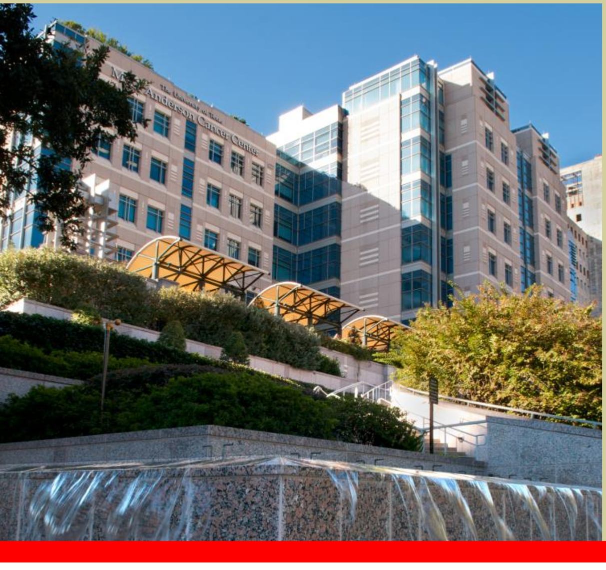

Predicting Patient-Reported Outcomes for Oropharyngeal Cancer Patients Treated With Radiotherapy: Evaluating the Efficacy of $AUC_{symptom}$

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Background

Patients with head and neck cancer (HNC) undergoing radiotherapy (RT) may experience chronic side effects, such as xerostomia and dysphagia, which can have a severe negative impact on quality of life (QoL)[1]. Predicting these symptoms in HNC patients is thus of clinical interest, and recent quantitative approaches have provided insight into these symptom trajectories.

Our lab recently developed a measure of symptom burden over time, the area under the symptom trajectory curve ($AUC_{symptom}$ or AUC_s), which condenses symptom data over the course of treatment and beyond into a single data point while maintaining its temporal nature (Fig 1)[2]. Previous studies have indicated that acute symptoms, particularly xerostomia and dysphagia, strongly predict late symptoms[3], but this relationship for the AUC_s has not been established. Further, the ability of the AUC_s to identify the impacts of specific symptoms on QoL is currently unknown. Consequently, our objectives for this study are to expand upon our lab's previous work to determine the predictive value of the acute AUC_s for late AUC_s and to use AUC_s data to identify symptoms associated with lower patient-reported QoL.

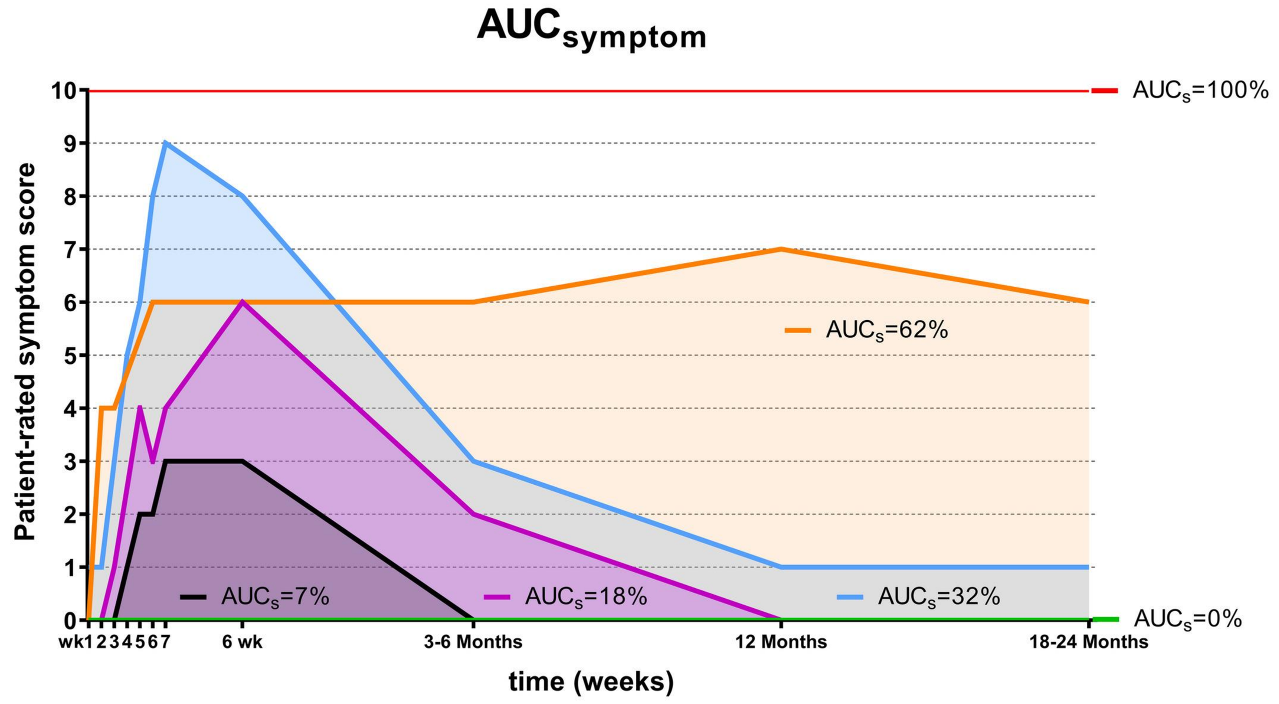
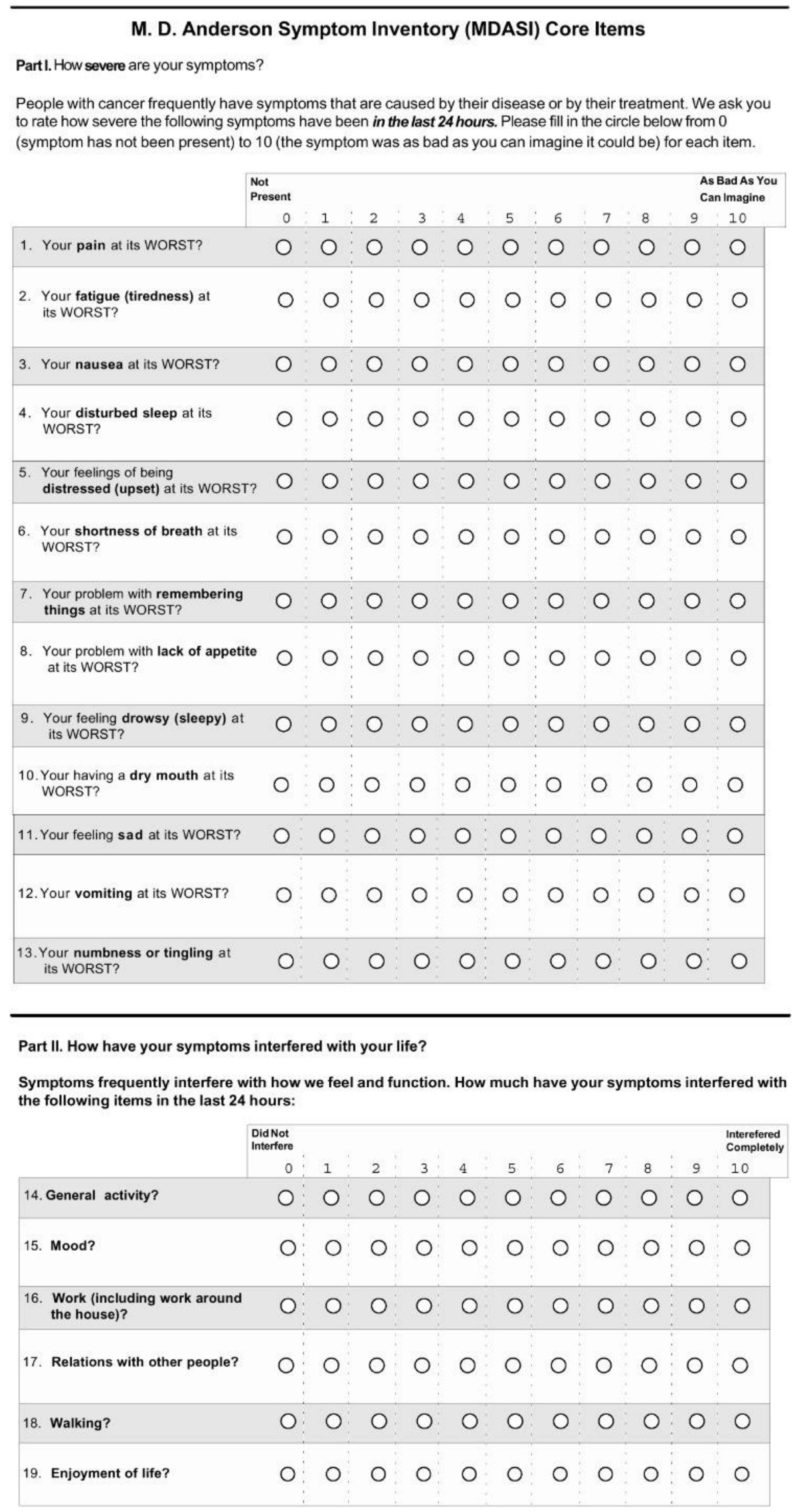


Figure 1. Sample illustration of the area under the symptom trajectory curve ($AUC_{symptom}$) for several symptom trajectories, adapted from Van Dijk et al.[2] The $AUC_{symptom}$ represents the percentage of area covered by the symptom score for a specific interval divided by the maximum potential area.

Methods

AUC_s data from 336 patients from a registry at MD Anderson Cancer Center of patients evaluated for a suspected or confirmed diagnosis of oropharyngeal cancer (OPC), previously calculated by our lab[2], was used in the present study. AUC_s data were originally derived from patient responses to the MDASI-HN, a validated, head and neck specific, 28-item symptom reporting tool in which patients rate symptoms from 0 (none) to 10 (worst imaginable). MDASI items are split into core symptoms and interference items, which patients use to rate the severity of their symptoms and estimate how much their symptoms interfere with normal life activities (Fig 2).



M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

Not Present 0 1 2 3 4 5 6 7 8 9 10 As Bad As You Can Imagine

1. Your **pain** at its WORST?
2. Your **fatigue (tiredness)** at its WORST?
3. Your **nausea** at its WORST?
4. Your **disturbed sleep** at its WORST?
5. Your feelings of being **distressed (upset)** at its WORST?
6. Your **shortness of breath** at its WORST?
7. Your problem with **remembering things** at its WORST?
8. Your problem with **lack of appetite** at its WORST?
9. Your feeling **drowsy (sleepy)** at its WORST?
10. Your having a **dry mouth** at its WORST?
11. Your feeling **sad** at its WORST?
12. Your **vomiting** at its WORST?
13. Your **numbness or tingling** at its WORST?

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

Did Not Interfere 0 1 2 3 4 5 6 7 8 9 10 Interfered Completely

14. General activity?
15. Mood?
16. Work (including work around the house)?
17. Relations with other people?
18. Walking?
19. Enjoyment of life?

Figure 2. Sample form depicting core and interference items for the M.D. Anderson Symptom Inventory (MDASI).[5]

MDASI-HN patient data was retrospectively collected at baseline, RT weeks 1-7, and 6-weeks post-RT (acute) and between 3-6 months and 18-24 months post-RT (late). Patients with both acute and late AUC_s <0.15 for a particular symptom were excluded from analysis for that symptom. Spearman's rho correlation coefficients and linear regressions were calculated between acute and late AUC_s, and correlations with p-values < 0.05 were considered significant.

Spearman's rho correlation coefficients between AUC_s for acute and late MDASI-HN symptoms and AUC_s for MDASI-HN interference items will then be calculated both individually and as a composite (average) interference score. Following these steps, the effects of treatment, TNM staging, age, and gender on these relationships will be evaluated using a non-parametric equivalent of linear regression.

Results

So far, correlations between acute and late AUC_s have been initially calculated. At this early stage, acute AUC_s does appear to be significantly correlated with late AUC_s for several locoregional symptoms, most notably dry mouth (Spearman's rho 0.47, $p < 0.0001$) and taste (Spearman's rho 0.40, $p < 0.0001$) (Fig 3). The relationships between acute and late AUC_s were also graphed as scatter plots and linear regressions were calculated; the plot for dry mouth is shown below ($R^2 = 0.24$, Fig 4). The next steps are to calculate composite interference scores, to calculate correlations between these scores and acute/late symptom AUC_s, and finally to assess the effects of treatment, staging, age, and gender on these relationships.

Symptom	Spearman's rho	p-value	n
dry mouth	0.4708	****	314
taste	0.4009	****	312
mucus	0.3203	****	301
fatigue	0.3142	****	287
drowsy	0.3114	****	245
swallow	0.2922	****	289
appetite	0.2693	****	280
pain	0.2544	****	291
mucositis	0.2417	****	262
sad	0.2191	0.0254*	104
activity	0.1909	0.0041**	224
sleep	0.1804	0.0042**	250
nausea	0.1618	0.0378*	165
enjoy	0.1486	0.0348*	202
work	0.1394	0.0402*	217
skin	0.1213	0.0825	206
constipation	0.1063	0.1566	179
distress	0.08211	0.3245	146
relations	0.05389	0.5332	136
mood	0.04811	0.5213	180
vomit	0.03714	0.7534	74
voice	0.02067	0.7824	181
walking	0.009144	0.9197	124
choke	0.0009205	0.9906	167
sob	-0.02445	0.8373	73
memory	-0.0311	0.7213	134
numb	-0.09869	0.3547	90
teeth	-0.144	0.0711	158

Figure 3 (right): Heatmap of Spearman's rho correlations between acute AUC_s and late AUC_s for each item on the MDASI-HN. P-values < 0.0001 are reported as extremely significant (****).

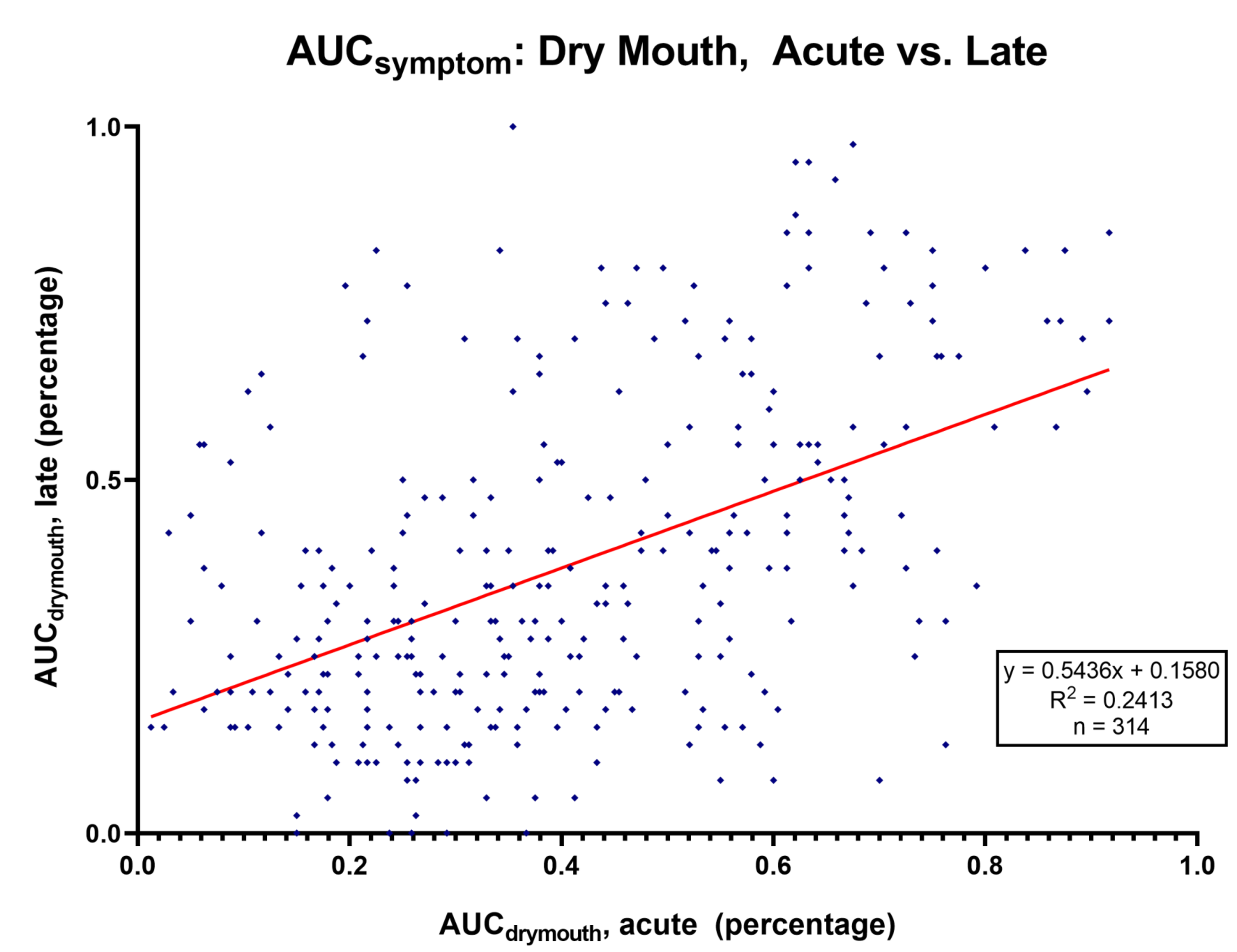


Figure 3. Scatter plot and linear regression of acute AUC_s for a single symptom (dry mouth) vs. late AUC_s for dry mouth. AUC_s values are reported as percentages.

Discussion

Although this project is still in progress, preliminary evidence suggests the $AUC_{symptom}$ measure may have utility for identifying patients that would benefit from individualized RT adaptation, at least for preventing chronic locoregional symptoms such as dry mouth, taste, and mucus. These symptoms have been shown to have a profound negative impact on patient QoL especially as they relate to nutrition[6]; malnutrition is common in HNC patients and is associated with lower overall survival[7]. While several acute and late symptoms, such as dry mouth, were relatively well correlated via Spearman's rho (0.47), their linear relationship was much weaker ($R^2 = 0.24$), suggesting that clinical variables such as treatment, staging, or age may also be important to the development of late symptoms. We expect that our final results including these variables, as well as our interference item analysis, will provide a more complete picture.

Conclusions

While it is premature to draw strong conclusions from our work so far, we anticipate that this project will demonstrate the validity of the $AUC_{symptom}$ measure and encourage further study of its potential for understanding treatment side effects that are most important to HNC patients. With further validation, $AUC_{symptom}$ may present an opportunity for clinicians to utilize data-driven or algorithmic approaches to provide individualized care proactively rather than reactively. In addition, while this measure was developed for HNC patients, it could easily be adapted for other cancers, and could be used to monitor and prevent any number of treatment side effects, especially those with well-known trajectories. Perhaps the $AUC_{symptom}$ may one day become an integral part of the clinician's toolbox in delivering individually personalized, highly effective cancer treatment.

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