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Discordance in routine second opinion pathology review of head and neck oncology specimens: A single-center five year retrospective review

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SUMMARY

Objectives: Second opinion review of pathology specimens is a common institutional practice, supported by large retrospective studies demonstrating significant histologic discordance. Since the most recent study of head and neck-specific pathology review was conducted, routine HPV and EBV testing is now recommended for certain specimens. We describe the frequency of and reasons for discordant reports and their potential impact on treatment recommendations and prognosis in a five-year retrospective cohort study at a single academic referral institution from 2005 to 2010.

Materials and methods: Following institutional review board review, 1003 cases referred to the Head and Neck Oncology Service were identified using a retrospective database search. Discordance between outside and second review pathology report was assessed by a board-certified medical oncologist.

Results: 667 cases were included, of which 22% were discordant. Discordance was associated with adenocarcinomas (AOR [adjusted odds ratio] 0.09, 95% CI 0.03–0.31; $p < 0.001$), poorly differentiated carcinomas (AOR 0.14, 95% CI 0.06–0.39; $p < 0.001$), and specimens of uncommon histology (AOR 0.18, 95% CI 0.07–0.45; $p < 0.001$) but not biopsy site in a multivariate model. The most common reasons for discordance included histology (61%), followed by the results of special studies (36%), and the presence or absence of stromal invasion (14%). Differences in tumor HPV status comprised 16% of discordant cases and were associated with better prognosis ($p < 0.001$) following second opinion review.

Conclusions: Routine second opinion pathology review may lead to clinically significant differences in treatment recommendations and prognosis.

Introduction

More than half a million cancers of the head and neck are diagnosed annually [1]. Treatment regimens for these neoplasms are increasingly refined and specific, and accurate histopathologic diagnosis is critical to initiation of optimal therapy. Consequently, many hospitals now require in-house second opinion review of pathology reports and specimens for new referral patients [2]. These recommendations are supported by large studies of mandatory review of head and neck pathology specimens [3–6], which demonstrate significant rates of discordance in histologic diagnosis leading to changes in disease prognosis and management. For instance, in a 10-year retrospective study of surgical pathology specimens submitted to a large academic referral center, Westra and colleagues describe conflicting histologic diagnoses in 7% of cases, 56% of which carried a worse prognosis [3]. These findings are echoed by similar studies of specimens from other organ systems [6–14].

However, recent research has identified other pathologic parameters of crucial importance to the clinical management of head and neck oncology patients. In head and neck squamous cell carcinomas, for instance, tumor human papillomavirus (HPV) status has emerged as a strong independent predictor of response to radiotherapy and improved survival [15–19]. Likewise, Epstein–Barr virus (EBV) positive nasopharyngeal carcinomas form a distinct subset of tumors with significantly improved prognosis [20,21]. Positive tumor HPV status, in particular, has the potential to alter the course of disease management from screening [22] to eligibility for trials of immunotherapeutics [23] or therapeutic de-intensification [24] to surveillance for relapse [25]. Despite these implications for patient care, as well as recommendations by the College of American Pathologists [26] and the American Joint Committee on Cancer [27], a sizable proportion of physicians managing head and neck cancer do not request testing for HPV [28,29].

Abbreviations: HPV, human papillomavirus; EBV, Epstein–Barr virus; PCR, polymerase chain reaction; AOR, adjusted odds ratio; NCCN, National Comprehensive Cancer Network.

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From the standpoint of the head and neck oncologist, therefore, in-house second opinion review of pathology specimens is important not only for establishing conventional tumor characteristics (histology, margins, and lymphovascular and perineural invasion, to name a few) but also for determining molecular parameters. To this end, we examined the frequency at which second opinion pathology slide review of patients referred for head and neck tumors were discordant in a retrospective cohort study design. We were additionally interested in characterizing second opinion reports yielding information that could potentially change prognosis or management recommendations. Finally, we investigated clinicopathologic factors associated with discordance and determined the proportion of discordant second opinion reports attributable to changes in HPV or EBV status.

Materials and methods

Following institutional review board approval, a retrospective search of the Stanford Cancer Center Research Database was conducted for all new patients referred to the Stanford Head and Neck Oncology service between 2005 and 2010 for which a pathology report from an outside institution was on file. Stanford's pathology department does not presently subscribe to an organ specific approach to assignment of individual pathologists for second opinion review. Therefore the distribution of these second opinion cases would have been made by random assignment within the pathology department. While in certain cases there may be substantial interaction between the Stanford pathologist and the Stanford clinicians or between the Stanford pathologist and external pathologist, these interactions are not routinely available in the medical record. Therefore we were not able to include these in our analysis. Stanford has no routine policy or algorithm for performing additional immunohistochemical stains or other molecular diagnostic tests on specimens submitted for review. Patient records were reviewed individually, and those with both an outside pathology report and a corresponding institutional specimen review were included in the study. If a given patient chart contained multiple outside pathology reports pertaining to a head and neck oncology referral, only the earliest report was included for analysis. The biopsy site (nasopharynx, oropharynx, oral cavity and lip, hypopharynx, larynx, paranasal sinuses, salivary glands, thyroid, or other), type of specimen (cytology or histology), the type of referring institution (academic or community), and specimen histology were recorded. Specimens were classified into broad histologic classes for analysis. For each report, we also coded whether the overall interpretation was consistent with a definitive malignant process and whether invasion (stromal, lymphovascular, or perineural) was present.

For each pair of pathology reports, discordance between institutional and outside reports was assessed by a board-certified medical oncologist. Discordance was defined as any difference in interpretation that may have implications on treatment options or outcome. Reports were also considered discordant if one included clinically-significant information that the other lacked, such as a definitive histological diagnosis. Possible reasons for discordance were identified *a priori* and included differences in histological diagnosis, the results of special studies (such as HPV for oropharyngeal or EBV for nasopharyngeal), presence of stromal invasion, presence of lymphovascular and/or perineural invasion, degree of differentiation, margin positivity, and whether a fine needle aspiration specimen was reported to have definitive or suspicious pathology. Some reports were discordant for more than one reason. For each reason for discordance, we recorded whether the pair of reports contained conflicting information or whether the second opinion report contained additional information.

Finally, we recorded whether the second opinion report contributed information that might alter prognosis and management recommendations. A board-certified medical oncologist reviewed outside and second opinion pathology reports while blinded to the remainder of the patient chart (including identifiers) and evaluated for differences in potentially clinically actionable information. Cases for which the change in prognosis could not be assessed, such as when one or more reports lacked sufficient information to establish a prognosis, were grouped under the "Other" heading when such data were reported (Tables 2–4).

Statistical analysis

Data collected were recorded in Excel (Microsoft) and analyzed in STATA 12 (StataCorp LP). For univariate analyses, chi-squared (if all cell counts > 5) and two-sided Fisher's exact tests (if at least one cell count was $\leqslant 5$) were used for categorical variables and two-sided *t*-tests assuming unequal variances were used for continuous variables. Since each pair of pathology reports could have one or many reason(s) for discordance, individual chi-squared or Fisher's exact tests were done for each reason for discordance in bivariate analyses. A multivariate logistic regression model was constructed to assess the relative effects of tumor histology and primary site on the likelihood of discordant reports.

Results

Out of 1003 cases identified using the database search, 667 (67%) were included in the final analysis (11 cases had primary

Table 1
Tumor and clinical characteristics.

Variable	All cases ($n = 667$)	Discordant cases ($n = 148$)	Concordant cases ($n = 519$)	*P*-value
Male sex, no. (%)	416 (62)	90 (61)	326 (63)	0.66[a]
Biopsy site, no. (%)				0.015[a]
Nasopharynx	63 (9)	22 (15)	41 (8)	
Oropharynx	171 (26)	40 (27)	131 (25)	
Hypopharynx	20 (3)	3 (2)	17 (3)	
Oral cavity and lip	193 (29)	29 (20)	164 (32)	
Larynx	43 (6)	11 (7)	32 (6)	
Paranasal sinuses	26 (4)	7 (5)	19 (4)	
Salivary glands	55 (8)	18 (12)	37 (7)	
Thyroid	88 (13)	18 (12)	70 (13)	
Other	8 (1)	0 (0)	8 (2)	
Specimen histology per institutional report, no. (%)				<0.001[b]
Squamous	433 (65)	74 (50)	359 (69)	
Thyroid	87 (13)	17 (11)	70 (13)	
Poorly differentiated carcinoma	38 (6)	21 (14)	17 (3)	
Lymphoma	18 (3)	5 (3)	13 (3)	
Adenoid cystic carcinoma	17 (3)	5 (3)	12 (2)	
Adenocarcinoma	15 (2)	9 (6)	6 (1)	
Mucoepidermoid carcinoma	14 (2)	2 (1)	12 (2)	
Melanoma	12 (2)	1 (1)	11 (2)	
Other	33 (5)	14 (9)	19 (4)	
Type of specimen, no. (%)				0.18[a]
Cytology	163 (24)	30 (20)	133 (26)	
Histology	504 (76)	118 (80)	386 (74)	
Referring institution, no. (%)				0.55[a]
Community	582 (87)	127 (86)	455 (88)	
Academic	85 (13)	21 (14)	64 (12)	

Column percentages shown.
[a] Chi-squared test.
[b] Fisher's exact test.