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Pre-treatment tumor-specific growth rate as a temporal biomarker that predicts treatment failure and improves risk stratification for oropharyngeal cancer

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SUMMARY

Purpose: To assess the relationship between tumor-specific growth rate (TSGR) and oropharyngeal cancer (OPC) outcomes in the HPV era.

Methods/materials: Primary tumor volume differences between a diagnostic and secondary scan separated $\geqslant$7 days without interval treatment were used to estimate TSGR, defined as percent volume growth/day derived from primary tumor volume doubling time for 85 OPC patients with known p16 status and smoking pack-years managed with (chemo)radiation. Variables were analyzed using Kruskal–Wallis or Fisher's exact test as appropriate. Log-rank tests and Cox proportional models analyzed endpoints. Using concordance probability estimates (CPE), TSGR was incorporated into RTOG 0129 risk grouping (0129RG) to assess whether TSGR could improve prognostic accuracy.

Results: Median time between scans was 35 days (range 8–314). Median follow up was 26 months (range 1–76). The 0129RG classification was: 56% low, 25% intermediate, and 19% high risk.

Median TSGR was 0.74%/day (range 0.01–4.25) and increased with 0129RG low (0.41%), intermediate (0.57%) and high (1.23%) risk, respectively ($p = 0.015$). TSGR independently predicted for TF (TSGR: HR (95%CI) = 2.79, 1.67–4.65, $p < 0.001$) in the Cox model.

On CPE, prognostic accuracy for TF, disease-free survival and overall survival was improved when 0129RG was combined with TSGR. Dichotomizing 0129RG by median TSGR yielded no observed recurrences in low risk patients with TSGR < 0.74% and demonstrated significant difference for intermediate risk (8% vs. 50% for TSGR < 0.74% vs. $\geqslant$0.74%, respectively, $p < 0.001$).

Conclusion: Tumor-specific growth rate correlates with increasing 0129RG and predicts treatment failure, potentially improving the prognostic strength and risk stratification of established 0129 risk groups.

Introduction

Solid tumor growth rate analyses are generally confined to the laboratory. Treatment delay in pursuit of growth rate estimation would engender risk and thus clinicians rarely observe this feature of tumor biology [1,2]. The practice of definitive head and neck treatment with radiation therapy (RT) offers a simple mechanism to observe growth rate; most patients undergo cross sectional imaging at the time of diagnosis and then have a similar scan performed for radiation treatment planning. In the United States the median time interval between the diagnosis of head and neck squamous cell carcinoma (HNSCC) and the initiation of RT is currently 34 days (and rising) [3], so usual care typically entails two cross sectional imaging scans of the tumor with a sufficiently long interval measure growth. Evaluating changes in primary tumor volume between the two studies estimates the rate of tumor progression.

The incidence of oropharynx cancer is increasing in the United States [4]. Sophisticated analyses posit that biomarkers (p16 expression) and lifetime cigarette exposure influence prognosis

Abbreviations: TSGR, tumor-specific growth rate; RT, radiation therapy; CRT, chemoradiation; HPV, human papillomavirus; CPE, concordance probability estimate.

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to an extent comparable with current staging systems [5,6]. These variables might be used to stratify patients before treatment. Low risk p16-positive tumors in patients with minimal smoking history could potentially be addressed with de-intensified treatment while p16-negative tumors are often refractory to best current therapy [7]. Although it is widely held that tumor growth rate influences prognosis and it is known that HPV-association affects the pace of progression in the recurrent/metastatic setting [8], tumor growth rate has never been evaluated as an adjunct to risk stratification models for HNSCC. We hypothesized that the primary tumor growth rate can be estimated by exploiting the time between a diagnostic and RT-planning scan, providing a simple and inexpensive maneuver to estimate prognosis that further informs pre-treatment risk stratification.

Methods

Patient eligibility

Patients with the following inclusion criteria were identified: squamous cell carcinoma from oropharyngeal primary tumor (OPC), known p16 status, known smoking status, treatment with primary RT or chemoradiation (CRT), and measurable primary tumor on an RT planning scan and on prior diagnostic imaging (with no interval therapy). Patients were excluded for the following criteria: tumors originating from another site in the upper aerodigestive tract, non-squamous histology, unknown p16 status, unknown smoking status, treatment with palliative intent, <7 days between interval scans, and treatment with primary surgery. All patients were staged according to American Joint Committee on Cancer (AJCC), 7th Edition. Positive p16 expression was defined as strong and diffuse nuclear and cytoplasmic immunohistochemical staining in 70% or more of tumor cells. Our institution began staining selected oropharyngeal primary tumors for p16 in 2007, initiating reflex testing in 2010.

Imaging, volume acquisition, and growth calculations

All patients had a diagnostic scan and an interval scan at least seven days apart. The radiation-planning CT scan had 2.5 mm slice thickness and was performed with IV contrast. All patients were immobilized with a thermoplastic mask for the planning scan. Diagnostic scan slice thickness varied from 1.25 mm to 5 mm. All scans were imported and contoured using *Velocity AI Version 3.1.0, Varian Medical Systems*. Primary tumor volumes were contoured using mediastinal window levels on axial slices for all patients on both the diagnostic scan (GTV_{dx}) and interval or planning scan (GTV_{plan}) and assimilated all clinical information available on imaging tests (CT, MRI or PET-CT) and the physical findings documented in the office examination, during diagnostic nasopharyngolaryngoscopy, or examination under anesthesia; contours were performed without knowledge of patient outcomes by radiation oncologists (C.M., L.W.) and reviewed and adjusted by a head and neck radiation oncology specialist (T.G.). When multiple interval scans were available, the earliest scan demonstrating measurable disease was used for volume calculations. Using tumor volumes at two distinct time points, a doubling time (DT) was calculated using the following equation:

$$DT = (T2 - T1) \times \frac{\ln 2}{\ln\left(\frac{GTV_{plan}}{GTV_{dx}}\right)}$$

where DT = tumor volume doubling time measured in days. GTV_{dx} is the gross tumor volume at time 1 ($T1$) (day on which the first scan demonstrated tumor) and GTV_{plan} is the gross tumor volume at time 2 ($T2$) on day of the planning or interval scan (Image 1). This study employed tumor specific growth rate (TSGR) for estimation of growth kinetics instead of DT due to inaccuracies with over- or underestimation of growth with short time intervals or high uncertainties in tumor volumes [9]. TSGR is the growth rate of the tumor per day, and uniformly estimates growth rates throughout all ranges. Thus, for growth assessment in this study, TSGR is defined as:

$$TSGR = \frac{\ln 2}{DT}$$

Multiplying TSGR by 100% gives the percentage tumor volume increase per day. Lymph node volumes were not contoured due to concerns that interval volume changes due to hemorrhage and necrotic debris within a cystic lymph node may inaccurately estimate growth rates when compared to growth of a solid lymph node; a larger node volume may thus not represent viable tumor [10,11]. Other factors with potential to frustrate growth calculations that could not be controlled in this analysis include: variable slice thickness and use of MRI vs. CT on diagnostic imaging, window leveling, and patient positioning differences with and without thermoplastic masks.

Statistical methods

Continuous variables were analyzed using the Mann–Whitney test or the Kruskal–Wallis test, as appropriate, and categorical variables were analyzed using the Fisher's exact test. Univariate log-rank tests and Cox proportional hazards models were used to analyze: freedom from treatment failure (FFTF), disease-free survival (DFS) and overall survival (OS). The 2-year and 3-year survival probabilities were computed for each endpoint using Kaplan–Meier methods, calculated from the date of completion of radiation therapy or planned post-radiation neck dissection and all patients were censored at the time of event. Covariates included in adjustment were: age, smoking pack years, p16 status, T-stage, N-stage, primary tumor volume and TSGR. Concordance probability estimates (CPE) were computed for each endpoint using RTOG 0129 risk group [5] and TSGR as predictors to generate C-indices. The C-index is the probability that, given two randomly drawn patients, a patient with an event will have a higher probability of the event predicted. The C-index ranges in value from 0 to 1, with 0.5 indicating complete lack of discrimination (random chance) and 1 indicating perfect ability to predict the time to event. The C-index is analogous to the area under the receiver operating curve. All tests were two-sided and used a Type I Error of 5% to determine statistical significance. The R statistical language and environment was used in the computations. TSGR was also evaluated as an endpoint to identify risk factors associated with TSGR, including p16 status, smoking status, T- and N-stage, tumor volume and RTOG 0129 risk group (0129RG).

All recurrences were biopsy proven. Local failure was defined as cancer recurrence within the pharynx, in or adjacent to the treatment volume. Regional failure was defined as recurrence within a draining lymph node basin within the cervical or supraclavicular basins, and distant recurrence was defined as recurrence outside of the head and neck (below the clavicles). Treatment failure was defined as any disease recurrence. Previously annotated patient demographics, tumor characteristics, and treatment-related information were entered into a database. The collection, storage, and retrieval of data were all done in compliance with the hospital's Institutional Review Board and the Health Insurance Privacy and Portability Act.

Results

Baseline patient characteristics

Eighty-five patients met eligibility requirements (Table 1). Median follow up was 26.5 months (range 0.5–76). Primary tumor sites