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Research article

A prospective comparison of common toxicity criteria adverse events Version 3 and 4 in assessing oral mucositis for oral and oropharyngeal carcinoma



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ABSTRACT

Background and purpose: Oral mucositis is an expected complication of radiotherapy in the management of carcinoma of the head and neck. The Common Terminology Criteria for Adverse Events (CTCAE) Version 3 (V3) and related systems based on mucosal appearance have been used in clinical trials historically. More recently, Version 4 (V4) which is based on patient symptoms has been employed. This study compares the use of V3 and V4 in the grading of mucositis in patients undergoing radiotherapy with or without concurrent systemic therapy for carcinoma of the oral cavity and oropharynx.

Methods: Oral mucositis was graded prospectively in patients receiving radiotherapy with or without concurrent systemic therapy using both V3 and V4. Grading was recorded during and after completion of therapy.

Results: Between November 2014 and November 2015, 555 measurements were taken from 73 patients. Mucositis scores were equal in both versions in 327 (59%) measurements. Significant differences between V3 and V4 were seen in patients receiving cetuximab-based concurrent therapy ($p < 0.001$) and beyond 8 weeks from the start of radiotherapy ($p = 0.004$).

Conclusion: Differences in grading of mucositis scored by V3 and V4 are frequent. Relationships between biologically effective dose and rates of grade 3 mucositis have historically been based on mucosal appearances. It is not known whether the same relationships apply when mucositis is graded based on symptomatic grading systems. Both V3 and V4 should be used in clinical trials to improve understanding of mucositis and its relationship to quality of life and late mucosal toxicity.

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Introduction

Oral mucositis is an expected complication of radiotherapy for oral and oropharyngeal cancers [1]. Radiotherapy, with or without concurrent systemic therapy, provides good local control of disease, but carries significant morbidity [2]. In order to evaluate the severity of oral mucositis, there are well established scoring systems that can be applied in the clinic to monitor patients before, during and after treatment. One of the most commonly used systems is the Common Terminology Criteria for Adverse Events (CTCAE) [3]. Several versions of this scoring classification have evolved. Version 3 (V3) (Table 1) (2006), or similar systems which grade on the basis of mucosal appearance have been employed in clinical trials over the last thirty years [4–15]. Grade 3 mucositis

in such systems typically requires the presence of confluent mucositis.

However, Version 4 (2009) (V4) (Table 1) grades mucosal reaction on the basis of patient symptoms. A patient whose mucosal pain requires strong analgesia is scored as grade 3. Most ongoing clinical trials in head and neck cancer are now employing V4. However, there is paucity of data examining the relationship between V3 and V4 [16–18].

One series in the literature investigated the differences in V3 and V4 in the setting of treatment of locally advanced nasopharyngeal carcinoma [19]. In this study, all 21 patients received the same treatment with neo-adjuvant chemotherapy, using docetaxel and cisplatin, followed by concurrent cisplatin-based chemoradiotherapy. Grading of oral mucositis was recorded using both V3 and V4 before treatment and through to completion of chemoradiotherapy on a weekly basis. There were differences noted in the rates of grade 1 and grade 3 oral mucositis, although no statistical analysis

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Table 1
CTCAE versions 3 and 4 for oral mucositis.

CTCAE version	Grade		3	4
	1	2		
3	Erythema	Patchy ulceration	Confluent ulceration	Tissue necrosis
4	No intervention	Mild pain not interfering with oral intake or modified diet	Severe pain interfering with oral intake	Life threatening Urgent intervention

was applied on these variations. Therefore, there remains a significant lack of prospective data comparing the two versions. Despite this, V4 has now been adopted in current clinical trials in head and neck cancer.

The purpose of this study was to compare the use of V3 and V4 in the grading of oral mucositis in patients undergoing radiotherapy, with or without concurrent systemic therapy, for carcinoma of the oral cavity and oropharynx.

Materials and methods

Grading of oral mucositis was performed in patients undergoing radiotherapy with or without concurrent systemic therapy for carcinoma of the oral cavity and oropharynx, as part of routine clinical examination. Mucositis scores were obtained using both CTCAE V3 and V4 for each patient during and after completion of therapy (Table 1). Data collection commenced in November 2014. Grading of mucositis was recorded by three clinical oncologists. Scores were recorded weekly during on-treatment assessment. At completion of (chemo) radiation, patients continued weekly or fortnightly follow up, as per departmental policy, until resolution of grade 3 mucositis.

A variety of dose/fractionation schedules were used (Table 2). The data was analysed for differences between the CTCAE versions using the chi-squared test according to the week of treatment, patient age, and use of concurrent systemic agent. Chi-squared test was also performed to examine whether the direction of difference (i.e. whether V3 or V4 was giving a higher grade) was significant.

Results

Between November 2014 and November 2015, 555 measurements were taken from 73 patients. Oral mucositis scores were concordant for both versions in 327 (59%) measurements, but differed in 228 (41%) measurements. Discrepancies between V3 and V4 for each variable measured are shown in Table 3.

Discrepancies in mucositis score were seen throughout the treatment episode, but particularly in the post-radiotherapy phase, i.e. beyond 8 weeks from the start of treatment, with differences in 81(49%) measurements. Discrepancies were recorded in 87 (42%) of measurements between weeks 0 and 4 of radiotherapy, and in 60 (32%) measurements between weeks 5 and 8 ($p = 0.004$). Of the 60 discrepancies between weeks 5 and 8, 45 were associated

Table 2
Dose/fractionation schedules.

Dose/fractionation schedule (Gy/#)	No. of patients
70/35 DEF	11
65/30 PO	10
65/30 DEF	33
64/25 DEF	1
60/30 PO	10
55/20 DEF	7
50/20 PO	1
Total	73

Gy = Gray; # = fraction; PO = Post-operative; DEF = definitive chemo radiotherapy.

Table 3
Rate of discrepancy between V3 and V4 according to the variables measured.

Variable measured	Discrepancies/total measurements (%)	p value using χ^2
<i>Time from start of RT (weeks)</i>		
0–4	87/205 (42)	0.004
5–8	60/186 (32)	
>8	81/164 (49)	
<i>Treatment received</i>		
RT alone	53/113 (47)	<0.001
Synchronous cetuximab	46/71 (65)	
Synchronous platinum	129/371 (35)	
<i>Age (years)</i>		
≤50	46/139 (33)	0.08
51–69	146/338 (43)	
≥70	36/78 (46)	

RT = radiotherapy; % = percentage; χ^2 = chi-squared test.

with a higher V3 score. In contrast, 55 of the 81 discrepancies recorded beyond week 8 were due to a higher V4 score ($p < 0.001$).

No significant difference was seen between patients in different age categories ($p = 0.08$). Variations between V3 and V4 grade 3 mucositis scores were recorded in 46 measurements (33%) in the 50 years and under group, 146 (43%) in the 51–69 years group, and 36 (46%) in the 70 years and over group.

More discrepancies were recorded in patients treated with concurrent cetuximab (46/71 measurements; 65%), compared to no concurrent agent (53/113 measurements; 47%) or concurrent platinum (129/371 measurements; 35%) ($p < 0.001$). Of the 46 discrepancies seen with the concurrent cetuximab group, 37 resulted from a higher V3 score ($p < 0.0001$).

There was no significant difference in the number of discrepancies when compared across the three scoring clinicians: 130/327 (40%), 65/141 (46%) and 33/87 (38%) ($p = 0.34$).

Discussion

This study demonstrates that differences in grading of oral mucositis recorded by CTCAE V3 and V4 are frequent (41%). The largest discrepancy was seen in patients receiving concurrent cetuximab, with 68% of measurements differing. This was a statistically significant finding despite the small number of patients treated with this regimen. In addition, a significant relationship between discrepancy in measurement on V3 and V4 with regards to time from treatment start date was identified.

The majority of discrepancies seen with cetuximab usage were associated with a higher V3 score. This could be interpreted as the mucositis visualised being better tolerated and associated with less pain in some of the cetuximab-treated patients. Only the results of randomised trials directly comparing cisplatin and cetuximab will provide more information on this finding. The predominance among the discrepancies seen between week 5 and 8 of a higher V3 score may be explained by patients managing their objective grade 3 mucositis with lower strength analgesia in the initial

weeks. Conversely, in the post-treatment period (beyond 8 weeks from the start of radiotherapy), improvement in visible mucositis may precede improvement in pain, resulting in both a greater number of grading discrepancies and higher V4 grade than V3 grade.

This latter finding underlines the value of V4 in illustrating the mismatch between physicians' objective visual assessment of mucositis (V3) versus clinical impact of mucositis in terms of pain and oral intake (V4). The value of continuing with V3 grading is discussed below, but patient-reported symptoms should always come first when managing mucositis. To this end, a prospective evaluation of V3, V4, and patient reported mucosal outcomes is required.

Duration of grade 3 confluent mucositis, as defined in CTCAE V3, has previously been reported as an independent predictor of late mucosal damage [20]. In one study of stage III/IV carcinoma of the head and neck, 191 patients were prospectively randomised to receive 70 Gy in 2 Gy once daily fractions over 47 days versus 59.4 Gy in 1.8 Gy fractions twice daily over 24 days. The authors concluded that the duration of grade 3 confluent mucositis was inversely related to the time to onset of the mucosal reaction in both treatment arms. As expected, the onset of grade 3 mucositis was more rapid using the accelerated schedule. However, the duration of grade 3 mucositis did not differ significantly between the groups. After correction for patient and treatment related factors, anatomical site and increasing duration of grade 3 mucositis were found to be independent predictors for late mucosal reactions. The anticipated reduction in late mucosal effects in the accelerated treatment arm, as predicted by the linear-quadratic (LQ) model, was seen only in those patients whose grade 3 mucosal reactions lasted less than 20 days. Thus, prolonged grade 3 mucositis lasting for more than 20 days has been used as a surrogate marker for risk of late mucosal damage in dose escalation studies [21]. It is unclear in the light of the current study whether such a relationship can be assumed if V4 is employed.

Similarly, biologically effective dose (BED) calculated using the LQ equation correlates well with rates of acute grade 3 mucositis measured using scoring systems measuring confluent mucositis similar to V3 [22,23]. Several groups have proposed either tolerable levels of acute mucosal BED or tolerable levels of BED cell kill (BEDck) which can be used as a guide to the mucosal tolerability of new fractionation schedules [24,25]. BED or BEDck can also be modified to account for the increased rates of mucositis seen with synchronous chemotherapy [26]. Given the findings of the current study, it is possible that studies scoring mucositis with V4 will not contribute further data to support or refute such models.

Intensity Modulated Radiotherapy is now the standard of care in the treatment of head and neck cancer. Modelling related to prescription dose is, therefore, less relevant and dose–volume data for oral mucosa organ at risk volumes may now be of more importance. However, future prospective trials should use V3, V4, and patient reported outcomes for reporting mucositis in order to allow both development of volumetric-based predictive models for future use with these endpoints, and permit comparison with historical models [27].

Conflicts of interest

There are no conflicts of interest.

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