cycles) (Lamont and Vokes, 2001; Browman et al., 2001). Moreover, the number of survivors could have been reduced by severe treatment-induced-effects, including non-cancer related deaths. Co-morbidities may be particularly evident in the patients with long-term follow-up and may greatly affect outcomes in elderly population, who seem to derive less benefit from CRT regimens. However, the inefficacy of current treatments may represent the main reason explaining why in our investigation the maximum value of reported 5y-OS did not exceed the value 66%. An important related question is whether intensification of CT is unavoidable. To definitely assess the benefit of induction CT plus CRT *versus* CRT alone in patients with un-resectable LA-HNSCC some randomized trials are ongoing. Additionally, the concomitant use of molecularly targeted drugs combined with RT could further improve anti-tumor efficacy with a likely limited increase in toxicity (Bonner et al., 2010), but this goal remains a promising avenue of exploration.

Another issue needs to be further discussed. The majority of patients affected by oropharyngeal-SCC presents tumor positive for HPV infection with a higher 5y-OS (75–80%) than patients with HPV-negative tumors (45–50%). This could result as a confounding factor for trials enrolling only or mostly HPV positive tumor patients. For this reason it has been included as prognostic factor in the MVA, by extending to the new population the results reported by Calais et al. (1998). In this regard, emerging evidence supports HPV association with better response and survival in HNSCC patients treated with RT (Dok et al., 2014), suggesting the intriguing role of p16INK4a status as an independent predictive marker. However, the mechanism triggering this biological effect still has to be fully understood and it is not taken into account in our model.

The behavior of specific endpoints (5y-LRFS/DM rates) was different from that of 5y-OS rates and this could depend on multiple factors and heterogeneity in investigated trials (*e.g.* doses to primary lesion and elective nodes, as well as to the type of CT and type of administration), or to the fact that study power can be lowered when only few events are reported. In particular, we observed some differences in delivered doses to uninvolved (low and medium recurrence risk) nodes, which received any dose (*e.g.* RTOG 0129) or doses ranging from 40 to 62 Gy in all the remaining studies. Unfortunately this could not be adequately taken into consideration as dose delivered to each patient and related outcomes are lacking. Accordingly, models are developed using outcomes and median dose as reported in each patient group, assuming trivial the variation of total dose of few Gy for some patients.

Of note, in principle this approach could be used in post-operative setting. However, number of clonogenic cells after surgery and the starting of post-surgery RT could represent another potential limit for this method introducing additional biases (Strigari et al., 2008).

Obviously, the value of lag time (T_{del}) and (T_{pot}) could affect the value of the estimated EQD_2. The observed and modeled improvement of CRT is expected to remain, being the EQD_2 calculated using the same parameters for both CRT and RT-alone. However, we used largely proposed radiobiological model parameters.

Another potential issue could regard trials heterogeneity in the reported rates of mucositis and difference in grading system used for recording this side effect. As an example, the same toxicity grading scale (CTC version 2) was used in two studies from EORTC and RTOG (Bernier et al., 2004; Cooper et al., 2004), respectively, which evaluated two very similar treatment schedules in quite similar populations of patients. In the RTOG study, the reported ≥G3 mucosal toxicity of CRT *versus* RT was 62% *versus* 37%, respectively; while in the EORTC study it was 41% *versus* 21%, respectively. However, the percentage of high risk patients was 67% *versus* 34% in the RTOG and EORTC study, respectively. These data could have affected the treatment volumes and consequently the patient mucosal toxicity. In this regard, we focused our analysis on locally advanced stage and evaluated the heterogeneity of investigated population, resulting the heterogeneity test non statistically significant. Regarding change in the assessment of ≥G3 mucosal toxicity over time, we compared the CTC scales published from 1994 to 2009. The criteria for assessing the ≥G3 mucosal toxicity have been improved over time by including more specific toxicity-related details to consider in reporting, but key aspects of mucosal toxicity remained substantially unchanged throughout the analyzed period.

Finally, it should be emphasized that the aim of our study was not limited to comparing treatments outcomes and toxicity, but the main purpose was to explore parameters that in CRT schedules could potentially affect toxicity, efficacy and how efficacy could depend on toxicity. In this regard, mathematical models may help to interpret clinical results and to propose/support novel more rational schedules of treatment. In our study, multivariate logistic regression models emerged as simple and valid tools that can be used in estimating the CRT effect in terms of OS and ≥G3-mucositis, contributing to the identification of novel treatment schedules. Randomized clinical trials still remain the best way to demonstrate the superiority of new designed treatments respect to the standard schedule.

Conflict of interest

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Appendix A. Supplementary data

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