

Use of the Clavien-Dindo Classification of surgical complications in neoadjuvant immunotherapy clinical trials for head and neck cancer

Marcus A. Couey, MD, DDS; Rom S. Leidner, MD; Ashish A. Patel, MD, DDS; Allen C. Cheng, MD, DDS; Phillip A. Harrison, MD, DDS; George Morris, BSN; Lessli Rushforth, RN; R. Bryan Bell, MD DDS

Earle A. Chiles Research Institute in the Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR, USA



Background

Immune checkpoint inhibitors are transforming the management of patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC). Recently, these agents have begun to be tested in the curative, preoperative setting. Numerous neoadjuvant clinical trials testing various immunotherapies prior to surgery for HNSCC are underway in the United States and Europe, however, there are no standard guidelines or criteria by which to report surgical complications. The lack of consensus on how to define and grade adverse postoperative events has hampered the evaluation of surgical procedures, particularly in the context of immune-related adverse events that may impact surgical outcomes.

Purpose

The purpose of this study is to assess the use of the Clavien-Dindo Classification (CDC)^{1,2}, which was first proposed for use in urological surgery in 1992, but has not been used as a tool to assess adverse events (AE) within neoadjuvant immunotherapy trials.

Methods

We utilized the CDC to prospectively assess surgical complications in 4 separate phase Ib, investigator-initiated neoadjuvant immunotherapy clinical trials that enrolled patients with resectable HPV-related and HPV-unrelated HNSCC from 2014-2019. If no AE were identified per CDC, a grade of 0 was assigned. Subjective severity of post-operative adverse events was then assessed on a 5-point scale (0-4) by physicians on our team. A weighted Kappa agreement analysis was performed to test the accuracy and reliability of the CDC as compared to physician perception of overall morbidity.

References:

1. Clavien PA, et al. Surgery. 1992;111:518–26.
2. Dindo D, et al. Ann Surg. 2004;240(2):205-213.
3. Myatt A, et al. Br J Med Surg Urol. 2012;5(2):54-60.

Table 1:

Patient characteristics and adverse events per Clavien Dindo Classification

National Clinical Trial number	NCT03247712	NCT02274155	NCT03336606	NCT02812524	Total
Neoadjuvant therapy	Nivolumab + SBRT ¹	OX40 (MEDI6469)	OX40 (MEDI0562)	Ipilimumab (intratumoral)	
Phase	Ib-II	Ib	Ib	Ib	-
Enrolled (n)	21	16	10	17	64
Tumor subsite					
Oral Cavity	3	6	2	17	28
Oropharynx	16	8	8	0	32
HPV+	16	6	8	0	30
HPV-	0	2	0	0	2
Hypopharynx	0	1	0	0	1
Larynx	2	1	0	0	3
AEs					
Median number of AE (per subject, CDC)	5	5	1	2	3
Median AE severity (CDC)	1	1	1.5	2	2
Most common AEs (CDC ≥ Gr I)					
Electrolyte disturbances	6	6	2	9	23
Surgical site pain	9	6	1	2	18
Cough / increased secretions	6	3	2	4	15
Nausea / vomiting	8	4	1	0	13
Anxiety / disorientation	5	4	0	2	11
Neurosensory changes	5	2	1	2	10
Delayed healing / dehiscence	7	1	1	1	10
Hematoma / seroma	5	0	2	0	7
Most common severe AEs (CDC ≥ Gr III)					
Pulmonary ²	1	5	3	2	11
Delayed healing / dehiscence	2	1	1	1	5
Inadequate oral intake (requiring G tube ³)	2	1	1	0	4
Hematoma / seroma	3	0	0	0	3
Surgical site infection	0	1	0	2	3
Highest AE severity (per subject, CDC)					
0 (none)	2	1	3	4	10
I	4	4	2	4	14
II	5	6	2	5	18
III	9	3	2	3	17
IV	1	2	1	1	5

¹Stereotactic body radiation therapy; ²Pneumonitis / pneumonia / respiratory failure / hemoptysis; ³Deviation from expected post-operative course
Abbreviations: AE = Adverse Events; CDC = Clavien-Dindo Classification; Gr = grade

Table 2:

Physician-assessed subjective post-op morbidity vs highest grade AE (CDC) per patient

Agreement						
CDC	Physician assessment of overall morbidity (0-4)					
		0	1	2	3	4
	0	10	0	0	0	0
	1	3	9	2	0	0
	2	0	7	11	0	0
	3	0	2	11	4	0
	4	0	0	0	2	3

Abbreviations: CDC = Clavien-Dindo Classification

Weights						
CDC	Physician assessment of overall morbidity (0-4)					
		0	1	2	3	4
	0	0	1	2	3	4
	1	1	0	1	2	3
	2	2	1	0	1	2
	3	3	2	1	0	1
	4	4	3	2	1	0

Results

64 patients with stage I-IVA HNSCC involving the oral cavity, oropharynx, hypopharynx or larynx who were treated on an IRB-approved protocol with either anti-PD-1 (NCT03247712), anti-OX40 (NCT02274155 and NCT03336606), or anti-CTLA-4 (NCT02812524) prior to definitive surgical resection were analyzed (Table 1). Surgical procedures included major composite resections with free flap reconstruction, laryngopharyngectomy, carotid resection, as well as transoral robotic assisted oropharyngectomy. The study demonstrated substantial agreement between the CDC and physician perception of morbidity (weighted Kappa 0.651; Table 2). The CDC tended to assign higher scores for AE than physician perception of morbidity, particularly for AE scored ≤2 by the investigators.

Conclusions

- The CDC is a valuable tool for grading postoperative adverse events in head and neck cancer patients enrolled in neoadjuvant immunotherapy clinical trials.
- The CDC tended to assign higher scores than physician perception of morbidity, particularly for AE deemed to be low-severity by the investigators. There was higher concordance between the CDC and subjective investigator assessment of AE when the investigator assessment of severity was ≥3..
- Use of suffixes as suggested by Myatt et al.,³ including “i” for intraoperative AE and “f” (“follow-up) for AE occurring >30 days after surgery, may improve the utility of the CDC particularly for neoadjuvant immuno-oncology trials, in which investigational non-surgical interventions may contribute or predispose to surgical complications. Further investigation of these and other modifications to the CDC is warranted in this setting.

Cohen's Weighted Kappa	
Alpha	0.05
kappa	0.651
std err	0.060
lower	0.532
upper	0.769