Oral Oncology 83 (2018) 140–146

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

# Validation and assessment of discordance of the 8th edition AJCC (American Joint Committee on Cancer) clinical and pathologic staging systems in patients with p16+ oropharyngeal cancer treated with surgery and adjuvant radiation at a single institution

Piyush Gupta[a], Jocelyn C. Migliacci[a], Ashley Hay[a], Matthew Rosenthal[a], Ximena Mimica[a], Nancy Lee[b], Richard J. Wong[a], Jatin Shah[a], Snehal Patel[a], Ian Ganly[a,*]

[a] Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States
[b] Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

ARTICLE INFO

*Keywords:*
Head and neck cancer
Neoplasm staging
Kaplan-Meier estimate
TNM stage
Human papillomavirus
Oropharyngeal cancer
Squamous cell carcinoma
Survival analysis

## Introduction

Major updates have been made in the latest (8th) edition of the American Joint Commission on Cancer (AJCC) manual for staging of oropharynx squamous cell cancer (OPSCC) [1,2] which are based on changes in epidemiology of OPSCC related to the emergence of Human Papilloma Virus (HPV) as the major cause for OPSCC [3,4]. It is now recognized that patients with HPV positive oropharyngeal cancer (HPV + OPSCC) have superior survival compared to patients with HPV negative oropharynx cancer (HPV − OPSCC) [5]. One of the key characteristics of patients with HPV + OPSCC is a markedly improved prognosis despite advanced nodal disease when compared to patients with HPV-disease [3,6–8]. Traditional risk factors, such as positive margins and extranodal extension (ENE), are not accurate predictors of outcome in HPV + patients [9].

Previous studies have reported that the AJCC 7th edition staging system has limited ability to differentiate prognosis accurately among stages in the HPV + OPSCC population [6–8]. As a result, a new clinical staging system (International Collaboration on Oropharyngeal cancer Network for Staging, ICON-S) and a new pathological staging system (HPV-Path) were introduced in 2016 specifically for HPV + OPSCC patients. The ICON-S staging system was developed from a study of 1907 HPV + OPSCC patients using an adjusted hazard ratio model that considered age, smoking status and use of cytotoxic chemotherapy [10]. This staging model was created from data of patients treated primarily with chemoradiation. In contrast, the HPV-Path system was created from a multi-institutional dataset of HPV + OPSCC patients treated with surgery, and thus the staging system was based on pathological variables that were not available in the ICON-S study [11]. The parameters of both staging systems have been incorporated into the new 8th edition of the AJCC staging system for OPSCC [1,2]. The ICON-S system is the new AJCC 8th edition clinical staging system and the HPV-Path system the pathological staging system. A recent report has suggested the two staging systems result in discordant staging [12].

The objective of our study was to validate the new clinical and pathological staging systems in an independent cohort of HPV + OPSCC

*Abbreviations:* AJCC, American Joint Commission on Cancer; OPSCC, Oropharyngeal Squamous Cell Cancer; HPV, Human Papilloma Virus; OS, Overall Survival; DSS, Disease Specific Survival

* Corresponding author. Department of Surgery, Head and Neck Service, Memorial Sloan Kettering Cancer Center , 1275 York Avenue, Room C-1079, New York, NY 10065, United States.

*E-mail addresses:* piyushesama@gmail.com (P. Gupta), migliaccij@mskcc.org (J.C. Migliacci), haya@mskcc.org (A. Hay), rosenthalm@mskcc.org (M. Rosenthal), mimicax@mskcc.org (X. Mimica), leen2@mskcc.org (N. Lee), wongr@mskcc.org (R.J. Wong), shahj@mskcc.org (J. Shah), patels1@mskcc.org (S. Patel), ganlyi@mskcc.org (I. Ganly).

https://doi.org/10.1016/j.oraloncology.2018.06.024
Received 12 May 2018; Received in revised form 18 June 2018; Accepted 19 June 2018

patients who had received surgery as the initial treatment modality. We also determined which staging system was more appropriate for patients treated with surgery and evaluated the degree of discordance between the clinical and pathological staging systems.

## Methods

After Institutional Review Board (IRB) approval, we performed a retrospective analysis of our surgical oropharyngeal patient database from 1985 to 2015. Patients with OPSCC who had surgery at our institution as the primary form of treatment were identified. HPV status was determined by p16 immunohistochemistry, which is now accepted as a surrogate marker [13,14]. The patients also received adjuvant treatment based on current National Comprehensive Cancer Network (NCCN) guidelines or, in some cases, after multidisciplinary team consultations. Patients with distant metastatic disease at presentation, those who were HPV negative or HPV unknown status, those with recurrent disease, and patients that had received any form of neoadjuvant treatment were excluded from the study.

The demographic, clinicopathologic, and outcomes data were extracted from the medical record for eligible patients. The clinical tumor (cT) and nodal status (cN) were verified by reviewing the radiological scans. Histopathological data were reviewed to ascertain the pathological tumor (pT) and pathological nodal (pN) status.

### *Staging systems*

The clinical and pathological staging systems are summarized in Fig. 1. For the clinical staging system, the cT category remains the same in both 8th and 7th edition AJCC staging system. However, nodal staging is different in the 8th edition: for the cN status, in HPV + ve patients, cN1, cN2a, and cN2b are combined together and have been reclassified as cN1, cN2c has been reclassified as cN2, and cN3 reclassified as N3. The AJCC 7th edition system determines nodal burden based on size, laterality, and number (single/multiple), whereas the AJCC 8th edition clinical system relies on laterality and size only. The HPV-Path system, on the other hand, is a pathological staging system. The pT categories are the same as AJCC 7th edition, but it has a different nodal status categorization that is based on the number of involved nodes. M stage remains consistent across all three staging systems. Finally, the new clinical and pathological systems stage HPV + OPSCC patients into only three stages (I–III) which differs from the AJCC 7th edition that has four stages (I–IV).

### *Outcomes data*

Overall survival (OS) was calculated from the date of surgery to either the last date the patient was known to be alive, regardless of disease status or death date. An OS event was defined as death from any cause. Disease-specific survival (DSS) was calculated from the date of surgery to last date of disease assessment or death date. A patient was only considered to have a DSS event if he/she died of disease or if the patient had active disease at the date of last disease assessment. All other patients were censored for DSS at the last date of disease assessment by a medical professional.

| HPV+ OPC Stages | Clinical Staging * | | | Pathological Staging ** | | |
|---|---|---|---|---|---|---|
| Stage | T Category | N Category | M Category | T Category | N Category | M Category |
| Stage 1 | T1 / T2 | N0: No LNs<br>N1: I/L LNs | M0 | T1, T2 | N0: No LNs<br>N1: 1-4 LNs | M0 |
| Stage 2 | T1 / T2 | N2: B/L or C/L LNs | M0 | T1, T2 | N2: ≥ 5 LNs | M0 |
| | T3 | N1: I/L LNs<br>N0: No LNs | M0 | T3, T4 | N0: no LNs<br>N1: 1-4LNs | M0 |
| Stage 3 | T4 | Any N | M0 | T3, T4 | N2: ≥ 5 LNs | M0<br>M0 |
| | Any T | N3: > 6 cm LN(s) | M0 | | | |
| Stage 4 | Any T | Any N | M1 | Any T | Any N | M1 |

| cTNM | cN0 | cN1 (I/L) | cN2 (B/L, C/L) | cN3 | | pTNM | pN0 | pN1 (1-4 LNs) | pN2 (≥ 5 LNs) |
|---|---|---|---|---|---|---|---|---|---|
| T0 | NA | I | II | III | | T0 | NA | I | II |
| T1 | I | I | II | III | | T1 | I | I | II |
| T2 | I | I | II | III | | T2 | I | I | II |
| T3 | II | II | II | III | | T3 | II | II | III |
| T4 | III | III | III | III | Stage IV - Any T, Any N, M1 | T4 | II | II | III |

* - Based on ICON-S Study [10]
** - Based on HPV Path Study [11]
HPV: human papillomavirus; TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

**Fig. 1.** HPV related oropharyngeal carcinoma TNM staging AJCC UICC 2017.