Can Positron Emission Tomography with Computed Tomography (PET/CT) Accurately Predict AJCC 8th Edition Pathologic Staging in Surgically Treated Patients with Human Papilloma Virus Associated (HPV +) Oropharyngeal Squamous Cell Carcinoma (OPSCC)?

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ABSTRACT

Objective:
The American Joint Committee on Cancer (AJCC) 8th edition introduced distinct clinical and pathological staging paradigms for human papilloma virus-associated (HPV+) oropharyngeal squamous cell carcinoma (OPSCC). Treatment planning for OPSCC often utilizes PET/CT to assess clinical stage. We hypothesize PET/CT will accurately predict final pathologic AJCC 8th ed. staging in patients with HPV+ OPSCC.

Study Design:
Retrospective Review

Methods:
All patients with primary HPV+ OPSCC with preoperative PET/CT who underwent transoral robotic surgery and neck dissection between 2011 and 2017 were identified. Pathologic data was collected via chart review. Two senior neuroradiologists performed blinded re-evaluation of all scans. Primary tumor size and cervical nodal disease characteristics were recorded and TNM staging was extrapolated. Cohen's kappa statistic was used to assess interrater reliability. Test for symmetry was performed when there was discordance between radiologic and pathologic staging.

Results:
49 patients met inclusion criteria. Interrater reliability was substantial between radiologists (A and B) for nodal(N) and overall staging(OS) (κ= 0.715 and 0.715). Radiologist A review resulted in identical OS for 67% of patients, over-staging for 31%, and under-staging for 2%. Radiologist B review resulted in 61% identical OS, 39% over-staging, and 0% under-staging. In misclassified cases, test of symmetry shows strong bias toward over-staging N stage and OS (p < 0.001). Radiologic interpretation of extracapsular extension showed poor interrater reliability (κ= 0.403) and poor accuracy.

Conclusion:
PET/CT predicts a higher nodal and overall stage than pathologic staging. PET/CT should not be relied upon for initial tumor staging, as increased FDG uptake is not specific for nodal metastases. PET/CT is shown to be a poor predictor of ECE.

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INTRODUCTION

The American Joint Committee on Cancer (AJCC) 8th Edition staging system recognizes Human Papilloma Virus (HPV+) related oropharyngeal squamous cell carcinoma (HPV+ OPSCC) as a distinct clinical entity from HPV negative (HPV -) disease. HPV + OPSCC has been demonstrated to behave in a less virulent, more treatment responsive manner[1-2]. AJCC 8 results in lower overall staging for patients with HPV+ OPSCC versus HPV-disease, which often allows for de-escalation of treatment. Still, while staging guidelines have changed, it is not yet clear how practice patterns and clinical guidelines also ought to change.

Unlike with AJCC7 staging, AJCC 8 also recognizes separate clinical and pathological staging systems for HPV+ OPSCC . This study's aim was to determine how accurately interpretations of PET/CT findings can predict the final pathologic staging, as confirmed by the surgical pathology specimens

MATERIALS AND METHODS

University of Pittsburgh Medical Center (UPMC) Institutional Board Review permission was obtained. All patients with primary HPV+ OPSCC with preoperative PET/CT who underwent transoral robotic surgery (TORS) between 2011 and 2017 were identified. Pathologic data was collected via chart review. Two senior radiologists performed blinded, independent review of all preoperative positron emission tomography with computed tomography (PET/CT) scans such that each patient scan underwent review by two separate senior radiologists. Primary tumor location, size, suspicious node location, size, presence of extracapsular extension (ECE) and morphology confidence were all documented. Staging was extrapolated from each radiologic analysis using AJCC8 pathologic staging criteria. Pathologic data was obtained via chart review and staging was extrapolated using AJCC8 pathologic staging criteria. Clinical T, N, M, and overall staging was compared with pathologic staging for each patient. Statistical analysis was conducted using modified McNemar's tests for symmetry between clinical and pathologic staging, and Cohen's kappa statistic to determine interrater reliability between radiologists.

RESULTS

Table 1 demonstrates the comparison between each independent clinical interpretation of PET/CT with final pathologic staging.

Variable	Radiologist	Misclassified	Under staged	Over staged	Test for symmetry
AJCC Stage	A	33 %	2 %	31 %	.0012
	B	39 %	0 %	39 %	< .0001
T Stage	A	36 % *	24 %	12 %	.3018
	B	45 % *	25 %	20 %	.8145
N Stage	A	36 % **	2 %	34%	.0002
	B	43 % **	0 %	43 %	< .0001
ECE	A	42 %	36 %	7 %	.0044
	B	34 %	23 %	11 %	.3018

Table 1: Clinical vs. Pathologic Staging
* excludes clinical T stage 0
** excludes pathologic N stage 0

Table 2 shows interrater reliability between radiologists with respect to T, N, overall staging, and presence of ECE.

		Radiologist B			Kappa	95% CI
T Stage	Radiologist A		Stage 0	Stage 1	Stage 2	.543	.343 - .743
		Stage 0	5	0	2		
		Stage 1	4	14	4		
		Stage 2	0	4	16		

		Radiologist B		Kappa	95% CI
N Stage	Radiologist A		Stage 1	Stage 2	.715	.524 - .907
		Stage 1	19	6		
		Stage 2	1	23		

		Radiologist B		Kappa	95% CI
AJCC Stage	Radiologist A		Stage 1	Stage 2	.715	.524 - .907
		Stage 1	19	6		
		Stage 2	1	23		

		Radiologist B		Kappa	95% CI
ECE	Radiologist A		No	Yes	.403	.139 - .667
		No	32	10		
		Yes	1	5		

Table 2: Radiology Interrater Reliability

DISCUSSION

AJCC 8 distinguishes between clinical and pathologic staging in HPV+ OPSCC. Our series examines the relationship between these two staging modalities in 49 patients with both preoperative PET/CT scans and surgical resection with TORS and neck dissection to elucidate both clinical and pathologic staging for each patient.

Application of pathologic staging criteria to radiographic findings was remarkably poor at predicting pathologic staging for both nodal (N) and overall staging (OS). Despite high interrater reliability between radiologists (κ= 0.715), PET/CT misclassified nodal disease between 36% and 43% of the time. The vast majority (94% - 100%) of misclassification of nodal disease resulted from radiologic overstaging. Comparison of clinical OS with pathologic OS demonstrated the same trend of high rate of misclassification (33% - 39%) and overstaging (94 – 100%) despite high interrater reliability between radiologists (κ= 0.715), Tumor staging (T) was also subject to high rate of misclassification (36% - 45%), but unlike N and OS, was more subject to understaging (69% - 70%) in our series.

Radiologic examination of extracapsular extension (ECE) in preoperative PET/CTs demonstrated poor accuracy in comparison to pathologic examination and poor interrater reliability between radiologists(κ= 0.403). PET/CT is not a reliable indicator of ECE in patients with HPV+ OPSCC.

CONCLUSIONS

- PET/CT predicts a higher nodal stage (and therefore overall stage) than eventual pathologic staging.
- Despite good interrater reliability, clinical N and OS staging poorly predicts pathologic N and OS staging in over one third of patients. In the patients who were misclassified, false-positive assessment of nodal disease was the most frequent error.
- PET/CT is a poor predictor of ECE.

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