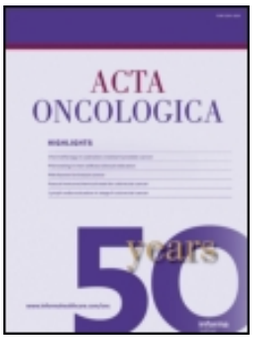

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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**To cite this article:** Nigel J. Anderson, Morikatsu Wada, Michal Schneider-Kolsky, Maureen Rolfo, Daryl Lim Joon & Vincent Khoo (2014) Dose-volume response in acute dysphagia toxicity: Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy, Acta Oncologica, 53:10, 1305-1311, DOI: 10.3109/0284186X.2014.933874

**To link to this article:** https://doi.org/10.3109/0284186X.2014.933874

*Acta Oncologica*, 2014; 53: 1305–1311

informa
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**ORIGINAL ARTICLE**

# Dose-volume response in acute dysphagia toxicity: Validating QUANTEC recommendations into clinical practice for head and neck radiotherapy

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## ABSTRACT

**Purpose.** To determine the validity of QUANTEC recommendations in predicting acute dysphagia using intensity-modulated head and neck radiotherapy.

**Material and methods.** Seventy-six consecutive patients with locally advanced squamous cell carcinoma (SCC) of the head and neck +/− systemic therapy were analyzed. Multiple dose parameters for the larynx (V50Gy, Dmean and Dmax) were recorded. Acute dysphagia toxicity was prospectively scored in all treatment weeks (week 1–6 or 1–7) using CTCAEv3 by three blinded investigators. QUANTEC larynx recommendations (V50Gy $<$ 27%, Dmean $<$ 44 Gy, Dmean $<$ 40 Gy, Dmax $<$ 66 Gy) were used to group the cohort (i.e. V50Gy $<$ 27% vs. V50Gy $>$ 27%). The proportion of patients with Grade 3 dysphagia was compared within each group.

**Results.** There was a significant reduction in the incidence of grade 3 toxicity in the V50Gy $<$ or $>$ 27% group at week 5 (14.3% vs. 45.2%, $p = 0.01$) and 6 (25.9% vs. 65.9%, $p < 0.01$). A significant reduction at week 5 (14.7% vs. 50.0, $p = 0.02$) and 6 (32.4% vs. 67.6%, $p = 0.01$) was seen in Dmean $<$ 44 Gy when compared to Dmean $>$ 44 Gy. Dmean $<$ 40 Gy also delivered a significant reduction at week 5 (5.6% vs. 42.3%, $p < 0.01$) and week 6 (23.5% vs. 59.3%, $p = 0.01$). A significant toxicity reduction at treatment week 6 (28.0% vs. 63.0%, $p = 0 < 01$) was seen from Dmax $<$ 66 Gy to Dmax $>$ 66 Gy. V50Gy $>$ 27% ($p < 0.01$), Dmean $>$ 40 Gy ($p = 0.01$) and Dmax $>$ 66 Gy ($p < 0.01$) were also predictors of Grade 3 dysphagia when analyzed with multiple clinical risk factors.

**Conclusions.** QUANTEC late toxicity recommendations for dose to larynx during IMRT are a useful predictor for acute dysphagia toxicity in this patient cohort. Furthermore, this included chemoradiotherapy regimes and post-operative radiotherapy patients, allowing for prophylactic implementation of supportive care measures.

The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) series of articles provides a summary of updated dose/volume/outcome data to refine current dose-volume recommendations, previously defined via the recommendations of Emami et al. [1]. The QUANTEC dose/volume/outcome data was generated to provide the radiotherapy planner with improved data to facilitate effective utilization of more sophisticated planning, delivery and imaging systems in steering precision dose deposition [2].

Radiation-induced dysphagia is strongly correlated to laryngeal dose in patients receiving definitive head and neck chemo-radiation. This was addressed by the QUANTEC report [3–5]. Inadvertent dose deposition to adjacent high dose target volumes often hastens the onset of radiotherapy (RT)-induced acute mucositis and laryngeal edema, resulting in a disruption to the swallowing mechanism and its associated structures. However, swallowing is a complex, multifaceted mechanism. The functional role of each

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*(Received 3 February 2014; accepted 23 May 2014)*

ISSN 0284-186X print/ISSN 1651-226X online 
DOI: 10.3109/0284186X.2014.933874

anatomical structure is inter-related. Therefore, isolating the role of each anatomical structure in RT-induced dysphagia can be somewhat challenging. The QUANTEC report suggests that late dysphagia is often a consequence of acute oral mucositis, and that acute dysphagia may be a predictor of late swallowing complication [6]. Our study aimed to address these questions, by validating the recommendations of the QUANTEC report to determine their usefulness in predicting acute dysphagia, through an analysis of dose/volume/outcome in glottic/supraglottic larynx in definitive head and neck patients treated at our center. Furthermore, this study aimed to establish if systemic therapy and RT delivered post-operatively (PORT) affects this dose/volume/outcome relationship, and whether late QUANTEC recommendations are still relevant in predicting acute dysphagia within chemo-radiotherapy and PORT regimes.

## Material and methods

Seventy-six consecutive patients with locally advanced squamous cell carcinoma (SCC) of the head and neck, treated with intensity modulated radiotherapy (IMRT 60–70 Gy) definitively or PORT +/− systemic therapy between 2008 and 2011 were analyzed. Patients with primary laryngeal disease and re-irradiation were excluded from this review. The study was approved by our institutional ethics committee.

### *Treatment planning*

The prescribed doses were planned via a simultaneous integrated boost (SIB), to a gross tumor volume (GTV), high risk clinical target volume (CTV) and low risk CTV. Dose to GTV (60–70 Gy), high risk CTV (60–63 Gy) and low risk CTV (54–56 Gy) was planned at five fractions per week over 6–7 weeks. Treatment regime (i.e. pre/post-operative RT, +/− systemic therapy) contributed to the RT treatment length. Each target was expanded with a departmental protocol margin (1 cm GTV to CTV, 0.5 cm CTV to PTV) to form $PTV_1$, $PTV_2$ and $PTV_3$, respectively.

Optimized IMRT plans, deliverable via 7–9 equally spaced step-and-shoot segmented beams on a 6 MV linear accelerator (Elekta Synergy, Elekta Oncology, Crawley, UK), were generated using both the Elekta CMS XiO and Monaco treatment planning systems (TPS) (Elekta CMS Software, St Louis, MO, USA) on 0.25cm computed tomography (CT) slices.

Dose mean (Dmean), dose maximum (Dmax) and V50Gy of glottic and supraglottic larynx (referred to as 'larynx' for the remainder of article) were recorded for each patient dataset. A dose-volume constraint of V50Gy $<30\%$ was used for all patients (if clinically achievable). The larynx was delineated by a single radiation oncologist (MW) for all patients. Larynx was defined by epiglottic tip superiorly, lower border of cricoid cartilage inferiorly, and laterally via the pharyngeal lumen/thyroid cartilage. Anterio-posterior boundaries were the posterior aspect of hyoid or laryngeal cartilage anteriorly, and encompassed pharyngeal constrictors bounded by prevertebral fascia posteriorly. All QUANTEC recommendations for the larynx (V50Gy $<27\%$, Dmean $<40$ Gy, Dmean $<44$ Gy, Dmax $<66$ Gy) were utilized to categorize the patient cohort, i.e. V50Gy $<27\%$ vs. V50Gy $>27\%$; Dmean $<40$ Gy vs. Dmean $>40$ Gy, Dmean $<44$ Gy vs. Dmean $>44$ Gy; Dmax $<66$ Gy vs. Dmax $>66$ Gy. Biological equivalent larynx V50Gy, Dmean and Dmax was additionally calculated and applied to patients where dose per fraction was in excess of 2 Gy per fraction (alpha/beta value of 4 was utilized for conversion). Equivalent biological doses have been analyzed in this paper.

### *Acute toxicity assessment*

Patients were prospectively scored on a weekly basis (weeks 1–6 or 7) by three radiation oncologists (blinded to previous scores or other adverse effects) for acute dysphagia toxicity using the common toxicity criteria for adverse events version three (CTCAEv3) assessment tool. Grade 3 toxicity was deemed clinically significant, and its incidence recorded. Symptomatic and severely altered eating/swallowing – with an indication for percutaneous endogastric (PEG) tube intervention and intravenous fluids – was suggestive of Grade 3 dysphagia. QUANTEC defined dose-volume categories were subsequently analyzed for grade 3 toxicity incidence within the cohort.

Several possible clinical risk factors were also recorded for analysis. These included:

1. Age;
2. Sex;
3. Chemo-radiotherapy (CRT);
4. Surgery [post-operative radiotherapy (PORT) vs. definitive];
5. Pre-existing dysphagia (CTCAEv3);
6. Pre-existing nutritional status [Patient-Generated Subjective Global Assessment (PG-SGA) Tool];
7. Pre-existing comorbidity (Charlson Comorbidity Measuring Tool) [7].

### *Statistical methods*

The proportion of patients with grade 3 toxicity according to either V50Gy ($<$ or $>27\%$), Dmean

(< or >40 Gy), Dmean (< or >44 Gy) or Dmax (< or >66 Gy) were compared across the entire treatment using the Friedman test (overall change in proportion across entire treatment) and $\chi^2$-test (change in the proportion of patients incidence between two groups at individual weeks of treatment, i.e. Dmax < 66% vs. > 66%/week). These statistical methods were subsequently applied to the stratified data of the CRT, RT only, PORT and definitive cohorts. A $\chi^2$-test was used to perform a univariate analysis of dosimetric and clinical risk factors associated with grade 3 acute dysphagia. All analyses were carried out using SPSS (version 18.0, Chicago, IL, USA). A p-level of $< 0.05$ was afforded significance.

## Results

Patient demographics, tumor and treatment characteristics are shown in the Supplementary Appendix (available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.933874). Statistically significant toxicity reduction was observed on the basis of multiple larynx QUANTEC dose-v olume recommendations (refer to Tables I and II for all acute grade 3 dysphagia incidences) in the combined cohort.

V50Gy < 27% resulted in a 68.4% reduction in grade 3 toxicity at treatment week 5 ($p = 0.01$) and a 60.7% reduction at treatment week 6 ($p < 0.01$) compared to V50 > 27%. The reduction in toxicity from week 6–7 was not significant. Not all patients were prescribed a seven-week treatment course. This dose parameter was not significant at week 7 due to the reduced patient numbers at this time point.

Dmean < 44 Gy resulted in a 69.8% reduction of grade 3 toxicity at treatment week 5 ($p = 0.01$) and 51.4% reduction at treatment week 6 ($p < 0.01$) compared to Dmean > 44 Gy. Dmean < 40 Gy further supported Dmean as a key predictor of acute dysphagia, with significant reduction at week 5 (5.6% vs. 42.3%, $p < 0.01$) and week 6 (23.5% vs. 59.3%, $p = 0.01$). Treatment with a Dmax < 66 Gy demonstrated a 55.6% reduction of toxicity at treatment week 6 ($p < 0.01$) compared to Dmax > 66 Gy.

Furthermore, analysis of larynx Dmean for patients with CTCAEv3 grading above and below 3 was undertaken. Patients who peaked at grade 3 toxicity ($n = 47$) reported an average larynx Dmean of 46.3 Gy ± 9.7 Gy compared to those below grade 3 ($n = 29$) who reported a Dmean of 42.5 ± 6.8 Gy ($p = 0.07$).

Subsequent stratification of the total cohort into PORT ($n = 29$) and Definitive ($n = 47$) (Table I) reports comparable trends to that of the entire cohort. Statistical significant toxicity disparity, however, is less frequent. A comparable trend is also reported in the CRT ($n = 40$) and RT Only ($n = 36$) cohorts (Table II). In the CRT cohort, all dose constraints are significant predictors at varying time points. The RT Only group (significant only at V50Gy > 27%, week 6) reports comparable trends in toxicity incidence

Table I. Incidence of CTCAEv3 grade 3 acute dysphagia (treatment weeks 1–6 /7*) in ALL patients compared to Definitive and PORT.

| | V50Gy < 27% n/N (%) | V50Gy > 27% n/N (%) | Dmean < 44Gy n/N (%) | Dmean > 44Gy n/N (%) | Dmean < 40Gy n/N (%) | Dmean > 40Gy n/N (%) | Dmax < 66Gy n/N (%) | Dmax > 66Gy n/N (%) |
|---|---|---|---|---|---|---|---|---|
| All Patients (n = 76) | | | | | | | | |
| Week 1 | 1/33 (3.0) | 1/42 (2.4) | 1/36 (2.8) | 1/39 (2.6) | 0/19 (0.0) | 2/56 (3.6) | 1/27 (3.7) | 1/48 (2.1) |
| Week 2 | 3/34 (8.8) | 2/41 (4.9) | 3/36 (8.3) | 2/39 (5.1) | 1/19 (5.3) | 4/56 (7.1) | 3/28 (10.7) | 2/47 (4.3) |
| Week 3 | 4/32 (12.5) | 5/41 (12.2) | 4/34 (11.8) | 5/39 (12.8) | 1/18 (5.6) | 8/55 (14.6) | 4/26 (15.4) | 5/47 (10.6) |
| Week 4 | 4/30 (13.3) | 5/41 (12.2) | 3/33 (9.1) | 6/38 (15.8) | 0/17 (0.0) | 9/54 (16.7) | 3/24 (12.5) | 6/47 (12.8) |
| Week 5 | 4/28 (14.3) | 19/42 (45.2)^ | 5/34 (14.7) | 18/36 (50.0)^ | 1/18 (5.6) | 22/52 (42.3)# | 6/26 (23.1) | 17/44 (38.6) |
| Week 6 | 7/27 (25.9) | 29/44 (65.9)# | 11/34 (32.4) | 25/37 (67.6)^ | 4/17 (23.5) | 32/54 (59.3)^ | 7/25 (28.0) | 29/46 (63.0)# |
| Week 7 | 9/14 (64.3) | 21/26 (80.8) | 13/19 (68.4) | 17/21 (81.0) | 3/7 (42.9) | 27/33 (81.8) | 3/6 (50.0) | 27/34 (79.4) |
| PORT Only (n = 29) | | | | | | | | |
| Week 1 | 1/14 (7.1) | 1/14 (7.1) | 1/14 (7.1) | 1/14 (7.1) | 0/9 (0.0) | 2/19 (10.5) | 1/19 (5.3) | 1/9 (11.1) |
| Week 2 | 3/15 (20.0) | 2/14 (14.3) | 3/15 (20.0) | 2/14 (14.3) | 1/9 (11.1) | 4/20 (20.0) | 3/20 (15.0) | 2/9 (22.2) |
| Week 3 | 3/14 (21.4) | 3/14 (21.4) | 3/14 (21.4) | 3/14 (21.4) | 1/8 (12.5) | 5/20 (25.0) | 4/19 (21.1) | 2/9 (22.2) |
| Week 4 | 3/12 (25.0) | 2/14 (14.3) | 3/13 (23.1) | 2/13 (15.4) | 0/7 (0.0) | 5/19 (26.3) | 3/17 (17.7) | 2/9 (22.2) |
| Week 5 | 2/13 (15.4) | 6/13 (46.2) | 2/14 (14.3) | 6/12 (50.0) | 0/9 (0.0) | 8/17 (47.1) | 4/18 (22.2) | 4/8 (50.0) |
| Week 6 | 4/12 (33.3) | 9/13 (69.2) | 5/13 (38.5) | 8/12 (66.7) | 2/8 (25.0) | 11/17 (64.7) | 6/17 (35.3) | 7/8 (87.5)^ |
| Week 7 | N/A | 3/3 (100.0) | 1/1 (100.0) | 2/2 (100.0) | N/A | 3/3 (100.0) | N/A | 3/3 (100.0) |
| Definitive Only (n = 47) | | | | | | | | |
| Week 1 | 0/19 (0.0) | 0/28 (0.0) | 0/23 (0.0) | 0/24 (0.0) | 0/10 (0.0) | 0/37 (0.0) | 0/9 (0.0) | 0/38 (0.0) |
| Week 2 | 0/19 (0.0) | 0/27 (0.0) | 0/22 (0.0) | 0/24 (0.0) | 0/10 (0.0) | 0/36 (0.0) | 0/9 (0.0) | 0/37 (0.0) |
| Week 3 | 1/18 (5.6) | 2/27 (7.4) | 1/21 (4.8) | 2/24 (8.3) | 0/10 (0.0) | 3/35 (8.6) | 0/8 (0.0) | 3/37 (8.1) |
| Week 4 | 1/18 (5.6) | 3/27 (1.1) | 1/21 (4.5) | 3/24 (12.5) | 0/10 (0.0) | 4/35 (11.4) | 0/8 (0.0) | 4/37 (10.8) |
| Week 5 | 3/18 (16.7) | 12/26 (46.2) | 4/21 (19.1) | 11/23 (47.8) | 1/9 (11.1) | 14/35 (40.0)^ | 2/9 (22.2) | 13/35 (37.1) |
| Week 6 | 4/18 (22.2) | 19/28 (67.9)# | 7/22 (31.8) | 16/24 (66.7)^ | 2/9 (22.2) | 21/37 (56.8) | 1/9 (11.1) | 22/37 (59.5)^ |
| Week 7 | 9/14 (64.3) | 18/23 (78.3) | 12/18 (66.7) | 15/19 (79.0) | 3/7 (42.9) | 24/30 (80.0) | 3/6 (50.0) | 24/31 (77.4) |

CTCAEv3, Common toxicity criteria for adverse events version three; n, no. of grade 3 recordings; N, no. of patients with recordings at treatment week; %, grade 3 dysphagia incidence; PORT, post-operative radiotherapy. * Treatment length dependent on treatment intent/concurrent treatments/pre or post-operative; ^ $p < 0.05$ following $\chi^2$-test; # $p < 0.01$ following $\chi^2$-test.

Table II. Incidence of CTCAEv3 grade 3 acute dysphagia (treatment weeks 1–6 /7*) in ALL patients compared to CRT and RT Only.

| | V50Gy < 27% n/N (%) | V50Gy > 27% n/N (%) | Dmean < 44Gy n/N (%) | Dmean > 44Gy n/N (%) | Dmean < 40Gy n/N (%) | Dmean > 40Gy n/N (%) | Dmax < 66Gy n/N (%) | Dmax > 66Gy n/N (%) |
|---|---|---|---|---|---|---|---|---|
| All Patients (n = 76) | | | | | | | | |
| Week 1 | 1/33 (3.0) | 1/42 (2.4) | 1/36 (2.8) | 1/39 (2.6) | 0/19 (0.0) | 2/56 (3.6) | 1/27 (3.7) | 1/48 (2.1) |
| Week 2 | 3/34 (8.8) | 2/41 (4.9) | 3/36 (8.3) | 2/39 (5.1) | 1/19 (5.3) | 4/56 (7.1) | 3/28 (10.7) | 2/47 (4.3) |
| Week 3 | 4/32 (12.5) | 5/41 (12.2) | 4/34 (11.8) | 5/39 (12.8) | 1/18 (5.6) | 8/55 (14.6) | 4/26 (15.4) | 5/47 (10.6) |
| Week 4 | 4/30 (13.3) | 5/41 (12.2) | 3/33 (9.1) | 6/38 (15.8) | 0/17 (0.0) | 9/54 (16.7) | 3/24 (12.5) | 6/47 (12.8) |
| Week 5 | 4/28 (14.3) | 19/42 (45.2)^ | 5/34 (14.7) | 18/36 (50.0)^ | 1/18 (5.6) | 22/52 (42.3)# | 6/26 (23.1) | 17/44 (38.6) |
| Week 6 | 7/27 (25.9) | 29/44 (65.9)# | 11/34 (32.4) | 25/37 (67.6)^ | 4/17 (23.5) | 32/54 (59.3)^ | 7/25 (28.0) | 29/46 (63.0)# |
| Week 7 | 9/14 (64.3) | 21/26 (80.8) | 13/19 (68.4) | 17/21 (81.0) | 3/7 (42.9) | 27/33 (81.8) | 3/6 (50.0) | 27/34 (79.4) |
| CRT (n = 40) | | | | | | | | |
| Week 1 | 0/15 (0.0) | 0/25 (0.0) | 0/20 (0.0) | 0/20 (0.0) | 0/8 (0.0) | 0/32 (0.0) | 0/10 (0.0) | 0/30 (0.0) |
| Week 2 | 0/15 (0.0) | 1/24 (4.2) | 0/19 (0.0) | 1/20 (5.0) | 0/8 (0.0) | 1/31 (3.2) | 0/10 (0.0) | 1/29 (3.5) |
| Week 3 | 1/15 (6.7) | 3/24 (12.5) | 1/19 (5.3) | 3/20 (15.0) | 0/8 (0.0) | 4/31 (12.9) | 1/10 (10.0) | 3/29 (10.3) |
| Week 4 | 1/15 (6.7) | 2/24 (8.3) | 1/19 (5.3) | 2/20 (10.0) | 0/8 (0.0) | 3/31 (9.7) | 0/10 (0.0) | 3/29 (10.3) |
| Week 5 | 2/14 (14.3) | 10/23 (43.5) | 2/18 (11.1) | 11/19 (57.9)# | 0/7 (0.0) | 13/30 (43.3)^ | 2/10 (20.0) | 11/27 (40.7) |
| Week 6 | 4/13 (30.8) | 18/25 (72.0)^ | 6/18 (33.3) | 16/20 (80.0)# | 1/6 (16.7) | 21/32 (65.6) | 2/9 (22.2) | 20/29 (69.0)^ |
| Week 7 | 8/10 (80.0) | 15/18 (79.0) | 10/13 (76.9) | 12/14 (85.7) | 3/5 (60.0) | 19/2 (86.4) | 2/3 (66.7) | 21/25 (84.0) |
| RT Only (n = 36) | | | | | | | | |
| Week 1 | 1/18 (5.6) | 1/17 (5.9) | 1/17 (5.9) | 1/18 (5.6) | 0/11 (0.0) | 2/24 (8.3) | 1/18 (5.6) | 1/17 (5.9) |
| Week 2 | 3/19 (15.8) | 1/17 (5.9) | 3/18 (16.7) | 1/18 (5.6) | 1/11 (9.1) | 3/25 (12.0) | 3/19 (15.8) | 1/17 (5.9) |
| Week 3 | 3/17 (17.7) | 2/17 (11.8) | 3/16 (18.8) | 2/18 (11.1) | 1/10 (10.0) | 4/24 (16.7) | 3/17 (17.7) | 2/17 (11.8) |
| Week 4 | 3/15 (20.0) | 3/17 (17.7) | 3/15 (20.0) | 3/17 (17.7) | 0/9 (0.0) | 6/23 (26.1) | 3/15 (20.0) | 3/17 (17.7) |
| Week 5 | 3/17 (17.7) | 8/16 (50.0) | 4/17 (23.5) | 6/16 (37.5) | 1/11 (9.1) | 9/22 (40.9) | 4/17 (23.5) | 6/16 (37.5) |
| Week 6 | 4/17 (23.5) | 10/16 (62.5)^ | 6/17 (35.3) | 8/16 (50.0) | 3/11 (27.3) | 11/22 (50.0) | 5/17 (29.4) | 9/16 (56.3) |
| Week 7 | 1/4 (25.0) | 6/8 (75.0) | 3/6 (50.0) | 5/7 (71.4) | 0/2 (0.0) | 8/11 (72.7) | 1/3 (33.3) | 6/9 (66.7) |

CRT, Concurrent Cisplatin Chemotherapy + Radiotherapy; CTCAEv3, Common toxicity criteria for adverse events version three; n, no. of grade 3 recordings; N, no. of patients with recordings at treatment week; %, grade 3 dysphagia incidence. * Treatment length dependent on treatment intent/concurrent treatments/pre or post-operative; ^ $p < 0.05$ following $\chi^2$-test; # $p < 0.01$ following $\chi^2$-test.

with the combined cohort. In the absence of more definitive dose/volume/outcome data, the QUANTEC recommendations appear a useful predictor of acute dysphagia in this RT Only cohort.

A univariate analysis of dosimetric and clinical risk factors supports the use of QUANTEC recommendations across the majority of head and neck RT patients. OnlyV50 > 27% ($p < 0.01$), Dmean > 40 Gy ($p = 0.01$) and Dmax > 66 Gy ($p < 0.01$) predicted for grade 3 dysphagia. No clinical risk factors – including PORT or CRT – significantly predicted grade 3 dysphagia (Table III).

The peak toxicity of any patient throughout treatment was grade 3 (60.5% of all patients). In total 25.0% of patients reported a peak grade 2 toxicity and 13.2% a peak grade 1 toxicity.

## Discussion

Our results have shown that the QUANTEC report dose recommendations for late dysphagia are a useful tool for predicting acute dysphagia in a typical group of head and neck cancers usually treated radically with RT. Reduction in the inadvertent dose delivery to laryngo-pharyngeal structures has been extensively investigated and reported [8,9]. Our findings support the recommendations of the QUANTEC report [6]. These recommendations are based on the dose/volume/outcome data from multiple studies, which have been derived from late toxicity endpoints including edema and aspiration.

Other publications have attempted to validate the QUANTEC recommendations in various critical organs [10–12]. Liu et al. reported consistent rectal bleeding complications to those of the NTCP QUANTEC model in prostate RT. However, due to

Table III. Dosimetric and clinical risk factors affecting incidence of CTCAEv3 Grade 3 acute dysphagia (Total Grade 3 patients, N = 47).

| | CTCAEv3 G3 n/N (%) | Univariate (p-value) |
|---|---|---|
| V50Gy > 27% | 34/47 (72.3) | 0.004* |
| Dmean > 44Gy | 27/47 (57.4) | 0.156 |
| Dmean > 40Gy | 40/47 (85.1) | 0.014* |
| Dmax > 66Gy | 36/47 (76.6) | 0.001* |
| Sex (Female) | 16/47 (34.0) | 0.445 |
| Age (≥ 65) | 27/47 (57.4) | 0.156 |
| CRT | 30/47 (63.8) | 0.063 |
| Dysphagia | 11/47 (23.4) | 0.383 |
| Pre-Tx NS | 13/47 (27.7) | 0.610 |
| Morb. Score | 12/47 (25.5) | 0.261 |
| PORT | 14/47 (29.8) | 0.088 |

CTCAEv3 G3, Common toxicity criteria for adverse events version three grade 3 acute dysphagia toxicity; Dysphagia, Pre-existing dysphagia; Morb. Score, pre-treatment morbidity score ≥ 2; PORT, post-operative radiation therapy; Pre-Tx NS, pre-treatment nutritional status identifying malnourishment (PG SGA Score ≥ B). p-value determined via $\chi^2$-test. *Statistically significant risk factors ($p < 0.05$).

relative homogeneity of rectal dose distributions, this study warned of a low predictive power in their cohort [10]. Appelt et al. combined the dose response function of radiation pneumonitis (based on QUANTEC recommendations) with known clinical risk factors, to increase confidence in predicting radiation pneumonitis and to individualize toxicity risk estimates [11]. Most recently, parotid dose recommendations were validated by Beetz et al. Their work reported significantly lower rates of patient-rated xerostomia based on QUANTEC recommendations. However, this group warned of decreased reliability in the model in the elderly and patients with minor pre-existing xerostomia [12].

Dose parameters significantly associated with late laryngeal edema were previously reported by Sanguineti et al. [4]. Their findings recommended a V50Gy of less than 27% and a dose mean of less than 43.5 Gy to the larynx to minimize edema incidence. However, it should be recognized that only a small percentage of this cohort (n = 12, 18.2%) underwent concurrent chemotherapy, with subsequent stratification eliminating chemotherapy as an edema predictor. Dose-volume relationships generated from this work may well be affected by this discrepancy. This should be considered when applying these constraints in the presence of systemic therapy.

Furthermore, Feng et al. generated dose variables for minimizing late aspiration, reporting that a dose mean to glottic/ supraglottic larynx should not exceed 50 Gy [9,13]. The role of the laryngeal dose in late vocal dysfunction has also been reported. Dornfeld et al. reported a steep decrease in vocal toxicity when the maximal laryngeal dose was kept below 66 Gy [3]. A limitation of this particular study, however, was the absence of full three-dimensional dose metrics. Specified points within swallowing anatomy were identified for dose analysis. Limitations in their planning software did not enable retrospective analysis of newly delineated structures.

While tumor control and late toxicity should and will always remain the primary outcome measure, treatment tolerance in the acute setting is becoming increasingly important [14]. The primary focus of this study was to address the current lack of acute dysphagia dose/volume/outcome data in the literature. The QUANTEC recommendations for reduction in late edema, aspiration and vocal dysfunction were shown to be clinically significant predictors of acute dysphagia in our study. The incidence of acute dysphagia toxicity was significantly higher in patient cohorts exceeding the specified dose goals.

There is an increasing awareness of the importance of minimizing the consequences of acute toxicities. Multiple publications emphasize the importance of maintaining planned patient geometry, to ensure optimal delivery of planned dosimetry and to prevent the decrement in the quality of the IMRT plan, in particular, in predicting parotid gland dose [15,16]. The ability to predict, prevent and manage severe dysphagia may reduce the incidence and the magnitude of significant weight loss thus in our cohort. Better understanding the acute dose/response/outcome correlation in head and neck RT could play a role in the development of safer treatment intensification protocols, with ultimately, the potential for improved tumor control loco-regionally. This has been investigated via various RT dose escalation strategies [17,18]. Increasing dose to sites of putative radiation resistance, as suggested by various PET substrates has been explored previously [19]. Predictive dosimetric measures for expected treatment tolerance may provide a basis for inclusion/exclusion of treatment intensification protocols, or enable the implementation of suitable prophylactic measures to increase the likelihood of treatment tolerance. Further to RT dose intensification, the ability to deliver less toxic loco regional treatment may allow intensification of systemic treatments. The benefits of concurrent platinum based systemic therapy and biologic agents are well established [20]. A greater understanding of the acute response to RT, and the knowledge to implement individualized prophylactic measures, can optimize delivery of such potentially toxic programs and reduce associated toxicities. Various allied health professionals, including dietetics and speech pathology, provide opportunity for on-treatment assistance to enable improved treatment tolerance.

On-treatment interventions and their early implementation have proven beneficial in enhancing treatment tolerance. Studies have proven the benefit of enteral feeding (via PEG) in reducing weight loss and interrupted treatment, amongst many other acute toxicity incidents [21]. Yet, there is also data suggesting that a long-term dependence on PEG feeding is detrimental to latter swallowing function, with increased risk of atrophy to masticatory and swallowing muscles [22]. The work of Sanguinetti et al. addressed this concern through the development of predictive dosimetric parameters (to oral mucosa) for PEG insertion throughout IMRT for oropharyngeal cancer [23]. Planned patient geometry and treatment tolerance is dependent on multiple contributing factors. A more comprehensive understanding of the role of dosimetric measures and their correlation to incidence of acute toxicity will allow for a greater focus on treatment planning dose steering. Yet, perhaps of greater importance, is the early instigation of supportive care intervention (i.e. dietetics, speech pathology) where dose avoidance is not possible. Such measures may be able to better maintain

or achieve optimal treatment tolerance, weight management and treatment delivery.

A limitation of this study is that the study population does encompass multiple tumor types and demographic characteristics, but this group is typically representative of the cases treated radically with RT. Despite this heterogeneity of disease sub-type entities, the outcome data were relatively consistent as reported. The role of systemic therapy or RT given definitively or post-operatively in influencing acute dysphagia incidence was addressed. Our results showed that systemic therapy or surgical intervention did not significantly affect the incidence of grade 3 dysphagia. This was performed to ascertain concurrent systemic therapy or surgery given in conjunction with RT in some patients was not a confounding factor in the outcome of our analysis (in conjunction with multiple other clinical risk factors). Quality of life accompanying scoring was not used in this study. Equivalent toxicity incidence was reported regardless of biological or physical laryngeal dose.

## Conclusion

This study demonstrated the usefulness of the QUANTEC late toxicity recommendations in predicting acute dysphagia toxicity. Precision RT demands optimal maintenance of planned geometry through optimizing the opportunity for improved treatment tolerance. A more comprehensive understanding of acute dose/volume/outcome correlation enables individualized treatment programs to be developed, to facilitate improved treatment tolerance via measured prophylactic interventions.

***Declaration of interest:*** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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## Supplementary material available online

Supplementary Appendix to be found online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.933874.