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ORIGINAL ARTICLE

Management of severe bio-radiation dermatitis induced by radiotherapy and cetuximab in patients with head and neck cancer: emphasizing the role of calcium alginate dressings

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Abstract

Purpose Severe bio-radiation dermatitis may develop in patients treated with concurrent radiotherapy and cetuximab for head and neck squamous cell carcinoma. The aim of our work was to report on the impact of a grade-specific management approach on treatment tolerability.

Methods Concomitant radiotherapy and cetuximab was prescribed for patients deemed ineligible for cisplatin-based chemoradiation. Since 2014, an advanced wound care nursing team was established in our clinic to implement a standardized policy for skin toxicity. A central role of calcium alginate dressings was defined in our management algorithm. The correlation between patient, disease, and treatment features with severe bio-radiation dermatitis and treatment tolerability was evaluated.

Results Between 2007 and 2018, 51 patients were treated at our center with radiotherapy and cetuximab. The incidence of G3/G4 bio-radiation dermatitis was 43.1%. Comparing two consecutive cohorts of 26 and 25 patients treated before and after January 2014, respectively, the adoption of a grade-specific dermatitis management allowed to improve treatment tolerability. A mean radiation treatment interruption of 8.42 days (SD, 6.73; 95% CI 5.7–11.1) was reduced to 0.86 days (SD, 2.66; 95% CI − 0.28–2.02) in the more recent group ($p < 0.0001$). Mean relative dose intensity of cetuximab was also significantly higher (86.3% vs 74.5%, $p = 0.0226$).

Conclusions Routine involvement of an advanced wound care management team and early consideration for calcium alginate dressings in case of moist desquamation should be warranted to ensure high compliance to radiotherapy and cetuximab in patients with head and neck cancer.

Keywords Head and neck cancer · Radiotherapy · Cetuximab · Bio-radiation dermatitis · Skin toxicity

Background

Cetuximab (CTX) is a chimeric mouse IgG1 monoclonal anti-epidermal growth factor receptor antibody approved for use in patients with metastatic colorectal and head and neck cancers. Since 2006, the combination of radiotherapy (RT) and CTX is an evidence-based treatment option [1] for the curative treatment of locally advanced head and neck squamous cell carcinoma (HNSCC). It has long been known that the acute skin effects induced by radiation are dose-, volume-, and treatment-time dependent [2]. No topical interventions have been demonstrated to prevent [3] the occurrence of radiation dermatitis in head and neck cancer patients. Nonetheless, severe reactions are relatively uncommon when Intensity-Modulated Radiotherapy (IMRT) is employed, thanks to its ability to avoid [4] excessive superficial dose accumulation. The concomitant use of CTX and RT in HNSCC is frequently associated with the development of overlapping "in-field" side effects, generally defined as "bio-radiation" dermatitis (BRD) [5, 6]. Compared with what can be observed with RT

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alone, BRD is characterized by peculiar clinical features which can present already in the first 2 weeks of treatment: an enhanced inflammatory response with coexistence of desquamation and acneifom rash can be associated with the development of confluent crusts, diffuse xerosis, and intense pruritus within the affected area. The severity of BRD can result in significant pain, impairment of quality of life [7], and predisposition to infections [8] and sepsis [9]. After the approval of CTX-RT in HNSCC, several authors [10–12] questioned the feasibility of the concomitant treatment due to excessive skin toxicity and risk of treatment breaks, a known detrimental factor [13] to the efficacy of RT. In order to address these issues, a series of consensus guidelines were published [5, 6, 14–16], providing expert recommendations on the optimal recognition and management of cutaneous side effects induced by CTX-RT. However, the impact of grade-specific algorithms on daily practice, as presented in these articles, has never been investigated in prospective trials [17]. In addition, the proposed strategies are not consistent regarding what should be the best approach required to treat severe reactions. In 2014, an advanced wound care nursing team was established in our clinic to prospectively monitor and manage the development of BRD in patients with HNSCC undergoing concurrent RT-CTX. From a therapeutic standpoint, based on our experience, we advocate the central role of calcium alginate fibers. Being highly absorbent dressings [18], these products are able to remove excessive exudate while maintaining adequate moisture in the affected tissue. Thus, they represent a very effective treatment option to deal with the extensive, multifactorial moist desquamation frequently observed in these cases.

The aim of our work was to assess the impact of an in-house skin policy protocol on the tolerability of concurrent RT and CTX in patients with HNSCC. In addition, we investigated whether the routine availability of an advanced wound care nursing team played a role in preventing the development of severe BRD.

Methods

Patient and treatment characteristics

Patients with locally advanced, histologically proven squamous cell carcinoma of the oropharynx, larynx, hypopharynx, and oral cavity were evaluated after the multidisciplinary team recommended a curatively intended non-surgical treatment. According to international guidelines [19] and institutional policy, concomitant CTX-RT was proposed in case of absolute cisplatin ineligibility (creatinine clearance < 60 ml/min, baseline hearing loss or neuropathy > G2 per CTCAE criteria v.4.1 [20]) or if patients were deemed at high risk of toxicity with given standard cisplatin-based chemoradiation (ECOG PS 2, borderline baseline hepatic, cardiovascular, and pulmonary dysfunction or impaired nutritional status due to involuntary weight loss > 20% in previous 3 months). In selected cases, such as rapidly growing latero-cervical lymph nodal masses with macroscopic skin infiltration, CTX-RT was also considered after induction chemotherapy. At diagnosis, the cumulative presence of comorbidities was reported according to the Charlson Comorbidity Index (CCI) [21]. A CT scan (Light Speed 16; GE Healthcare Medical Systems, Milwaukee, WI, USA) was acquired at 3-mm slice width for radiation treatment planning. A personalized thermoplastic head, neck, and shoulder mask was created for all patients. A total dose of 66–70 Gy was delivered in 30–35 fractions, according to the RT technique employed. Since 2011, in our clinic three-dimensional conformal radiotherapy (3DCRT) was replaced with IMRT for all HNSCC patients. In line with standard practice, CTX was given weekly at a dose of 250 mg/m^2 following a loading dose of 400 mg/m^2 7 days before the start of RT. Informed consent was obtained from all individual participants included in the study.

Skin toxicity management

According to our institutional policy, no visiting nurses or home-care services were usually involved to manage acute toxicity. Since Jan. 2014, an advanced wound care nursing team was routinely available in our clinic for the management of all patients undergoing RT for HNSCC. A standardized skin-monitoring program was established: a weekly assessment was usually scheduled for the first 3 weeks of RT followed by bi-weekly (usually on Monday/Thursday) controls for the remainder of treatment. In case of outpatient cases in need of wound care, daily assessments were performed. In addition, a specific skin policy management was implemented for patients treated with RT-CTX. Following consensus recommendations, BRD severity was graded according to Bernier's et al [15] proposal.

Our in-house protocol was as follows:

- G1 (faint erythema or dry desquamation): a galenic product (cold cream, consisting of white wax, 12 g; borax, 0.56 g; spermaceti wax, 12.5 g; vaseline oil, 56 g; rose water) was distributed on the first day of RT as moisturizer. The use of a neutral pH soap (Vea Marseille) was also advised.
- G2 (moderate to brisk erythema and/or dry desquamation; patchy moist desquamation, or nonhemorrhagic crusts mostly confined to skin folds and creases):

  moderate to brisk erythema and/or dry desquamation: same as G1

non-hemorrhagic crusts: usually, a gentle mechanical debridement was performed to prevent the confluence of isolated crusts and their potential septic complication. In our experience, the main drawback of this approach was patient's discomfort and sometimes pain elicited by the procedure. Only in selected cases of major intolerance to mechanical debridement, a hydrocolloid dressing (i.e., Duoderm, ConvaTec, UK) was applied for 24 h between two consecutive RT fractions to soften the crusts, provided that the skin was intact.
confined patchy moist desquamation: even at an early stage, such as an isolated area developing along skin folds, a calcium alginate dressing (i.e., Biatain^{R} Alginate, Coloplast) was the preferred option. By applying the absorbent fiber onto the exudative lesion, a gradual regeneration of the underlying skin was usually observed, on average within 7–10 days. During radiotherapy, daily dressing changes were performed from this stage on, allowing also to monitor the evolution of the lesion.

– G3 (moist desquamation or hemorrhagic crusts; nonhemorrhagic crusts other than in skin folds and mostly confined to skin folds and creases; bleeding induced by minor trauma or abrasion; superinfection requiring oral antibiotics)

moist desquamation: same as G2; in case of confluent, generalized lesions, again the approach was to take advantage of the properties of dry dressings in order to remove the excessive exudate whereas favoring a moist environment to help the healing process. Usually, a thin Mepitel^{R} film (Mölnlycke Health Care) was applied beneath the alginate fiber. It could also be kept in place during RT to prevent a direct contact between the inner part of the thermoplastic mask and the ulcerated skin. In complex cases, a secondary dressing (i.e., Mepilex LITE, Mölnlycke Health Care) was used to keep the primary dressing in place, which was occasionally difficult due to head and neck anatomy
the management of crusts was the same as previously described for G2; again, the use of hydrocolloid dressings was not routinely considered in order to avoid excessive exudation and risk of skin maceration. Only for patients developing severe BRD after the end of RT, where the need for daily dressing changes was less demanding, a Duoderm dressing could be also left in place to slowly soften the crusts.
superinfections requiring oral antibiotics: as in cases of lighter toxicity, we did not apply topical antibiotics routinely. In case of clinical suspicion, a swab of the affected area was preferably taken to identify potential pathogens.

– G4 (life-threatening consequences; extensive confluent hemorrhagic crusts or ulceration (> 50% of involved field); extensive spontaneous bleeding from involved site (> 40% of the involved site); skin necrosis or ulceration of full-thickness dermis or any size ulcer with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures with or without full-thickness skin loss; skin graft indicated; ulceration associated with extensive superinfection with i.v. antibiotics indicated)

in our experience, skin necrosis or ulceration of full-thickness dermis with massive tissue destruction were never observed. The rare cases with G4 BRD were due to the presence of extensive confluent hemorrhagic crusts. In principle, our management was the same as for G3 toxicity. In addition, hospitalization and ev antibiotics were immediately recommended. Local metronidazole application and antimicrobial dressing (i.e., Cutimed® Sorbact® dressing pad) were also taken in consideration.

Outcome measures and statistical analysis

We performed a retrospective analysis of HNSCC treated with RT-CTX in our clinic. Acute toxicity (radiation dermatitis, acneiform rash, mucositis, and dysphagia) was graded according to CTCAE v.4.1. Following Bernier's recommendations and in line with our management protocol, the radiation dermatitis descriptor included also in-field side effects attributable to CTX, thus is presented as "bio-radiation dermatitis." Tolerability of both RT and CTX was analyzed according to the number of radiation treatment interruptions and CTX relative dose intensity (RDI), defined as the proportion of CTX prescribed total dose actually received by every patient. By definition, 2150 mg/m^2 corresponded to the maximum dose of CTX which could be administered in 8 cycles (1 loading and 7 maintenance administrations). The presence of weight loss on the last day of treatment compared with baseline was reported by absolute values (less than 5 Kg, between 5 and 10, more than 10 Kg) and percentage values (less than 5%, between 5 and 10%, more than 10%), respectively. Descriptive statistics were used to report patient (ECOG PS; smoking status; CCI), disease- (primary site; stage) and treatment- (RT technique; degree of weight loss; use of skin management protocol) related characteristics as mean and median values, with range for continuous variables and as proportions for categorical variables. To assess whether any patient, disease, and treatment—characteristics correlated with the development of G3/G4 BRD and RT-CTX tolerability, continuous parametric and

non-parametric variables were tested with *t* test and Mann-Whitney test, respectively, while chi-square test was used for categorical variables. A p value ≤ 0.05 was considered statistically significant. A multivariate Cox regression analysis was performed when multiple risk factors with a p value < 0.05 were identified in the univariate analysis. In terms of treatment efficacy, progression-free survival (PFS), locoregional control (LRC), and overall survival (OS) were analyzed. PFS was defined as the time from the last day of RT to the date of the first of the following events:

- the first day when the RECIST criteria for PD were met
- salvage surgery or elective neck dissection performed after 15 weeks from the last day of treatment performed on the clinical or radiological evidence of progression;

Table 1 *ECOG*, Eastern Cooperative Oncology Group; *CCI*, Charlson Comorbidity Index; *AJCC*, American Joint Committee on Cancer 7th edition. p value: differences reported according to cohort 2014–2018 vs cohort 2007–2013 (two-way Anova)

Characteristic	No. of patients (%), $n = 51$	Cohort 2007–2013 (%), $n = 26$	Cohort 2014–2018 (%), $n = 25$	p value
Median age, years (range)	65 (44–81)	63.5 (44–74)	66 (56–81)	0.0085
Sex				
Male	38 (74.5%)	18 (69.3%)	20 (80%)	0.125
Female	13 (25.5%)	8 (30.7%)	5 (20%)	
ECOG performance status				
0	15 (29.4%)	12 (46.2%)	3 (12%)	0.382
1	28 (54.9%)	11 (42.4%)	17 (68%)	
2	8 (15.7%)	4 (15.4%)	5 (20%)	
Charlson Comorbidity Index (age-adjusted)				
< 4	6 (11.8%)	2 (7.7%)	4 (16%)	0.056
4–7	36 (70.6%)	17 (65.4%)	19 (76%)	
> 8	9 (17.6%)	7 (26.9%)	2 (8%)	
Smoking history (pack/years)				
0	8 (15.7%)	4 (15.4%)	4 (16%)	0.041
< 10	2 (3.9%)	1 (3.8%)	1 (4%)	
10–20	11 (21.6%)	8 (30.8%)	3 (12%)	
> 20	30 (58.8%)	13 (50%)	17 (68%)	
Primary tumor site				
Oropharynx	24 (47.1%)	13 (50%)	11 (44%)	0.094
Hypopharynx	6 (11.8%)	1 (3.8%)	5 (20%)	
Larynx	14 (27.4%)	9 (34.7%)	5 (20%)	
Oral cavity	7 (13.7%)	3 (11.5%)	4 (16%)	
HPV status (oropharynx primary only)				
Positive	9 (37.5%)	1 (7.7%)	8 (72.8%)	0.794
Negative	4 (16.6%)	3 (23%)	1 (9%)	
Unknown	11 (45.9%)	9 (69.3%)	2 (18.2%)	
T stage				
T1-T2	10 (19.6%)	7 (27%)	3 (12%)	0.535
T3	18 (35.3%)	11 (42.3%)	7 (28%)	
T4a	14 (27.5%)	5 (19.2%)	9 (36%)	
T4b	9 (17.6%)	3 (11.5%)	6 (24%)	
N stage				
N0	14 (27.5%)	7 (27%)	7 (28%)	0.228
N1	9 (17.6%)	6 (23%)	3 (12%)	
N2a/N2b	10 (19.6%)	6 (23%)	4 (16%)	
N2c	13 (25.5%)	6 (23%)	7 (28%)	
N3	5 (9.8%)	1 (4%)	4 (16%)	
AJCC stage				
III	14 (27.5%)	9 (34.6%)	5 (20%)	0.382
IVA	25 (49%)	14 (53.8%)	11 (44%)	
IVB	12 (23.5%)	3 (11.6%)	9 (36%)	

Table 2 *RT*, radiotherapy; *3DCRT*, three-dimensional conformal radiotherapy; *IMRT*, intensity modulated radiotherapy; *IQR*, interquartile range; *RDI*, relative dose intensity; *RT-CTX*, radiotherapy-cetuximab

Characteristic	No. of patients (%), $n = 51$
Induction chemotherapy (ICT)	
Yes	8 (15.7%)
No	43 (84.3%)
ICT regimen	
TPF	7 (87.5%)
PF	1 (12.5%)
No. ICT cycles (median, range)	3 (2–4)
RT technique	
3DCRT	17 (33.3%)
Static IMRT	3 (5.8%)
Dynamic IMRT	31 (60.9%)
RT compliance	
No interruptions	26 (51%)
Temporary interruptions (total)	25 (49%)
Median of interruptions (days, range)	10 (1–21)
< 3 days	7 (13.7%)
> 7 days	18 (35.3%)
Permament discontinuations	3 (5.8%)
Frequency of dressing changes	
Heterogeneous	26
Standardized per protocol	25 (49%)
Cetuximab compliance	
No. cycles (median, IQR)	6 (5–8)
1 cycle	2 (4%)
2–6 cycles	25 (49%)
≥ 7 cycles	24 (47%)
RDI (%; median, IQR)	77 (65–100)
Weight loss at the end of RT-CTX (absolute decrease)	
< 5 Kg	20 (39.2%)
> 5 < 10 Kg	19 (37.3%)
> 10 Kg	12 (23.5%)
Weight loss at the end of RT-CTX (relative decrease compared with baseline)	
< 5%	21 (41.2%)
> 5% < 10%	14 (27.5%)
> 10%	16 (31.4%)

– death for any cause

LRC was defined as the time from the last day of RT to local and/or regional disease progression. Overall survival (OS) was defined as the time from the last day of treatment to death from any cause. Median LRC, PFS, and OS were calculated. The relative estimates of LRC, PFS, and OS at 12 and 24 months were estimated by the Kaplan-Meier method, with corresponding 95% confidence intervals.

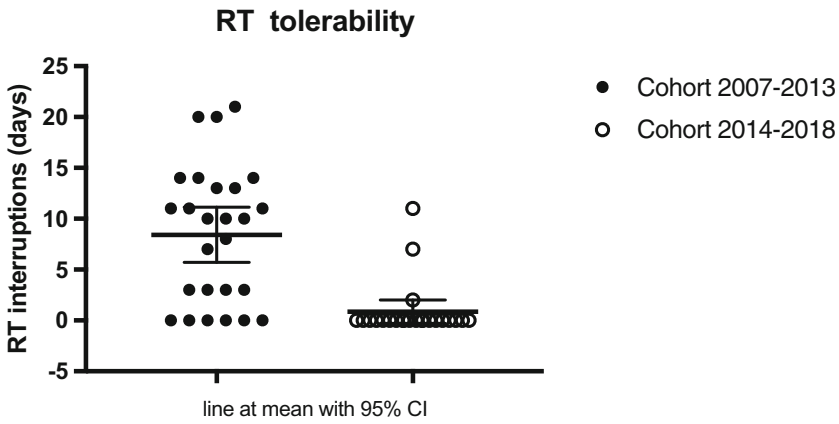
Results

Between February 2007 and January 2018, 51 patients were treated with RT-CTX for HNSCC. Patients' characteristics are summarized in Table 1. The median age of the cohort was 65 years (range 44–81). Most patients were burdened with multiple comorbidities, with an overall median CCI of 6 at cancer diagnosis. All were deemed cisplatin-unsuitable whereas almost a fourth had very advanced disease (stage IVB disease in 23.5% of cases). A sequential approach based on induction chemotherapy followed by RT-CTX was prescribed only for selected patients (15.7%). All patients received curatively intended radiation, in most cases (66.7%) delivered with modern IMRT technique. Treatment features and compliance data are shown in Table 2. Regarding acute toxicity, the rates of G3/G4 mucositis, BRD, dysphagia, and acneiform rash were 54.9%, 43.1%, 31.3%, and 13.7%, respectively. Sepsis developed in 4/51 patients (7.8%), in one of them during the fourth week of RT-CTX. Altogether, a permanent discontinuation of treatment before reaching a curative dose of 66 Gy was observed in three cases because of sepsis, massive tumor bleeding, and patient's refusal, respectively. In terms of patients' tolerability, a prolonged RT treatment break (> 7 days) was required for about one third of the whole cohort (35.3%), mainly due to excessive acute toxicity or worsened general conditions. In order to assess whether the routine availability of an advanced wound care nursing team played a role in preventing the development of severe skin toxicity, two groups of patients were identified: 26 subjects treated between February 2007 and November 2013 were compared with 25 patients who underwent RT-CT between March 2014 and January 2018. In the latter group, two patients had G3 infusional reaction at first CTX introduction and were therefore not considered for toxicity analysis. The incidence of G3/G4 mucositis, BRD, dysphagia, and acneiform rash were 73% (19/26), 38.4% (10/26), 53.8% (14/26), 7.6% (2/26) in the first group and 39.3% (9/23), 47.8% (11/23), 8.6% (2/23), and 21.7% (5/23) in the second group.

No significant differences were therefore found between the two groups in terms of G3/G4 BRD and acneiform rash ($p = 0.65$ and $p = 0.9$, respectively) nor in terms of mucositis and dysphagia ($p = 0.48$ and 0.46, respectively). Overall, only posttreatment relative weight loss > 10% compared with baseline correlated significantly with the development of G3/G4 BRD in the whole cohort (39% vs 18% if weight loss below 10%; $p = 0.013$).

In terms of treatment tolerability, the implementation of a standardized in-house skin protocol by January 2014 was correlated with a significant improvement of both RT and CTX compliance. In particular, a mean RT interruption of 8.42 days (SD 6.73; 95% CI 5.7–11.1; median 10 days) was reported in the older group vs 0.86 days in the more recent cohort (SD 2.66; 95% CI − 0.28–2.02, median 0 days; $p < 0.0001$)

Fig. 1 RT tolerability

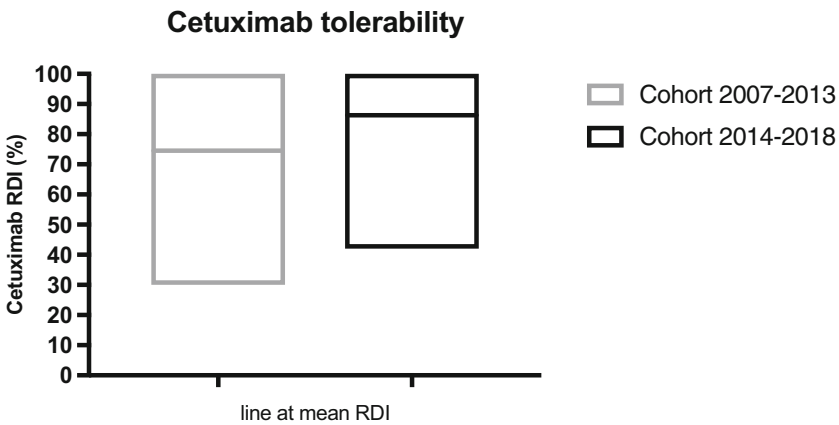


(Fig. 1). Notably, the adoption of our standardized skin management protocol allowed to complete the treatment without any interruption in 20/23 patients (89.6%) vs only 6/26 (23%) in the older cohort. At univariate analysis, also the use of IMRT ($p = 0.0033$) was correlated with better tolerability; however, at multivariate analysis, only the absence of a standardized supportive approach was independently associated with RT interruptions longer than 7 days (OR 23.4, 95% CI 4.3–125.6, $p = 0.0003$). In addition, a higher mean CTX RDI (86.3% vs 74.5%) was significantly correlated only with the use of our skin toxicity protocol at univariate analysis ($p = 0.0226$) (Fig. 2). At time of analysis, 47% of patients are alive. At a median follow-up of 13 months (range, 0–133), the 1- and 2- year rates of LRC, PFS, and OS were 59% and 55.5%, 50% and 37.5%, and 65% and 44%, respectively (Fig. 3 and supplementary material).

Discussion

The exact incidence of the development of G3/G4 BRD in head and neck cancer is a matter of debate. A large variability can be observed by analyzing phase 3 and randomized phase 2 trials where a combination of RT and CTX was adopted, either alone or as backbone of concurrent treatment (Table 3). Despite the fact that expert consensus recommendations were published with the aim to guide supportive skin care, the impact of grade-specific management on the tolerability of RT-CTX was not assessed in these large prospective studies. Notably, a multicenter randomized double-blind trial [22] failed to demonstrate the efficacy of a topical glycosaminoglycan analog (OTD70-DERM) over placebo in reducing the incidence and severity of BRD. On a broader scale, no high-level evidence [23] supports the adoption of any specific measures to prevent radiation dermatitis, nor of therapeutic interventions to manage it when RT alone is employed, as well. Identifying the best approach to deal with severe cutaneous reactions poses therefore a significant challenge in head and neck cancer curative treatment, pending the need to avoid treatment breaks. A large multi-cohort randomized study on 357 patients [24] was designed to compare the efficacy of a hydrogel (Intrasite) and a dry dressing (Tricotex) for moist desquamation. Most common primary tumor site was breast (63.3%) followed by HNSCC (28.8%). The results of this study did not warrant the use

Fig. 2 Cetuximab tolerability



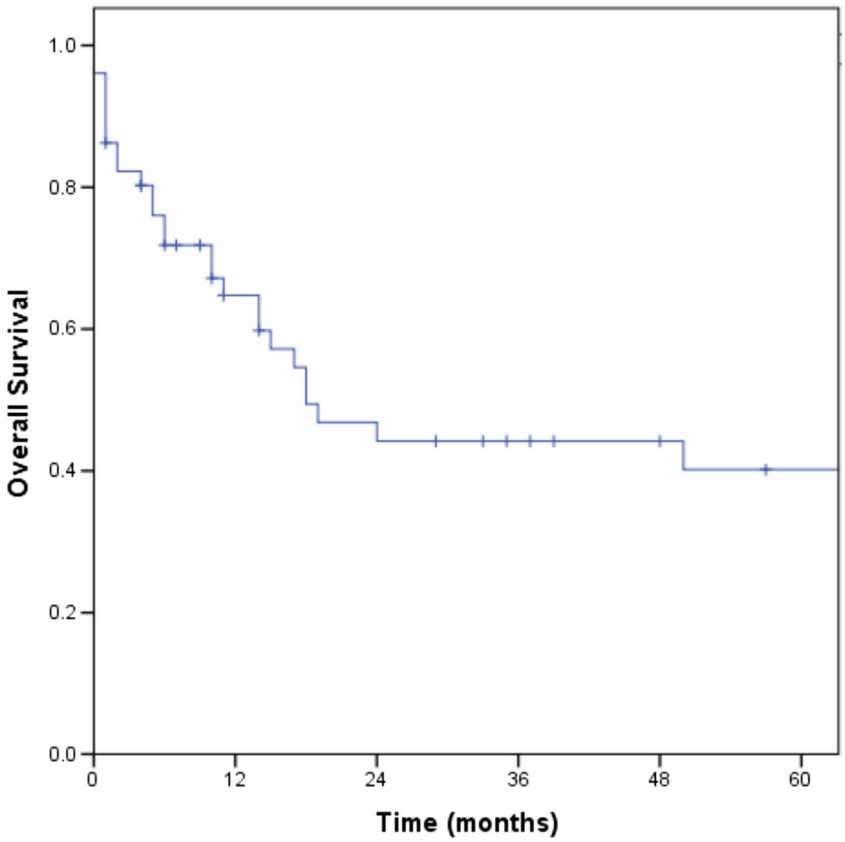


Fig. 3 Overall survival for the entire population

of gel dressings for severe reactions induced by RT, since their use was associated with a significantly prolonged time to healing (HR, 0.64; 95% CI, 0.42–0.99). In breast cancer patients, the prophylactic use of a dry dressing (Mepitel film) was shown [25] to be very effective in preventing moist desquamation, reducing overall skin reaction severity by 92% compared with standard aqueous cream. The same group performed a feasibility study [26] on the application of Mepitel Film in a cohort of 36 head and neck cancer patients undergoing standard cisplatin-based chemoradiation. In comparison with standard moisturizers, the incidence of moist desquamation was reduced by 37% and 28% in subjects treated in China and New Zealand, respectively. Of note, the ongoing Rarest-01 randomized trial [27] was planned to demonstrate a reduction of $\geq$ G2 radiation dermatitis from 85 to 65% through the preventive use of Mepitel Film versus standard management in a cohort of 168 HNSCC patients. With the exception of the GORTEC 2009-01 trial [22], the adoption of supportive measures for skin toxicity was not tested in HNSCC patients treated with concurrent RT and CTX. Taking into account the underlying biologic interplay between the EGFR pathway and molecular effects of radiation [28], ad-hoc supportive treatments have to be designed to counterbalance the marked inflammatory response commonly observed in the irradiated field when CTX is administered on top of radiation. In our experience, the use of a standardized, in-house protocol for the management of BRD was an effective strategy to increase patients' tolerability to RT-CTX and, importantly, to crucially minimize treatment breaks. Heterogeneity in skin care among different RT departments [29] may be particularly relevant when dealing with overlapping/complex side effects such as those induced by RT and CTX. The early employment of calcium alginate fibers to handle moist desquamation was a key feature of our wound care approach. Unlike previous recommendations [5, 6], the use of topical dressings was anticipated from G3 to G2 BRD. Another relevant difference from consensus publications [15, 16] regards the role of hydrocolloid agents. In contrast to them, their role was much less relevant in our routine practice. Essentially, their use was limited to wound care taking place after the end of RT or as secondary dressings to conform the primary fiber to head and neck anatomy. Several limitations have to be acknowledged in interpreting our data. First, the retrospective nature of the study and its small sample size restrain the generalizability of our findings. Second, the absence of a control group, being it patients treated with RT alone or cisplatin-based chemo-radiation, does not allow to draw firm conclusions on how large is the benefit of our skin policy on treatment tolerability. Third, the need for daily dressing changes as described in our protocol can be labor

Table 3 *CRT*, chemotherapy + radiotherapy; *CCRT*, chemotherapy + cetuximab + radiotherapy; *BRT* cetuximab + radiotherapy, *TPF*, doses according to European regimen (as follows: 3 cycles, docetaxel 75 mg/m^2 day1, cisplatin 75 mg/m^2 day 1 and 5-fluorouracil 800 mg/m^2/day 120 h) unless *; *ENE*, extranodal extension; PCC, as follows: 2 4-week cycles of carboplatin AUC 6, paclitaxel 100 mg/m^2 on days 1, 8, 15, and cetuximab 400 mg/m^2 loading dose followed by weekly administration of 250 mg/m^2; *HFRT*, hyperfractionated radiotherapy; *AFRT*, accelerated radiotherapy; *TPF-E*, as follows: docetaxel 75 mg/m^2 day1, cisplatin 75 mg/m^2 day1, and 5-fluorouracil 750 mg/m^2/day 120 h plus cetuximab 400 mg/m^2 loading dose followed by weekly administration of 250 mg/m^2

Trial (first author, ref)	Type of study (*n*)	Regimen	≥ G3 RD	≥ G3 Rash
IMCL 9815 (Bonner JA, NEJM 2006)	Phase 3 (*n* = 424)	RT alone vs BRT (cetuximab)	18% vs 23% (*p* = ns)	1% vs 17% (*p* < 0.001)
RTOG 0522 (Ang KK, J Clin Oncol 2014)	Phase 3 (*n* = 891)	CRT (cisplatin 100 mg/mq 1, 22) vs CCRT (cisplatin 100 mg/mq 1, 22 + cetuximab)	15% vs 25% (*p* < 0.001)	1% vs 20% (*p* < 0.001)
Interceptor (Merlano. M, ECCO 2015)	Phase 3 (*n* = 228; preliminary data)	CRT (cisplatin 100 mg/mq 1, 22, 43) vs TPF × 3 + BRT (cetuximab)	3% vs 15% (*p* = ns)	n.a.
GORTEC 2007–01 (Bourhis J, ASCO 2016)	Phase 3 (*n* = 406)	CCRT (carboplatin 70 mg/mq/day + 5FU 600 mg/mq/day 1–4, weeks 1, 4, 7 + cetuximab) vs BRT (cetuximab)	63% vs 59% (*p* = ns)	4% vs 4% (*p* = ns)
GORTEC 2007–02 (Geoffrois L, ASCO 2016)	Phase 3 (*n* = 370)	CRT (carboplatin 70 mg/mq/day + 5FU 600 mg/mq/day 1–4, weeks 1, 4, 7) vs TPF × 3 + BRT (cetuximab)	29% vs 53% (*p* = ns)	0% vs 11% (*p* = ns)
TTCC 2007–01 (Hitt R, ASCO 2016)	Phase 3 (*n* = 530; 407 rdm after ICT)	TPF × 2/3 + CRT (cisplatin 100 mg/mq 1, 22, 43) vs TPF × 2/3 + BRT (cetuximab)	2% vs 22% (*p* = ns)	0% vs 7% (*p* = ns)
GGTCC (Ghi MG, Ann Oncol 2017)	Phase 2/3 (*n* = 414)	CCRT (cisplatin 20 mg/mq/day + 5FU 800 mg/mq/day 1–4, weeks 1, 6) or BRT (cetuximab) vs TPF* × 3 + CCRT (cisplatin 20 mg/mq/day + 5FU 800 mg/mq/day 1–4, weeks 1, 6) or + BRT (cetuximab)	14% vs 15% (aggregated) (*p* = ns)	6% vs 1.5% (aggregated) (*p* = 0.028)
Tremplin (Lefebvre JL, J Clin Oncol 2013)	Phase 2 rdm (*n* = 153; 116 rdm after ICT)	TPF × 3 + CRT (cisplatin 100 mg/mq 1, 22, 43) vs TPF × 3 + BRT (cetuximab) [both arms: if response to TPF > 50%]	26% vs 57% (*p* = ns)	n.a.
RTOG 0234 (Harari PM, J Clin Oncol 2014)	Phase 2 rdm (*n* = 238)	CCRT (cisplatin 30 mg/mq q7 + cetuximab) vs CCRT (docetaxel 15 mg/mq q7 + cetuximab) [adjuvant setting; R1 ± ENE ± 2 N positive]	7% vs 17% (*p* = ns)	11% vs 15% (*p* = ns)
CTXMAB+RT (Magrini SM, J Clin Oncol 2016)	Phase 2 rdm (*n* = 70)	CRT (cisplatin 40 mg/mq q7) vs BRT (cetuximab)	21% vs 44% [single grading] (*p* = .039)	21% vs 44% [single grading] (*p* = .039)
UPMC (Argiris A, Ann Oncol2016)	Phase 2 rdm (*n* = 78)	CCRT (pemetrexed 500 mg/mq 1, 22, 43 + cetuximab) vs CCRT (pemetrexed 500 mg/mq 1, 22, 43 + bevacizumab 15 mg/kg 1, 22, 43 + cetuximab; maintenance beva for 6 months)	14% vs 27% (*p* = ns)	8% vs 7% (*p* = ns)

Table 3 (continued)

Trial (first author, ref)	Type of study (*n*)	Regimen	≥ G3 RD	≥ G3 Rash
Chicago (Seiwert T, IJROBP 2016)	Phase 2 rdm ($n = 110$)	PCC × 2 + Cetux-FHX (cetuximab + 5FU 600 mg/mq/day, HU 500 mg/mq BID, d 0–5, q 14; HFRT up to 75 Gy) vs PCC × 2 + Cetux-PX (cetuximab + cisplatin 100 mg/mq 1, 22; AFRT up to 72 Gy)	81% vs 51% [single grading] ($p < .01$)	81% vs 51% [single grading] ($p < .01$)
EORTC (Specenier P, Ann Oncol 2017)	Phase 2 rm. ($n = 47$; 30 rdm after ICT)	TPF-E × 4 + CCRT (cisplatin 40 mg/mq q7 + cetuximab) vs TPF-E × 4 + CCRT (carboplatin AUC 1.5 q7 + cetuximab)	13% vs 33% (p = ns)	7% vs 7% (p = ns)

intensive and discomforting for the patients requiring them. When dealing with skin toxicity induced by anti-EGFR treatment, consideration should be given to patients' preferences [30, 31] also regarding the potential need of lengthy supportive care. In this perspective, quality of life measures were not formally evaluated in our study. In line with previously published studies [17], > G3 BRD was not negligible in our cohort. As recommended by expert consensus recommendations, our data underline the importance of tailored supportive care interventions for the management of "in-field" skin toxicity induced by concurrent RT and CTX, allowing for a marked improvement of compliance to treatment. In light of the paucity of data available on this topic, our experience may be regarded as hypothesis-generating in relation to the central role of alginate dressings we described.

Conclusions

The combination of RT and CTX is a possible treatment option for curative treatment of HNSCC in patients deemed unfit for cisplatin-based chemoradiation. In order to maximize treatment efficacy, patients' tolerability to both therapies should be assured by managing the frequent occurrence of severe bio-radiation dermatitis through standardized, grade-specific interventions. For this purpose, routine involvement of an advanced wound care management team and early application of calcium alginate dressings for moist desquamation are warranted.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

The authors have full control of all primary data and agree to allow the journal to review the data if requested

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