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Prospective Imaging Biomarker Assessment of Mortality Risk in Patients Treated with Head and Neck Radiotherapy

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Abstract

Purpose—The optimal roles for imaging-based biomarkers in the management of head and neck cancer remain undefined. Unresolved questions include whether functional or anatomic imaging biomarkers might improve mortality risk assessment for this disease. We addressed these issues in a prospective institutional trial.

Methods and Materials—Ninety-eight patients with locally advanced pharyngolaryngeal squamous cell cancer were enrolled. Each underwent pre-and post-chemoradiotherapy contrast-enhanced CT and FDG-PET/CT imaging. Imaging parameters were correlated with survival outcomes.

Results—Low post-radiation primary tumor FDG avidity correlated with improved survival on multivariate analysis; so too did complete primary tumor response by CT alone. Although both imaging modalities lacked sensitivity, each had high specificity and negative predictive value for disease-specific mortality risk assessment. Kaplan-Meier estimates confirmed that both CT and

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CONFLICTS OF INTEREST NOTIFICATION

None exist.

FDG-PET/CT stratify patients into distinct high- and low-probability survivorship groups on the basis of primary tumor response to radiotherapy. Subset analyses demonstrated that the prognostic value for each biomarker was primarily derived from patients at high risk for local treatment failure (HPV-negative disease, non-oro-pharyngeal primary disease, or tobacco use).

Conclusions—CT- and FDG-PET/CT-based biomarkers are useful clinical tools in head and neck cancer-specific mortality risk assessment following radiotherapy, particularly for high-risk HPV-unrelated disease. Focus should be placed on further refinement and corroboration of imaging-based biomarkers in future studies.

Keywords

Radiotherapy; head and neck cancer; PET; CT; survival

INTRODUCTION

Long-term survival rates of approximately 50 percent on recent phase III trials for squamous cell carcinomas of the head and neck (HNSCC) highlight the continued need to reduce mortality from this disease^{1–3}. Multiple retrospective series suggest that the metabolic response of HNSCC to chemoradiotherapy correlates directly with overall survival, raising the possibility that outcomes might be improved by using FDG-PET to triage non-responding patients to further therapy^{4–6}. However, these data are limited by the biases inherent in conducting retrospective studies. They have also largely ignored the important issues of comparing the utility of PET to more affordable imaging alternatives, such as CT imaging alone. As a result, the appropriate role of imaging in predicting survival outcomes for HNSCC patients remains undefined.

We previously reported the results of a prospective clinical trial comparing radiation response assessment with FDG-PET/CT and contrast-enhanced CT, demonstrating equivalent accuracies for the general population and superiority of FDG-PET/CT for a subset of patients at high risk for local treatment failure⁷. We now present a formal survival outcome analysis from this trial to address the potential roles of FDG-PET/CT- and CT-based biomarkers in mortality risk assessment for head and neck cancer.

METHODS AND MATERIALS

Patients

Between 2005 and 2007, 107 consecutive locally advanced HNSCC patients dispositioned to receive definitive (chemo)-radiotherapy were screened for enrollment onto a prospective IRB-approved trial. Screened patients were eligible for enrollment if they were 18 years of age and had biopsy-proven American Joint Commission on Cancer (AJCC) version 6 stage II–IVb squamous cell carcinoma of the pharyngolaryngeal axis. Nine patients were ineligible for inclusion; two withdrew consent, five underwent surgical resection, and two had FDG-PET/CT scans performed outside the window of timing stipulated by protocol. This left an enrolled study cohort of 98 patients.

Radiotherapy and Systemic Treatment

Patients were treated with intensity modulated radiotherapy (IMRT) as previously described^{8, 9}. Doses ranged from 66 to 70 Gy in 30 to 35 fractions. IMRT was delivered via step-and-shoot multi-leaf collimation through a static gantry. Treatment planning was performed using a Pinnacle³ system (version 6.2b or later, Philips Medical Systems, Andover, MA). Most patients received concurrent systemic therapy (Table 1).

FDG-PET/CT Imaging

Each patient underwent two FDG-PET/CT scans: the first within 4 weeks prior to starting therapy, and the second as near as possible to the 8th week following the end of treatment. FDG-PET/CT images were acquired with an integrated PET/CT device (Discovery ST-8; GE Medical Systems, Milwaukee, Wisconsin), as previously described ⁷.

The intensity of metabolic activity within foci of increased FDG uptake in disease sites was analyzed on the FDG-PET images using a semiautomated vendor-provided tool (GE Advantage workstation). The maximum standard uptake value (SUV_{max}) within the volume of interest was calculated as previously described (7). A single observer (VR) calculated SUV_{max} for all regions of gross disease on each study performed on this protocol. For patients with multiple sites of lymphadenopathy, nodal SUV_{max} was calculated on each FDG-PET/CT scan for the node with the highest initial SUV_{max}. FDG-PET/CT scans were interpreted with knowledge of contrast enhanced CT scans.

CT Imaging

Two contrast-enhanced CT scans were scheduled for each patient: the first within 4 weeks prior to starting therapy, and the second as near as possible to the 8th week following completion of treatment. LightSpeed (General Electric) scanners were used for all studies. An average of 120 mL of contrast was injected intravenously, at 3 mL/second, 90 seconds prior to scanning. Scans were typically acquired using a 220 mA current, 140 kVp voltage, 1 second revolution time, and a pitch of 1:1. Images were reconstructed with 1.25mm thickness. All images were reviewed on a General Electric workstation and interpreted by a board-certified neuroradiologist (LG).

Post-Treatment Surveillance and Surgical Management

Patients returned for routine surveillance 8 weeks following treatment, then every 3–4 months for clinical examination and serial contrast-enhanced CT imaging; chest X-rays were performed annually. Consolidative neck dissections were performed at the discretion of the treating physicians.

Human Papillomavirus (HPV) Detection

When archived tissue was available, in-situ hybridization (ISH), and immunohistochemistry (IHC) were run on paraffin-embedded tumor samples to detect HPV. A high-risk ISH cocktail (INFORM HPV III Family 16 Probe [B], Ventana) was used according to the manufacturer's instructions. p16 IHC (clone 16P07, Labvision) was also performed according to the manufacturer's instructions. Samples were regarded as positive if p16-immunoreactive and HPV was detected by ISH.

Data Analysis

Disease-specific and overall survival, measured from the date of treatment completion, was estimated by the Kaplan-Meier method (SPSSv16). Student's t-Tests were used to evaluate correlations between FDG-PET/CT parameters and survival, with correction for multiple comparisons (Microsoft Excel). Univariate regression analysis was used to evaluate covariates for correlation with survival; those showing significant correlation were then subjected to multivariate regression analysis (SPSSv16). A threshold level of 10 pack-years of use was chosen to distinguish tobacco users from non-users, as this level of exposure is correlated with increased risk of developing HNSCC ¹⁰. Receiver operating characteristic (ROC) curves were plotted from the post-radiation primary and nodal FDG-PET/CT data. To find SUV_{max} thresholds with maximal accuracy in predicting survival, the curves were fit to polynomial equations which were then solved for a slope of 1 (Microsoft Excel).

Threshold values were then applied to the post-radiation FDG-PET/CT data to calculate the accuracy of predicting survival. Unless otherwise stated, significance was defined as a *P* value of 0.05, throughout.

RESULTS

Patient Characteristics

Demographic and clinical characteristics of study patients are detailed in Table 1. Most were Caucasian men with stage IV oropharyngeal cancers treated over 6 weeks to 70 Gy with concurrent weekly cisplatin. The median follow-up for all patients at the time of this analysis was 2 years (range 1.2–2.5). Estimated two-year overall and disease-specific survival rates were nearly identical at 85.7% and 86.7%, respectively (Figure 1).

Correlating SUVmax with Survival

Since overall and disease-specific survival correlated well in this cohort, we focused the remainder of our analysis on disease-specific survival (DSS) for simplicity. We first examined whether pre- or post-radiation tumor FDG-avidity correlated with DSS (Table 2). The only parameters correlating significantly with DSS were primary tumor post-radiation SUVmax and the percent change in primary tumor SUVmax between the pre- and post-radiation scans. Nodal tumor SUVmax parameters showed no correlation with DSS, nor did baseline SUVmax for either primary or nodal tumors.

Regression analyses were then performed to better understand how metabolic response to therapy of the tumor correlates with DSS in the context of other important covariates, including anatomic radiographic response (Table 3). Analyzed as a continuous variable, low post-radiation primary tumor SUVmax predicted for improved DSS on univariate analysis, as did complete radiographic response by CT at the primary site, Caucasian race, and negative tobacco use. On multivariate analysis, metabolic and anatomic primary tumor response both retained significance in predicting improved DSS, as did negative tobacco use.

Accuracy of Post-Treatment SUVmax in Predicting Survival

Since absolute post-radiation SUVmax showed the best correlation with survival of all FDG-PET metrics analyzed, we focused the remainder of our analyses on this parameter. ROC curves were generated from the post-radiation data in order to compare the accuracies of CT and FDG-PET/CT in predicting DSS. Applied to the entire cohort, both of these imaging biomarkers were inaccurate, with ROC curves approaching unity (Figure 2A). We then censored those patients developing distant metastases (DM) as a first site of failure within 6 months of completing therapy (*n* = 6), reasoning that locoregional tumor control was unlikely to influence DSS in these patients. Applied to the remainder (*n* = 92), both imaging biomarkers showed modestly improved accuracy (Figure 2B).

The ROC curves generated from the entire data set (*n* = 98) were then used to define threshold post-radiation tumor SUVmax values with optimal accuracy for predicting DSS. These values were calculated to be 6.0 and 3.4 for primary and nodal tumors, respectively. Using these threshold values, the sensitivity, specificity, positive predictive value, and negative predictive value were determined for post-radiation SUVmax as a biomarker of DSS. For comparison, these parameters were also determined for the CT data set. Overall, both sets of biomarkers demonstrated similar accuracies in predicting DSS (Table 4). Sensitivity and positive predictive values were low for each; specificity and negative predictive values were comparatively high.

Imaging Biomarkers for Mortality Risk Assessment

SUVmax thresholds and radiographic CR were then applied as imaging biomarkers for discriminating DSS in the entire cohort. Kaplan Meier curves were generated for good- and poor-prognosis groups (determined by each imaging biomarker), and compared by log rank analysis (Figure 3). Primary tumor imaging response – metabolic and anatomic – stratified patients into groups differing significantly in the likelihood of DSS ($P < 0.005$ for each). Neither imaging biomarker discriminated the cohort into useful survivorship groups on the basis of nodal disease ($P = \text{NS}$ for each). Repeating these analyses for the group censored for early distant failures produced qualitatively and quantitatively similar results (data not shown).

Finally, we applied our previously-reported locoregional failure risk stratification schema to determine whether this risk grouping influenced DSS. High-risk patients ($n = 32$) were those with human papilloma virus (HPV)-negative disease, tobacco use (any type), or non- oropharyngeal primary tumors; low-risk patients ($n = 66$) were those with HPV-positive disease or those with oropharyngeal primary tumors *and* no tobacco use⁷. Indeed, these risk groups differed significantly in DSS (Figure 4A). Sub-stratifying low-risk patients by imaging biomarkers provided no additional prognostic information (not shown). For high-risk patients, however, sub-stratification by either CT or FDG-PET/CT-based biomarkers provided significant additional prognostic information (Figure 4B–C). Based on this finding, we propose a straightforward clinicoradiographic DSS risk stratification algorithm for future corroborative clinical testing (Figure 5).

DISCUSSION

There are currently few clinical tools available to assess mortality risk for advanced HNSCC. Recursive partitioning analysis has been used to create reliable survivorship groupings on the basis of readily accessible clinical criteria (stage, age, performance status, and primary tumor site), but considerable overlap in outcome between groups suggests there is room for further refinement of prognostic capacity^{11–13}. Lifetime non-smokers may enjoy improved survival outcomes following head and neck cancer treatment relative to prior smokers^{14, 15}, but these results await further validation. Since prognostic factors such as these are currently used by cooperative groups to risk-stratify patients enrolled onto randomized trials, their accuracy is critical to the ultimate utility of these phase III studies.

Several histologic biomarkers have prognostic value beyond the standard clinical risk factors for HNSCC^{16–19}, but few of these have been prospectively evaluated and none has yet been widely adopted in routine clinical practice. Owing to the excellent prognosis for HPV-associated HNSCC^{20, 21}, HPV-specific biomarkers appear to provide significant prognostic value by allowing accurate dichotomization of cohorts by viral status^{15, 22, 23}. However, these markers are not useful to sub-stratify risk for patients with HPV-unrelated disease; for these patients, further efforts will be necessary to improve biomarker-based mortality risk assessment.

Imaging-based biomarkers offer the potential for providing complementary or alternative value for prognostic risk assessment. Validated imaging biomarkers would have the theoretical advantage of being non-invasive, amenable to serial collection, unsusceptible to tissue sampling issues, and widely available to clinicians.¹⁸F-FDG-PET/CT has been the most studied imaging modality to date for this purpose in HNSCC. Previous retrospective series suggest that highly elevated baseline HNSCC primary tumor FDG SUV predicts for worse prognosis^{24–28}. Our prospective results call this conclusion into question. A separate group of retrospective studies suggest that high post-radiation primary tumor FDG avidity is predictive of poor overall survival^{4–6}. Our prospective data confirm this finding for primary

tumors, but supports no such correlation for nodal disease. The lack of correlation with nodal response to radiotherapy suggests that consolidative neck dissection adequately salvage residual regional disease without a sacrifice in ultimate survival probability. The same does not appear to be true of surgical salvage of primary tumor failures, emphasizing the need for adequate up-front local therapy of primary disease.

A novel aspect of our study was the evaluation of imaging biomarker mortality risk assessment in the context of competing clinical risk factors. It is interesting to note that even after stratifying patients by risk group on the basis of tumor HPV status, primary site, and tobacco use – factors which achieved stratification with an absolute difference in DSS of over 25% – post-radiation primary tumor imaging response still added significant prognostic value for high-risk patients (Figure 4). The ultimate difference in survival probability for low-risk patients compared to high-risk patients with unfavorable post-radiation imaging was striking (absolute difference ~60%), warranting further study for inclusion in routine clinical risk assessment (Figure 5).

We were also able to prospectively compare the prognostic value of FDG-PET/CT and CT alone. Their equivalent performance and disparate cost provides a compelling financial argument against the use of FDG-PET/CT for this indication. The value of CT alone for head and neck cancer management has been well demonstrated and argued for previously^{29, 30}. Regardless, our previously-reported data support the use of FDG-PET/CT in patients at high risk for locoregional failure (HPV-negative disease, tobacco use, non-oro-pharyngeal primary tumors) for the purpose of radiotherapy response assessment⁷. Since FDG-PET/CT was equivalent to CT alone for mortality risk assessment, a more compelling argument for serial FDG-PET/CT imaging of high-risk patients could be made on the basis of improved locoregional control assessment.

Whether technical improvements advances will tangibly improve imaging biomarker risk assessment of HNSCC radiotherapy outcomes remains unsettled. Both of the imaging modalities we studied predicted disease-specific mortality with limited sensitivity. This finding reflects the fact that approximately half of all cancer-related deaths on this study occurred in patients who died of distant metastases despite locoregional disease control. Currently, there are no data available to estimate the specific risk of distant metastatic failure based on locoregional imaging findings for HNSCC. Imaging biomarkers do an adequate job of predicting mortality in patients without distant metastases – i.e. those who die from locoregional disease progression – but this, of course, does not address the total patient population.

It is important to note that although our imaging and treatment outcomes data were collected prospectively, this series remains limited in size and enjoys its most direct relevance to high-volume referral centers. It is possible that the relative benefit of FDG-PET/CT and CT survival outcome assessment varies according to the level of neuroradiology and radiotherapy expertise found across different facilities. The recently closed Radiation Therapy Oncology Group (RTOG) 0522 phase III trial included a formal study of FDG-PET/CT which closely mirrored our series design, and holds promise as a corroborative experience in the multi-institutional setting.

In summary, our findings support the selective use of imaging biomarkers in mortality risk assessment for HNSCC, although these conclusions will require independent corroboration. The ability to discriminate high-risk patients into groups differing in disease-specific survival by three-fold, if confirmed, could have a major impact on risk-stratification for this diagnosis.

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Figure 1. Survival Characteristics

Kaplan-Meier plots for overall (grey) and disease-specific (black) survival are shown for the entire patient cohort. Ticks mark censored events.

Figure 2. Accuracy of Imaging Response as a Predictor of Disease-Specific Survival

ROC curves are shown for the accuracy of FDG-PET/CT imaging (lines) and CT imaging (symbols) in predicting disease-specific survival in (A) the entire cohort ($n = 98$) and in (B) the subset censored for DM as first site of failure ($n = 92$). The line of unity is displayed for comparison.

Figure 3. Imaging Biomarkers of Disease-Specific Survival

Kaplan-Meier curves for the entire cohort subdivided by post-radiation SUVmax threshold values for primary tumors (A) and nodes (C), and by radiographic CT response for primary tumors (B) and nodes (D). FDG-PET/CT and CT both discriminate survivorship groups by primary tumor biomarker (log rank, $P < 0.005$), but not by nodal tumor biomarker (log rank, $P = \text{NS}$).

Figure 4. Locoregional Failure Risk Grouping and Survival

Kaplan-Meier curves are shown for the entire cohort (A) stratified by locoregional radiotherapy failure risk grouping (high-risk [$n = 32$]: human papilloma virus (HPV)-negative disease, tobacco use, or non-oro-pharyngeal primary disease; low-risk [$n = 66$]: HPV-positive disease or those with oro-pharyngeal primary tumors *and* no tobacco use). The high-risk group was then sub-stratified by primary tumor imaging biomarker risk status – FDG-PET/CT-based (B) or CT-based (C). P values are derived from log-rank analyses.

Figure 5. Proposed Clinicoradiographic Risk-Stratification Algorithm

Clinical low-risk status (HPV-positive disease or those with oropharyngeal primary tumors *and* no tobacco use) predicts for excellent survival regardless of imaging findings. Post-radiotherapy imaging of primary disease treatment response improves stratification of mortality risk in patients with a high-risk clinical profile (HPV-negative disease, tobacco use, or non-oropharyngeal primary disease).

Table 1**Patient Characteristics**

Baseline data are shown for all study patients. Mean values are shown, with range or percentage of total in parenthesis.

Characteristic		
Age		58 (36–79)
Sex	Male	83 (85)
	Female	15 (15)
Race	White	82 (84)
	Black	7 (7)
	Hispanic	7 (7)
	Other	2 (2)
Tobacco Use	Non-User	49 (50)
	User	49 (50)
Overall Stage	I	0 (0)
	II	3 (4)
	III	22 (22)
	IV	73 (74)
T Stage		x
		4 (4)
0		0 (0)
1		8 (8)
2		27 (28)
3		37 (38)
4		22 (22)
N Stage		x
		2 (2)
0		16 (16)
1		13 (13)
2a		4 (4)
2b		39 (40)
2c		22 (22)

Characteristic		
	3	2 (2)
Site	Oropharynx	77 (79)
	Larynx	12 (12)
	Hypopharynx	9 (9)
Radiation	Dose	70 (66–72)
	Duration	44 (30–57)
Chemotherapy	Platinum	65 (66)
	None	21 (21)
	Cetuximab	11 (11)
	Taxane	1 (1)

Table 2
SUVmax and Disease-Specific Survival

Shown are mean SUVmax values as well as relative and absolute change in SUVmax from pre- to post-radiation imaging. Parameters significantly different between survivors and non-survivors are bolded.

	Parameter	Survivors	Non-Survivors	P Value
Primary	Pre-RT	19.6	18.0	0.51
	Post-RT	4.2	7.2	< 0.01
	% Chng	74	58	0.01
	Abs Chng	15.3	10.8	0.07
Nodal	Pre-RT	12.7	14.6	0.38
	Post-RT	2.4	3.1	0.06
	% Chng	72	74	0.81
	Abs Chng	10.2	11.4	0.58

Table 3**Covariate Analysis**

Shown are *P* values for correlations between disease-specific survival and covariates by univariate (UVA) and multivariate (MVA) analyses. *P* values for significant covariates are bolded.

	UVA	MVA
Age	0.84	--
Gender	0.99	--
Race	0.02	0.14
Tobacco Use	0.01	0.02
RT Dose	0.85	--
Primary Site	0.33	--
T stage	0.07	--
N stage	0.23	--
Primary post-RT SUVmax	< 0.01	< 0.01
Nodal post-RT SUVmax	0.06	--
Primary rCR	< 0.01	< 0.01
Nodal rCR	0.78	--

Table 4
Disease-Specific Survival Imaging Biomarker Accuracy

Comparatively similar accuracies are seen with both CT and FDG-PET/CT-based biomarkers.

	Primary		Node	
	FDG-PET/CT	CT	FDG-PET/CT	CT
Sensitivity	50	50	25	33
Specificity	85	88	50	62
Positive Predictive Value	50	38	6	13
Negative Predictive Value	92	93	85	84