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Grading Dysphagia as a Toxicity of Head and Neck Cancer: Differences in Severity Classification based on MBS DIGEST and Clinical CTCAE Grades

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Abstract

Background: Clinician-reported toxicity grading through Common Terminology Criteria for Adverse Events (CTCAE) stages dysphagia based on symptoms, diet, and tube dependence. The new Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) tool offers a similarly scaled 5-point ordinal summary grade of pharyngeal swallowing as determined through results of a modified barium swallow (MBS) study. This study aims to inform clinicians on the similarities and differences between dysphagia severity according to clinical CTCAE and MBS-derived DIGEST grading.

Methods: A cross-sectional sample of 95 MBS studies was randomly selected from a prospectively- acquired MBS database among patients treated with organ preservation strategies for head and neck cancer. MBS DIGEST and clinical CTCAE dysphagia grades were compared.

Results: DIGEST and CTCAE dysphagia grades had "fair" agreement per weighted κ of 0.358 (95% CI.231-.485). Using a threshold of DIGEST ≥3 as reference, CTCAE had an overall sensitivity of 0.50, specificity of 0.84, and area under the curve (AUC) of 0.67 to identify severe MBS-detected dysphagia. At less than 6 months, sensitivity was 0.72, specificity was 0.76, and AUC was 0.75 while at greater than 6 months, sensitivity was 0.22, specificity was 0.90, and AUC was 0.56 for CTCAE to detect dysphagia as determined by DIGEST.

Conclusions: Classification of pharyngeal dysphagia on MBS using DIGEST augments our understanding of dysphagia severity according to the clinically derived CTCAE while maintaining the simplicity of an ordinal scale. DIGEST likely complements CTCAE toxicity grading through

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improved specificity for physiologic dysphagia in the acute-phase and improved sensitivity for dysphagia in the late-phase.

Keywords

Deglutition and deglutition disorders; Head and Neck Cancer; Toxicity Grading; Clinical Trials

Introduction

Dysphagia is arguably the most important long-term toxicity of patients after treatment for head and neck cancer (1, 2). This is particularly true among HPV-associated oropharyngeal carcinoma patient who, generally speaking, have favorable disease specific outcomes compared to non-HPV associated cancer, which in turn necessitates more careful consideration of treatment toxicities many years into survivorship (3). As efforts continue to establish the optimal methods to treat these cancers while preserving high rates of survival and potential reduction of toxicities, accurate quantification of these toxicities (i.e. dysphagia) is paramount (4, 5). When grading outcomes such as oncologic treatment toxicity, whether in the context of designing a clinical trial or in routine clinical practice, both the timing of assessment(s) and type of information provided by a particular metric or diagnostic test acquired must be carefully weighed (6). Alteration of eating and swallowing in the acute phase of radiotherapy can be a manifestation of many issues including mucositis, thick secretions, and dysgeusia (7). Surgery has its own acute impact on swallowing, largely dependent on the extent and location of tumor in addition to the surgical approach (8–11). While these acute toxicities can co-exist with pharyngeal dysphagia, they are certainly distinct from long-term sequelae such as soft tissue fibrosis, xerostomia, stricture, and late neuropathies (4, 12, 13). Nevertheless, a single tool, the Common Terminology Criteria of Adverse Events (CTCAE), is typically used to classify toxicity throughout the continuum of care, despite the fact that different tools may possess a unique ability to understand the severity of dysfunction or symptomatology.

Prior literature and clinical practice both support the notion that comprehensive assessment of a complex problem such as pharyngeal dysphagia may be best captured through a composite index that includes various metrics (3, 6, 13). Clinical trials have historically measured dysphagia toxicity principally through clinician determined means, namely the CTCAE, and through surrogate measures of swallowing dysfunction such as gastrostomy tube presence (14–17). Nevertheless, prior work demonstrates that clinician-reported dysphagia through CTCAE or other clinically-derived information may not accurately characterize the impact, nature, or severity of swallowing dysfunction compared to MBS (4, 18–21). Rather than symptomatology, diet alterations, and feeding tube dependence (i.e., the criteria for clinical CTCAE stage), MBS measures physiologic swallowing dysfunction and can identify dysphagia in asymptomatic patients. Despite the ability of MBS to identify silent aspirators in addition to providing specific anatomic/physiologic information that can guide efforts to maximize safer and more efficient swallowing during treatment and into survivorship, the information provided through MBS can be challenging to summarize using common toxicity reporting mechanisms and, therefore, less easily described in oncology clinical trials and by less familiar clinicians (22–24). As such, an effort was made to

standardize reporting of MBS findings with regard to the safety and efficiency profiles of pharyngeal swallowing using the ordinal toxicity grading framework of the CTCAE. The Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) tool addresses this need, offering a 5-point ordinal summary grade to standardize reporting of MBS findings using benchmarks of safety and efficiency of bolus clearance through the pharynx (25). In an effort to understand how DIGEST reporting compares to traditional CTCAE quantification of swallowing toxicity, this study analyzes the similarities and differences between these metrics and their comparative diagnostic impressions.

Methods

Eligibility and Design

With approval from the institutional review board, prospectively collected records of MBS conducted at MD Anderson Cancer Center between 2005 and 2013 were retrospectively identified. MBS from patients with a history of laryngeal and/or pharyngeal carcinoma were eligible for inclusion. Swallow studies in patients with history of “open” aerodigestive tract surgery (i.e. transmandibular or transcervical including total laryngectomy) were excluded as were those with known recurrent or second primary malignancy of the head and neck at the time of MBS. Patient who underwent neck dissection without entrance into the aerodigestive tract were not excluded. Indications for MBS in these patients included evaluation of clinical concern for dysphagia in addition to those performed as part of routine treatment pathways. Ninety-five MBS were then randomly selected from eligible cases, of which 10% represented swallow studies prior to treatment. Additionally, MBS were proportionally sampled 2:1 for abnormal Penetration Aspiration Scale (PAS) scores, defined as a score greater than or equal to three. The standard MBS protocol included in the following order: 2 trials each of 5-mL, 10-mL, and self-administered cup sip volumes of Varibar thin liquid barium (40% weight/volume), Varibar barium pudding, and a saltine cracker coated in barium paste in lateral plane video-recorded at 30 frames per second. As detailed in the DIGEST validation study, two blinded, trained laboratory raters who previously met 80% agreement on a training set of MBS independently scored MBS with random re-sampling and re-rating of 32 MBS to ensure inter- and intra-rater reliability (inter-rater weight-κ 0.67, intra-rater weight-κ 0.82–0.84) (25). Given the combination of surgical and non-surgical treatments, classification of tumor and nodal stage was completed clinically using pre-treatment imaging.

CTCAE

The most recent CTCAE (version 4) was published in 2009 by the National Cancer Institute as part of an ongoing effort to standardize adverse event (AE) reporting within oncology (26). AEs are graded according to an ordinal scale where zero represents no toxicity and five represents death from the AE. In between, grade one is mild, two is moderate, three is severe, and four is life-threatening. With regard to dysphagia, the CTCAE uses the descriptive terminology listed in Table 1, columns 1 and 2. CTCAE dysphagia grades are based on symptoms, diet, and tube dependency. These grades were assigned on the MBS date based on a standardized interview by the speech pathologist with normalcy of diet grading per Performance Status Scale of Head and Neck Cancer (PSS-HN) and a single

question, “do you have difficulty swallowing?”, asked of each patient (27). CTCAE grades were assigned independently (without knowledge) of DIGEST scores using clinical documentation from the MBS encounter.

DIGEST

DIGEST combines an interaction of the 1) safety and 2) efficiency profiles of pharyngeal bolus transport on MBS to determine an overall rating of pharyngeal swallow function in a manner analogous to the American Joint Cancer Committee staging system’s combination of tumor, nodal, and metastatic information to quantify disease stage. In short, a patient’s safety profile is derived by assigning the maximum Penetration-Aspiration Scale (PAS) observed across a series of standard bolus trials with modifiers to account for the frequency and quantity of high grade penetration/aspiration events (PAS≥5). The efficiency profile is assigned through estimation of the maximum percentage of pharyngeal residue (<10%, 10–49%, 50–90%, and >90%) also with modifiers to account for variations across bolus types. Final DIGEST ratings combine the safety and efficiency profiles, which are demarcated using a similar scale as the CTCAE (0=no pharyngeal dysphagia, 1=mild, 2=moderate, 3=severe, 4=life threatening). Specific descriptions of the grading criteria and cross validation of the DIGEST rating are detailed elsewhere (25). Similar to CTCAE grading, DIGEST scores were assigned without knowledge of CTCAE grade.

Statistical methods

Patient, tumor, and treatment characteristics as well as CTCAE grades and DIGEST ratings were summarized using descriptive statistics. Agreement between DIGEST score and clinical CTCAE dysphagia grade was plotted by histogram with determination of the level of agreement between the two scales using the weighted Cohen’s kappa index. Diagnostic accuracy was determined by sensitivity, specificity, and area under the curve (AUC). Statistical analyses were performed using using STATA v14.0 (StataCorp LP, College Station, TX) and JMP, version 12.1 (SAS Institute Inc, Cary NC).

Results

A cross-sectional sample of 95 patients referred for MBS were included in the analysis. Patient demographics, primary tumor location, tumor stage, treatment type, and timing of MBS are detailed in Table 2.

MBS derived DIGEST and clinical CTCAE dysphagia grades had a weighted κ of 0.358 (95% CI .231, .485), which is generally considered as a “fair” level of agreement (28). Figure 1 plots this relationship. Relative to MBS (DIGEST), clinical CTCAE grades over-estimated dysphagia severity in 25% (i.e., CTCAE higher than DIGEST) of exams and under-estimated dysphagia severity in 39% (i.e., CTCAE lower than DIGEST). Considering a threshold of severe dysphagia as determined by the CTCAE (grade ≥3, i.e., tube-fed patients), 17.4% (4/23) of patients had a DIGEST rating of no or mild dysphagia (DIGEST <2) and all were less than 6 months from completion of treatment. Conversely, 50% (10/20) of patients with a severe dysphagia per DIGEST (MBS grade≥3, i.e., severe inefficiency or chronic aspiration on MBS) had a lower CTCAE grade (<3), of which 80% (8/10) were 6

months or more beyond completion of therapy. Two of these latter patients were eating a regular diet with mild or no reported symptomatology on CTCAE despite severe dysphagia on MBS per DIGEST.

In terms of diagnostic accuracy, using a threshold of DIGEST ≥3 as reference, CTCAE had an overall sensitivity of 0.50, specificity of 0.84, and area under the curve (AUC) of 0.67 to identify severe MBS-detected dysphagia. For patients less than 6 months after treatment, sensitivity was 0.72, specificity was 0.76, and AUC was 0.75 whereas for greater than 6 months, sensitivity was 0.22, specificity was 0.90, and AUC was 0.56 for CTCAE to detect dysphagia as determined by MBS-derived DIGEST ratings.

Discussion

In this cohort of surgically and non-surgically treated patients, 85% of whom received multimodality organ preservation treatment, agreement between clinical CTCAE staging and MBS DIGEST is fair but agreement varies depending on the severity of dysphagia and length of follow-up. It is well-established that MBS provides distinct information in comparison to diagnostic observations from clinical examination and patient-reported symptoms (23, 29–32). Both CTCAE and MBS DIGEST grading were developed for the explicit purpose of grading the severity of swallowing toxicity in cancer patients. However, since DIGEST summarizes MBS findings and CTCAE grade relates to a clinical assessment of patient function, these measures report correlated and complementary rather than duplicative information. Indeed, a high degree of alignment between CTCAE and DIGEST would be unusual and supports our finding of fair agreement between them. Precisely because difficulty swallowing may represent the interplay of symptomatology, physiologic dysfunction, and anatomic alternations in addition to being influenced by patient adaptations over time that make clinical assessments less sensitive, swallowing dysfunction may best be encapsulated through a combination of metrics (33–36). It is the authors' recommendation to include a combination of clinician-derived symptom reporting (CTCAE), radiographic data on swallowing via MBS (e.g., DIGEST), and validated, dysphagia-specific patient-reported outcome (PRO) measures to provide a broad representation of the patient's swallowing function when planning toxicity analyses in oncology.

The relationship between CTCAE and MBS DIGEST graded dysphagia severity appears to vary over time. This study aggregated patients from all treatment times, but the sensitivity and specificity of CTCAE to detect MBS-derived dysphagia differed according to the post-treatment interval timing, broadly defined by less than or greater than 6 months (i.e. acute- vs late-phase). The results suggest that MBS-derived DIGEST adds specificity for dysphagia compared to CTCAE in the short term perhaps explained by the impact of acute toxicities of treatment on oral intake that necessitate alternate alimentation but do not represent true pharyngeal dysphagia (i.e., in acute phase DIGEST avoids false positives when a patient is not eating regular foods due to acute toxicities other than pharyngeal dysphagia). That is, the presence of a feeding tube (the most common reason for CTCAE grade ≥3 dysphagia), particularly in patients <6 months post-treatment, does not necessarily mean a patient has pharyngeal dysphagia on MBS.

Furthermore, DIGEST may be more sensitive to clinically-meaningful pharyngeal dysphagia, particularlyin later follow-up (>6 months post-treatment), by identifying patients who maintain a full oral diet (asymptomatic on CTCAE) but with a severely dysfunctional swallow on MBS (i.e., in the chronic phase, DIGEST avoids false negatives of clinical CTCAE grading). In other words, severe non-feeding tube dependent dysphagia detected by MBS-derived DIGEST was most commonly observed in this study in long-term follow-up, beyond 6 months. These time-dependent discrepancies between CTCAE and DIGEST grading demonstrate the ability of MBS graded measures of toxicity to provide sensitive, specific, and dynamic physiologic-based information on a patient's ability to swallow along the continuum of survivorship.

All patients in this study had prospectively collected, standardized interviews incorporating a validated oral intake measure (PSS-HN) with uniform questions of feeding tube utilization and swallowing symptomology acquired at point of service at the time of each MBS study. This clinical practice allowed for tight control of CTCAE grading that is likely more sensitive to subtle low grade toxicity classifications (i.e., grade 1 or 2 CTCAE events) than unstructured toxicity reporting that is routine in many clinical settings. Similar standardization of clinical procedures, data collection, and interpretation occurred with MBS studies and DIGEST rating lending to a robust comparison of methods (25). Nevertheless, this is a retrospective analysis of prospectively acquired data on swallowing toxicity as determined by CTCAE grade and DIGEST rating. Though patients were systematically selected at random across the spectrum of treatment to allow for diversity in sampling during the validation study, this study is not sufficiently powered to analyze findings by timing before or after treatment. As a result, time-dependent factors that may affect swallowing must be taken into account secondarily as exploratory or hypothesis-generating observation. Prospective, longitudinal validation of these observations is underway. This analysis combines surgical and non-surgical patients with tumors from various upper aerodigestive subsites. Though this is representative of a contemporary head and neck cancer cohort in a large, North American center, combination of patients treated by different modalities may limit generalizability and the ability to identify subsets of patients where CTCAE and DIGEST may be either more or less complementary for the purposes of trial design and clinical decision-making.

In conclusion, use of a standardized metric for classification of pharyngeal dysphagia on MBS augments our understanding of dysphagia severity according to the clinically derived toxicity endpoints of the CTCAE while maintaining the simplicity of an ordinal, clinician-graded scale. DIGEST likely complements CTCAE toxicity grading through improved specificity for pharyngeal dysphagia (versus other toxicities impacting oral intake) in the acute-phase and through improved sensitivity for dysphagia in the late-phase (when gastrostomy-free does not equate to dysphagia-free). Though incorporation of this grading mechanism, MBS-derived data on pharyngeal dysphagia can be distilled into an intuitive, rank-based scale that harmonizes with ordinal standards for toxicity reporting in oncology trials.. This could improve advocacy for dysphagia management among all members of the multidisciplinary head and neck cancer team.

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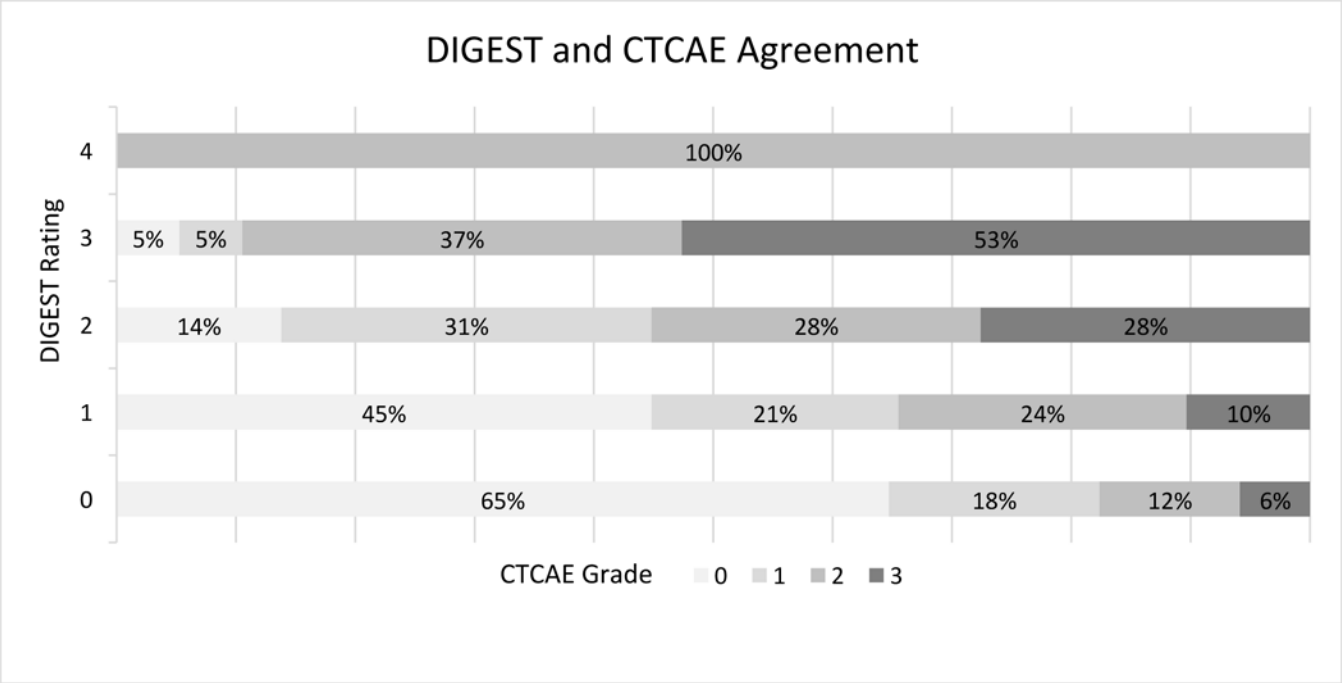

Figure 1:
Graphical representation of agreement between MBS-derived DIGEST score and clinical CTCAE dysphagia grade

Table 1:

CTCAE Dysphagia Description and Patient Proportion in this Study

Grade	Description	No. of Patients (%)
0	Asymptomatic	29 (31)
1	Symptomatic, able to eat regular diet	18 (19)
2	Symptomatic and altered eating/swallowing	25 (26)
3	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	23 (24)
4	Life-threatening consequences; urgent intervention indicated	0(0)

Table 2:

Patient Characteristics (n = 95)

	No. of Patients (%)
Age (mean(SD))	64.5 (8.0)
Sex	
Male	78 (82)
Female	17 (18)
Primary Tumor Site	
Nasopharynx	6 (6)
Oropharynx	59 (62)
Hypopharynx	6 (6)
Larynx	20 (21)
Unknown Primary	4 (4)
T Classification	
0	4 (4)
1	16 (17)
2	41 (43)
3	22 (23)
4	12 (13)
N Classification	
0	26 (27)
1-2a	8 (8)
2b	23 (24)
2c	31 (33)
3	7 (7)
Treatment Combination	
Surgery alone[a]	9 (9)
Surgery + adjuvant[b]	14 (15)
Radiation alone	5 (5)
Radiation + chemotherapy[c]	67 (71)
Timing of CTCAE/DIGEST	
Pre-treatment	10 (10)
0-3 months[d]	20 (21)
4-6months[d]	13 (14)
7-12months[d]	29 (31)
>12months[d]	23 (24)

[a] Includes induction chemotherapy in one patient

[b] Includes post-operative radiation and chemoradiation

[c] Includes induction with or without concurrent chemotherapy

$d_{\text{Post-treatment}}$

Table 3:

DIGEST Component Breakdown

	S0	S1	S2	S3	S4	S Total
E0	17	6	1	1	0	25
E1	13	4	4	3	1	25
E2	6	6	7	1	0	20
E3	4	7	7	6	0	24
E4	0	0	0	1	0	1
E Total	40	23	19	12	1	

DIGEST Rating	No. of Patients (%)
0, no dysphagia	17 (18)
1, mild	29 (31)
2, moderate	29 (31)
3, severe	19 (20)
4, life-threatening	1 (1)

No. of patients in each box.

Abbreviations: E, Efficiency profile; S, Safety profile