Metabolic Tumor Volume as a Predictive Imaging Biomarker in Head and Neck Cancer – Pilot Results from RTOG 0522

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ABSTRACT

Purpose: To evaluate predictive capability of FDG-PET/CT for head and neck chemoradiotherapy outcomes in the cooperative group trial setting.

Methods: RTOG 0522 randomized patients with locally advanced head and neck cancer to either radiation with concurrent cisplatin (arm A) or radiation with concurrent cisplatin and cetuximab (Arm B) between 11/2005 to 3/2009. Patients consenting to a secondary FDG-PET/CT sub-study were serially imaged at baseline and 8 weeks following radiation. Maximum standardized uptake value (SUVmax), SUV peak (mean SUV within a 1 cm sphere centered on SUVmax), and metabolic tumor volume (MTV) using 40% of SUVmax as threshold were obtained from primary tumor and involved nodes. Treatment outcomes were correlated with these measures as continuous values or by using median as dichotomy.

Results: Out of 940 patients entered onto RTOG 0522, 74 enrolled onto this FDG-PET sub-study. Primary sites included oropharynx (78%), larynx (12%) and hypopharynx (9%). T stage distribution was T2 (39%), T3 (35%), and T4 (26%). N stage distribution was N2A (7%), N2B (46%), N2C (39%), and N3 (8%). Fifty-seven percent were treated in Arm A and 43% in Arm B. Baseline SUVmax or SUVpeak from either primary or nodal disease was not predictive for treatment outcomes. Primary tumor MTV as a continuous variable was associated with local-regional control (LRC, hazard ratio [HR] 1.046, p < 0.01), distant metastasis (HR 1.044, p = 0.02), and progression-free survival (PFS, HR 1.045, p < 0.01). Patients presenting with primary tumor MTV above the cohort median suffered significantly worse LRC (HR 4.01, p = 0.02) and PFS (HR 2.34, p = 0.05). Although MTV and T stage appeared to correlate (mean MTV 6.4, 13.2, 26.8 for T2, T3, and T4 tumors, respectively), MTV remained a strong independent predictor for PFS in multivariate analysis that included T stage.

Conclusion: High baseline primary tumor MTV was associated with poor treatment outcomes in this limited patient subset of RTOG 0522. Additional confirmatory work will be required to validate primary tumor MTV as a predictive imaging biomarker for patient stratification in future trials.

BACKGROUND

- Effective patient selection drives successful clinical cancer trial design. Tissue-based biomarkers have been used towards this end, but tumor collection is expensive and burdensome. Imaging provides an alternative means to define disease phenotype and treatment outcomes.
- Some series suggest FDG-PET measures, such as maximum or peak standardized uptake values (SUV), can serve as imaging biomarkers for radiotherapy outcomes. However, other reports refute the predictive value of SUV, and quantitative head and neck FDG-PET outcome measures remain untested in the cooperative group setting.
- RTOG 0522 subjects were eligible for baseline and post-treatment PET/CT imaging analysis. We evaluated SUV measurements and metabolic tumor volume (MTV) [1-3] as candidate biomarkers for treatment outcomes.

OBJECTIVES

- Correlation of pre- and post-treatment PET/CT scan findings with progression-free survival, overall survival, and local-regional control in patients participating in this sub-study of the trial.

PROTOCOL TREATMENT

STRATIFY

Primary Site
1. Larynx
2. Non-Larynx

Nodal Status
1. N0
2. N1, N2a, N2b
3. N2c, N3

Zubrod Status
1. 0
2. 1

Use of IMRT
1. No
2. Yes

Pre-Treatment PET/CT
1. No
2. Yes

RANDOMIZE

Arm 1
Accelerated Fractionation by Concomitant Boost (AFX-CB) or IMRT plus cisplatin

Arm 2
Accelerated Fractionation by Concomitant Boost (AFX-CB) or IMRT plus cisplatin plus cetuximab

8-9 Weeks Post-Treatment Reassessment
Required CT scan or MRI for N2-N3 and N1-N2c patients. These patients could also receive post-treatment PET/CT scan

METHODS

- Patients enrolled to RTOG 0522 with nodal disease ≥ 3cm (N2-3) were eligible to participate in this optional PET/CT study.
- Patients who agreed to participate in the PET/CT study and for whom at least one PET image set was available for central review were included in this analysis.
- All centers participating in this imaging study had to provide one test case to the ACRIN PET Core Lab to credential their file transfer capabilities and image quality.
- SUV normalized by specific injected dose and patient weight was calculated on centralized review by two clinically specialized head and neck radiation oncologists (DLS and MY) employing commercial image analysis software (MIM Software, v.5.2, Cleveland, OH).
- Detection of primary and nodal disease by FDG-PET/CT was determined qualitatively as FDG uptake greater than surrounding normal soft tissue within a CT-delineated anatomic (primary disease or nodal) abnormality.
- SUVpeak for primary and nodal disease was automatically defined with a 10-mm diameter circular (2-dimensional) region of interest (ROIpeak) centered on SUVmax. Primary and nodal MTV was defined as tumor volume above 40% of SUVmax.

RESULTS

Table I. Patient Characteristics

	Included in PET/CT study (n=74)	Eligible for PET/CT study but excluded (n=577)
Assigned treatment, p=0.26 [1]		
RT + cisplatin	42 (56.8%)	287 (49.7%)
RT + cisplatin + cetuximab	32 (43.2%)	290 (50.3%)
Age (years), p=1.00 [2]		
Mean	56.8	56.7
Std. Dev.	6.67	8.22
Median	56	57
Min - Max	42 - 73	34 - 79
Q1 - Q3	53 - 61	51 - 62
Gender, p=0.68 [1]		
Male	65 (87.8%)	516 (89.4%)
Female	9 (12.2%)	61 (10.6%)
Zubrod performance status, p=0.03 [1]		
0	58 (78.4%)	380 (65.9%)
1	16 (21.6%)	197 (34.1%)
Smoking history: pack-years, p=0.03 [2]	(n=54)	(n=512)
Mean	38.8	36.1
Std. Dev.	29.88	26.96
Median	35	35
Min - Max	0 - 135	0 - 162
Q1 - Q3	0 - 50	0 - 40
Primary site, p=0.72 [1]		
Oropharynx	58 (78.4%)	449 (77.8%)
Hypopharynx	7 (9.5%)	43 (7.5%)
Larynx	9 (12.2%)	85 (14.7%)
p16 status, oropharynx only, p=0.90 [1]	(n=33)	(n=229)
Negative	8 (24.2%)	55 (24.0%)
Positive	25 (75.8%)	174 (76.0%)
T stage, p=0.04 [2]		
T2	29 (39.2%)	303 (52.5%)
T3	26 (35.1%)	157 (27.2%)
T4	19 (25.7%)	117 (20.3%)
N stage, p=0.23 [2]		
N2a	5 (6.8%)	73 (12.7%)
N2b	34 (45.9%)	259 (44.9%)
N2c	29 (39.2%)	207 (35.9%)
N3	6 (8.1%)	38 (6.6%)

Std. Dev. = standard deviation; Q1 = first quartile; Q3 = third quartile.
[1] Pearson chi-square test.
[2] Wilcoxon rank-sum test.

Table II. SUV and Outcomes

Variable	Endpoint	Events/total	Hazard ratio (95% CI)	p-value
Primary SUVmax (> vs. ≤ median)	Local relapse	0/34 vs. 8/34	Cannot estimate	
	Local-regional relapse	4/34 vs. 12/34	0.31 (0.10, 0.97)	0.04
	Distant metastasis	2/34 vs. 6/34	0.32 (0.06, 1.57)	0.16
	Progression-free survival	6/34 vs. 18/34	0.30 (0.12, 0.75)	0.01
	Overall survival	4/34 vs. 11/34	0.38 (0.12, 1.20)	0.10
Nodal SUVmax (> vs. ≤ median)	Regional relapse	6/32 vs. 7/33	0.89 (0.30, 2.66)	0.84
	Local-regional relapse	6/32 vs. 9/33	0.72 (0.26, 2.05)	0.54
	Distant metastasis	2/32 vs. 5/33	0.40 (0.08, 2.05)	0.27
	Progression-free survival	8/32 vs. 15/33	0.56 (0.24, 1.33)	0.19
	Overall survival	4/32 vs. 10/33	0.44 (0.14, 1.39)	0.16
Primary SUVpeak (> vs. ≤ median)	Local relapse	1/34 vs. 7/34	0.15 (0.02, 1.23)	0.08
	Local-regional relapse	6/34 vs. 10/34	0.60 (0.22, 1.65)	0.32
	Distant metastasis	3/34 vs. 5/34	0.62 (0.15, 2.62)	0.52
	Progression-free survival	9/34 vs. 15/34	0.62 (0.27, 1.42)	0.25
	Overall survival	5/34 vs. 10/34	0.55 (0.19, 1.62)	0.28
Nodal SUVpeak (> vs. ≤ median)	Regional relapse	6/32 vs. 7/33	0.93 (0.31, 2.77)	0.90
	Local-regional relapse	6/32 vs. 9/33	0.75 (0.27, 2.13)	0.59
	Distant metastasis	3/32 vs. 4/33	0.81 (0.18, 3.63)	0.79
	Progression-free survival	9/32 vs. 14/33	0.74 (0.32, 1.72)	0.49
	Overall survival	5/32 vs. 9/33	0.61 (0.20, 1.82)	0.37

CI = confidence interval.
Hazard ratios estimated from Cox models.

Table III. Baseline Primary MTV and Treatment Outcomes

Variable	Endpoint	Events/total	Hazard ratio (95% CI)	p-value
Primary MTV (continuous)	Local relapse	8/68	1.05 (0.99, 1.09)	0.06
	Local-regional relapse	16/68	1.05 (1.02, 1.08)	<.01
	Distant metastasis	8/68	1.04 (1.01, 1.08)	0.02
	Progression-free survival	24/68	1.05 (1.02, 1.07)	<.01
	Overall survival	15/68	1.03 (0.99, 1.06)	0.08
Primary MTV (> vs. </= median)	Local relapse	5/33 vs. 3/35	1.96 (0.47, 8.23)	0.36
	Local-regional relapse	12/33 vs. 4/35	4.01 (1.28, 12.52)	0.02
	Distant metastasis	6/33 vs. 2/35	3.62 (0.73, 18.04)	0.12
	Progression-free survival	15/33 vs. 9/35	2.34 (1.02, 5.37)	0.05
	Overall survival	8/33 vs. 7/35	1.40 (0.51, 3.86)	0.52

CI = confidence interval.
Hazard ratios estimated from Cox models.

Figure I. Baseline Primary MTV and Local-Regional Relapse

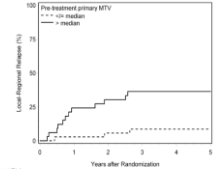

Figure II. Baseline Primary MTV and Progression-Free Survival

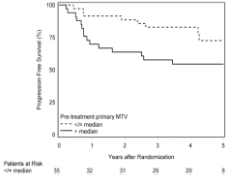

Table IVa. Local-Regional Relapse: Primary MTV vs. T Stage

Model	AIC [1]	Covariate(s)	Hazard ratio (95% CI)	p-value
1	120.28	Primary MTV (> vs. </= median)	4.01 (1.28, 12.52)	0.02
2	124.63	T stage (T4 vs. T2-3)	2.34 (0.83, 6.59)	0.11
3	121.98	Primary MTV (> vs. </= median) T stage (T4 vs. T2-3)	3.59 (1.07, 12.11) 1.36 (0.45, 4.11)	0.04 0.58

CI = confidence interval.
Hazard ratios estimated from Cox models.
[1] Akaike information criterion.

Table IVb. Progression FreeSurvival: Primary MTV vs. T Stage

Model	AIC [1]	Covariate(s)	Hazard ratio (95% CI)	p-value
1	183.20	Primary MTV (> vs. </= median)	2.34 (1.02, 5.37)	0.05
2	186.52	T stage (T4 vs. T2-3)	1.54 (0.63, 3.74)	0.34
3	185.19	Primary MTV (> vs. </= median) T stage (T4 vs. T2-3)	2.31 (0.94, 5.707) 1.03 (0.39, 2.71)	0.07 0.95

CI = confidence interval.
Hazard ratios estimated from Cox models.
[1] Akaike information criterion.

CONCLUSIONS

- This sub-study from RTOG 0522 suggests a strong inverse correlation between baseline primary tumor MTV and chemoradiotherapy outcomes for locally advanced head and neck cancer.
- This finding remains preliminary, and requires technical refinement and clinical confirmation in the cooperative group setting.
- There is need to better match clinical trials to individual patient risk. Validation of a prognostic imaging biomarker such as MTV could be an important step towards this goal.

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