



Original Article

Big data analysis of associations between patient reported outcomes, observer reported toxicities, and overall quality of life in head and neck cancer patients treated with radiation therapy [☆]



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ARTICLE INFO

Article history:

Received 29 October 2018
Received in revised form 17 April 2019
Accepted 25 April 2019
Available online 22 May 2019

Keywords:

Patient reported outcomes
Quality of life
Big data

ABSTRACT

Purpose: To assess associations between a variety of patient-reported outcomes (PROs), observer reported toxicities (ORTs), and patient-reported overall quality of life (QOL) for head and neck cancer patients treated with radiotherapy, in order to identify important items for inclusion in prospective patient reporting in the clinic.

Methods: 612 patients completed 27 PRO items from three questionnaires at 1273 follow-up visits, and clinicians provided ORTs according to CTCAE criteria. Using a big data approach, we measured associations among all PROs, between all PROs and ORTs, and between PROs/ORTs and QOL with Pearson (ρ) and Kendall (τ) correlation coefficients, and a novel analysis method based on receiver operating characteristic (ROC) curves used to detect thresholds in response levels demonstrating strong interactions.

Results: PROs most strongly associated with QOL were recreation/entertainment, activity, and fatigue, with $\rho = 0.51$ – 0.60 . Several PROs assessing a common functional outcome (eg. xerostomia) were highly associated with each other (PRO-PRO), with maximum $\rho = 0.84$. Maximum ORT-PRO correlations were $\rho = 0.61$ (dysgeusia versus taste), and $\rho = 0.5$ for ORT-QOL (dry mouth – day). The ROC method identified response thresholds with high area under the curve (AUC) scores for many ORT-PRO associations with maximum $AUC_{avg} = 0.78$.

Conclusions: PRO associations identified activity, lifestyle and fatigue as items for strong consideration for inclusion in questionnaires in the clinic, and suggest that outcome information can be captured in fewer items than the 27 in this study. The ability of clinicians to assess patient toxicities is highest with more severe toxicities, underscoring the need for PRO collection in patient visits to understand and address patient symptoms.

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Patient reported outcomes (PROs) have become a common component of data collection in clinical trials in oncology in recent years [1–8]. They can provide information about treatment toxicity that is complementary to the observer-reported Common Terminology Criteria for Adverse Events (CTCAE) rating system that is typically employed in US-based oncology trials [9]. Although the CTCAE system is essential for assessing the safety of treatments being investigated, studies generally show only fair to moderate

associations between clinician and patient reported outcomes, with clinicians typically underestimating symptom severity as rated by patients [10–15]. Moreover, PROs are able to capture the impact of treatment and disease on the patient's daily function and overall quality of life (QOL) [16–26], and are thus now commonly used as endpoints in oncology clinical trials [3,27]. Additionally, PROs have themselves been shown to provide prognostic information in multiple trials, with lower QOL (the most commonly studied PRO) being negatively associated with survival [26,28,29].

Several groups have investigated incorporating the use of PROs into routine clinical practice, as a method to improve communication, flag important symptoms to discuss in patient visits, and optimize overall patient care [1,18,25,30–34]. However, the most effective and efficient method to capture PROs in the clinical

Abbreviations: ORT, observer reported toxicity; XQ, xerostomia questionnaire; SAQ, symptom assessment questionnaire.

[☆] Supported in part by research grant AWD010438 from Varian Medical Systems. They had no role in the study design, data collection, analysis or writing of the report.

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environment is unknown. Not only is there a wide range of reporting options for PROs (e.g. phone calls, written responses, electronic responses on computers or tablets, etc.), but also the types of questions contained in PRO questionnaires can range from highly specific treatment-related side effects, to general measures such as overall QOL that can even be ascertained in a single question [6–8,12,35,36]. Although validated questionnaires are needed for evaluation of treatment regimens on clinical trials, most of these are lengthy and may not be needed to obtain benefit from PRO use in routine clinical practice. Selecting the ideal number of questions and the most important items from among the tremendous number of available questions is a major challenge. A greater number of questions could decrease the likelihood of an important issue being missed, but also make it less likely for patients to answer all questions accurately as a result of response fatigue [37]. An ideal compromise would be to focus questions on symptoms and side effects that are most strongly associated with QOL, while dropping redundant questions to capture this information with minimal response burden. This would be expected to lead to higher compliance, meaning the benefit of PRO use in the clinic would apply to more patients. When done electronically, an efficient method of PRO collection could also be adapted to individual patient responses, by including targeted questions based on these prior responses (eg. more specific xerostomia questions for patients who answer that they have moderate or greater xerostomia) [38]. An analysis of individual questions from PRO questionnaires is needed in the process of determining which items are most important to include when limiting the number of questions in a questionnaire. When many patients and questions are included, a large volume of data (Big Data) results, and analysis is more easily accomplished with a big data analytics resource system (BDARS) that aggregates clinical data from multiple sources for this purpose.

As part of a process to implement an effective and efficient method of incorporating PROs into our radiation oncology clinic, we first designed a pilot study to compare patient responses across different PRO questionnaires at follow-up visits for head and neck cancer patients previously treated with radiation therapy (RT) in our department. This group was chosen because side effects from RT for head and neck cancers are common, and multiple PRO questionnaires specific to this group are available. The PRO surveys used in this study include a range of questions related to general QOL, head and neck specific QOL, and highly specific measures of xerostomia, which is one of the most common long-term side effects from head and neck RT [39]. Associations among each PRO, between all PROs and observer-reported toxicities (ORTs), and between PROs/ORTs and patient-reported QOL were compared. The study goals were to identify toxicities most strongly associated with QOL, and to identify highly correlated PROs to help in selecting those most appropriate to include in patient clinic visits.

Materials and methods

In an institutional review board approved protocol, 612 patients previously treated in the Department of Radiation Oncology at the University of Michigan for head and neck cancers completed components from three PRO questionnaires at 1273 office visits between October 2016 and June 2018 for a total of 33,100 questions answered. All patients treated in our department for any head and neck cancer were included if they completed the PRO questionnaires for a follow-up visit during this time period, regardless of when the treatment occurred. The median follow-up after completing radiation therapy was 6 months, ranging 0–60 months. The questions included: 15 head and neck specific questions in a mod-

ified version of the University of Washington Quality of Life Questionnaire (UW-QOL) versions 1–3 that was being used in our clinic [40,41] (supplementary data); 9 questions from the University of Michigan Xerostomia Questionnaire (XQ) (8 original items plus an additional item addressing discomfort of dentures due to dryness that was being used in our clinic) [42]; 3 questions from the Symptom Assessment Questionnaire (SAQ), consisting of pain, fatigue, and overall QOL from the linear analog self-assessment scale (supplementary data) [31]. The latter survey has the advantage of being short, applicable to any disease site, only includes items that have been shown to be prognostic indicators for how well a patient will handle the effects of cancer and its treatment, and are a subset of the 12 items recommended by the National Cancer Institute (NCI) for assessment on clinical trials [6].

These 27 questions were asked by medical assistants (MAs) at visit rooming or over the phone prior to follow-up visits, and the answers were entered into the electronic medical record (EMR). MAs were instructed to read the questions and answer choices and ask the patient to select the best response, without themselves interpreting the response. For patients who had multiple follow-up visits during this period, we used the visit with the worst patient reported *overall QOL* from the SAQ for the PRO analysis. ORTs were also recorded in the EMR during many of the patient visits using the CTCAE version 4.03 scale [9], with a modification as dry mouth was separately graded for during the day and at night. In order to measure accurate associations between PROs and ORT, PRO–ORT pairs were only included if they were obtained within the following time frame: 1 week for the first 6 months after treatment, 1 month for 6 months to one year after treatment, and 3 months for greater than one year after treatment. We required at least 100 cases for the PRO–ORT pairs to be included in the analysis. 13 ORTs (supplementary data) met these inclusion criteria, with a median of 147 PRO–ORT pairs (range 104–238) for each of these ORTs.

PRO responses and ORTs are automatically extracted from our EMR into our Big Data Analytics Resource System called the University of Michigan Radiation Oncology Analytics Resource (M-ROAR) [43], where they are integrated with information extracted from our Radiation Oncology Information System (ROIS) and Treatment Planning System (TPS) [43,44]. We analyzed interactions among all individual items of the PROs (351 PRO–PRO pairs from 27 PRO items), and between PROs and ORTs (351 PRO–ORT pairs from 27 PRO items and 13 ORT items). Patient-reported QOL was defined by the item *overall quality of life* from the SAQ survey. Associations between this individual item and all other PROs and ORTs were highlighted, in order to assess those most likely to be impacting QOL. We separately assessed interactions between XQ sum (sum of the original 8 XQ questions) and each individual component of the XQ, to see if any particular item stood out as most associated with the validated XQ. In order to test whether tumor HPV status affects PRO and ORT associations with QOL, we also compared the associations for patients with HPV positive versus HPV negative tumors.

All associations were quantified by three metrics using R programming language and environment, version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria): Pearson's correlation coefficient (ρ), Kendall's correlation coefficient (τ), and a receiver operating characteristic (ROC) analysis method that was used to account for potential thresholds in response above which associations were stronger than associations from responses below the threshold. For the latter method, we generated unique ROC curves for each response threshold (PRO response or ORT grade \geq level n) from the PRO–PRO or ORT–PRO pair using pROC [45]. We identified response thresholds that generated ROC curves with a minimum AUC value of 0.65, a minimum of 10 “true positive” cases and 10 “true negative” cases, and a p -value from Fisher's exact test of

≤ 0.05 at a dichotomy with cutoff at the maximum Youden index on the ROC curve. The average AUC value from the curves meeting these criteria (AUC_{avg}) was used as the third association metric. For all three metrics, we established benchmarks for response consistency using 95% confidence intervals from the associations between two very similar PROs: *pain general* from UW-QOL and *severity of your pain on average* from SAQ. Other associations are compared with the benchmarks, and we defined strong associations as $\rho \geq 0.6$, $\tau \geq 0.5$ and $AUC_{avg} \geq 0.8$.

Results

Patient, tumor, and treatment characteristics of the 612 patients who completed PROs are listed in Table 1. The most common primary disease sites were oropharynx, oral cavity, and larynx/hypopharynx. Most patients were treated with volumetric modulated arc therapy (VMAT) with a prescription dose between 60 and 70 Gy using 2 Gy per fraction. 43.8% of patients had surgery (definitive or salvage) and 60.8% had chemotherapy as part of their treatment course. Response rates for each question ranged from 96% to 98%, with the exception of *discomfort of your dentures due to dryness*, which had a response rate of 84%.

Associations between *pain general* from UW-QOL and *severity of your pain on average* from SAQ (benchmarks for response consistency) are shown in Fig. 1. The different ordinal response options for these two questions are evident on the axes in the scatter plot (Fig. 1a). The ROC curves generated using each response threshold from *severity of your pain on average* are shown in Fig. 1b. AUC values from these curves are similar at each response threshold, and all ROC curves meet our inclusion criteria, suggesting a strong association between these two PROs for all response cutoffs.

Forest plots of the association metrics from all PRO-PRO pairs with strong associations are shown in Fig. 2 compared to the benchmarks. Kendall's correlation coefficients are not shown as they have a similar trend to Pearson's correlation coefficients. Of the 18 PRO-PRO pairs shown, 11 are from items within XQ, 4 are from items within UW-QOL, 2 are between items from UW-QOL and XQ and one is between *recreation/entertainment* from UW-QOL, and *overall QOL* from SAQ. There were no significant differences between the PRO-PRO associations for patients with HPV+ tumors and those with HPV- tumors (supplementary data).

Associations for each of the 8 initial components of the XQ questionnaire with the XQ sum are strong, ranging $\rho = 0.64$ – 0.89 , $\tau = 0.50$ – 0.74 , $AUC_{avg} = 0.84$ – 0.96 . They are also independent of response threshold, with high AUC values from ROC curves at all response cutoffs. The correlative association with *discomfort of your dentures due to dryness* was weaker ($\rho = 0.32$, $\tau = 0.21$) but the threshold response association was strong ($AUC_{avg} = 0.82$) for answers ≥ 1 .

Forest plots of the absolute values of the association metrics between *overall quality of life (QOL)* from SAQ and all other PROs and ORTs are shown in Fig. 3. The PRO items most highly associated with *overall QOL* are *recreation/entertainment* from UW-QOL, *activity* from UW-QOL, and *level of fatigue on average* from SAQ. Interestingly, pain appears to be less associated with *overall QOL* than *activity* and *recreation/entertainment*, and to a lesser extent, *fatigue*, as is eating-swallowing. The remaining PROs are also mildly associated with *overall QOL*, with the exception of *employment*, and *discomfort of dentures due to dryness*. Results were similar for patients with HPV+ and HPV- tumors, with the strongest associations for HPV+ tumors: *recreation/entertainment* $\rho = 0.59$ [0.49–0.67], *level of fatigue* $\rho = 0.57$ [0.47–0.66], *activity* $\rho = 0.55$ [0.44–0.64], and for HPV- tumors: *recreation/entertainment* $\rho = 0.60$ [0.52–0.66], *activity* $\rho = 0.58$ [0.50–0.64], *level of fatigue* $\rho = 0.48$ [0.39–0.55] (supplementary data). There were no significant differences in associations between these groups.

Table 1

Patient, tumor, and treatment characteristics.

Characteristic	N	%
Age (median, sd)	63.2	11.6
Gender		
Male	448	73.2
Female	164	26.8
Smoking status		
Current/former	344	56.2
Never smoker	268	43.8
ECOG		
0	147	24.0
1	362	59.2
2+	55	9.0
Unknown	48	7.8
Primary site		
Oropharynx	239	39.0
HPV+	221	92.5
HPV-	18	7.5
Oral cavity	116	19.0
Larynx/hypopharynx	90	14.7
Skin	38	6.2
Salivary gland	31	5.1
Nasopharynx	25	4.1
Other	73	11.9
T stage		
$\leq T1$	151	24.7
T2	146	23.9
T3	80	13.1
T4	187	30.5
N/A	48	7.8
N stage		
N0	178	29.1
N1	71	11.6
N2	294	48.0
N3	21	3.4
N/A	48	7.9
Other therapy		
Surgery	268	43.8
Chemotherapy	372	60.8
Radiation dose		
>70 Gy	3	0.5
70 Gy	305	49.8
60–69 Gy	246	40.2
50–59 Gy	32	5.2
<50 Gy	26	4.3
Dose per fraction		
>2.50 Gy	17	2.8
2.25–2.50 Gy	34	5.5
2.10–2.20 Gy	50	8.2
2.0 Gy	501	81.9
<2.0 Gy	10	1.6
Treatment technique		
3D CRT	18	3.0
IMRT	65	10.6
VMAT	519	84.8
SBRT	10	1.6

Abbreviations: ECOG (Eastern Cooperative Oncology Group), HPV (Human Papillomavirus), CRT (conformal radiation therapy), IMRT (intensity modulated radiation therapy), VMAT (volumetric modulated arc therapy), SBRT (stereotactic body radiation therapy).

The associations between *overall QOL* from SAQ and ORTs are generally not as strong as those for PROs (Fig. 3), but there are nonetheless several ORTs that have a statistically significant association with QOL, despite being limited to fewer cases in this analysis. Of the 13 ORTs included, 6 have both correlation coefficients that do not overlap with 0 and at least one ROC curve meeting our selection criteria. *Dry mouth* (day and/or night), *pain* and *fatigue* are most highly correlated with *overall QOL* in our data ($\rho > 0.4$ and $\tau > 0.3$), and these also have at least 2 ROC curves

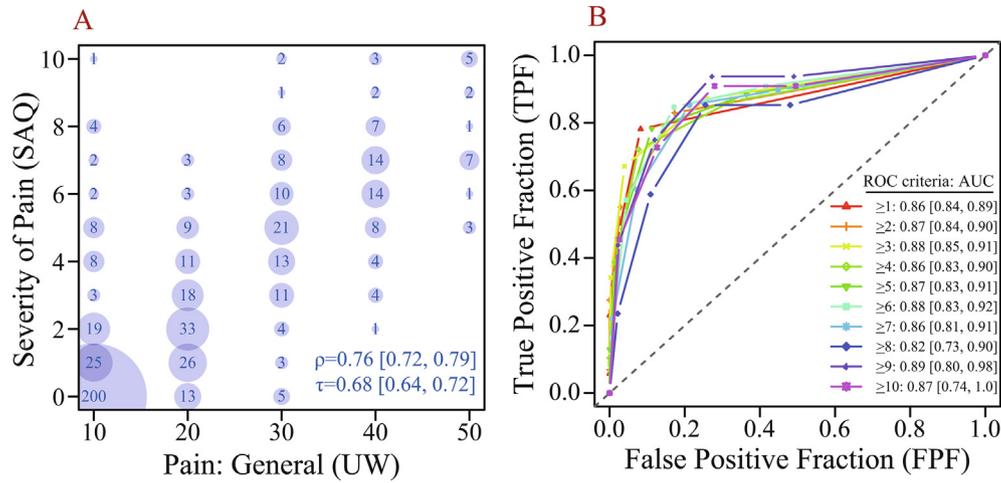


Fig. 1. Benchmark associations. Bubble plot of patient responses to PRO items *severity of pain on average* from symptom assessment questionnaire (SAQ) and *pain: general* from University of Washington Quality of life (UW-QOL) questionnaire (A), and corresponding ROC curves using each response threshold (B). The Pearson (ρ) and Kendall (τ) correlation coefficients are listed (A) with 95% confidence intervals in brackets. AUC values from the ROC curves (B) at each response threshold are listed with 95% confidence intervals in brackets.

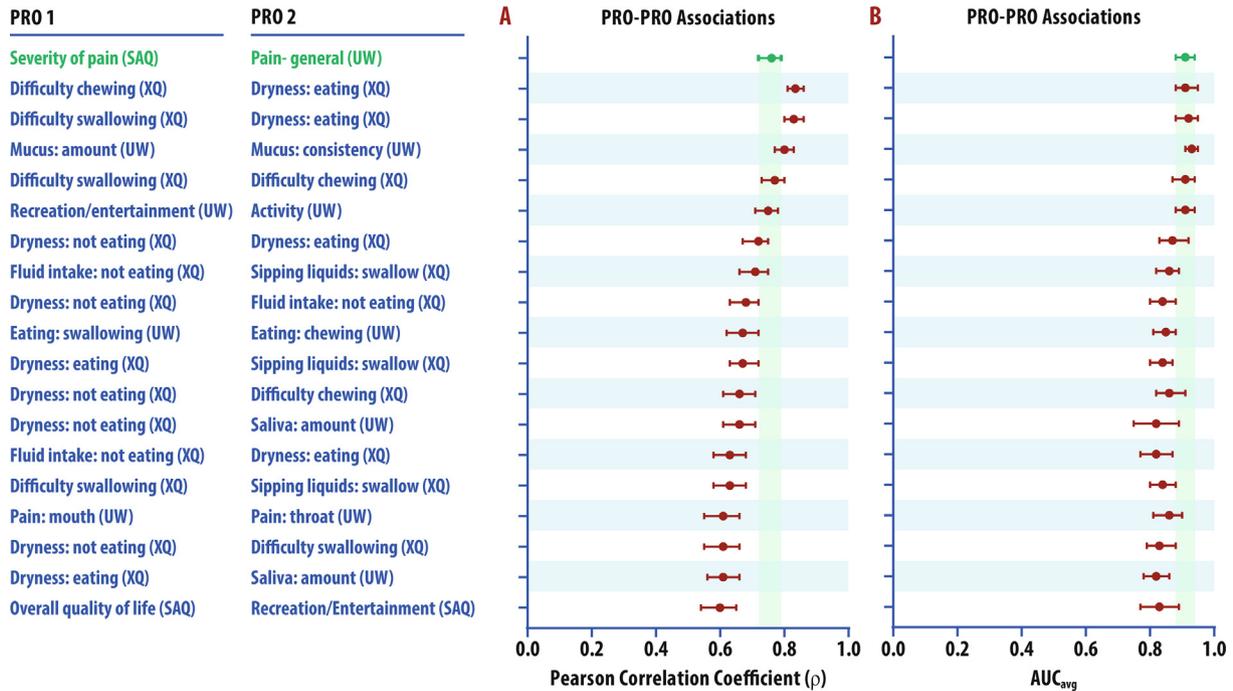


Fig. 2. Strong PRO-PRO associations. Forest plots of PRO-PRO pairs with $\rho \geq 0.6$, $\tau \geq 0.5$ and $AUC_{avg} \geq 0.8$, showing (A) Pearson's correlation coefficients, and (B) average AUC values from ROC curves meeting association criteria ($AUC \geq 0.65$, number of true positives ≥ 10 , number of true negatives ≥ 10 , p -value from Fisher's exact test ≤ 0.05), with corresponding 95% confidence intervals. The benchmark is shown (top row, gray column) for comparison. The questionnaire for each PRO is listed in parentheses: SAQ = symptom assessment questionnaire, XQ = xerostomia questionnaire, UW = University of Washington quality of life questionnaire (UW-QOL). The PRO titles are abbreviated for display purposes.

meeting the selection criteria. There were no significant differences in associations with *overall QOL* between patients with HPV+ and HPV- tumors (supplementary data).

Forest plots of the association metrics between correlated ORT-PRO pairs are shown in Fig. 4. These associations are generally moderate to strong, with some even overlapping the benchmarks for response consistency established for PRO-PRO pairs. For some of the ORTs, the minimum grade was recorded for the majority of patients. An example is shown in Fig. 5a, in which the PRO *eating: swallowing* is plotted against the ORT *dysphagia*. The ROC curves in Fig. 5b show an increasing AUC value with increasing PRO threshold, suggesting the association is stronger for worse

patient reported swallowing. Of the 16 ORT-PRO associations from Fig. 4, only one had a significant difference between HPV+ and HPV- cases, with a stronger association between the ORT *dysphagia* and PRO *eating: swallowing* (UW-QOL) among patients with HPV- tumors (supplementary data).

Discussion

In this study, we found that self-reported *overall QOL* for patients with head and neck cancer treated with radiotherapy in our department was most strongly associated with *recreation/*

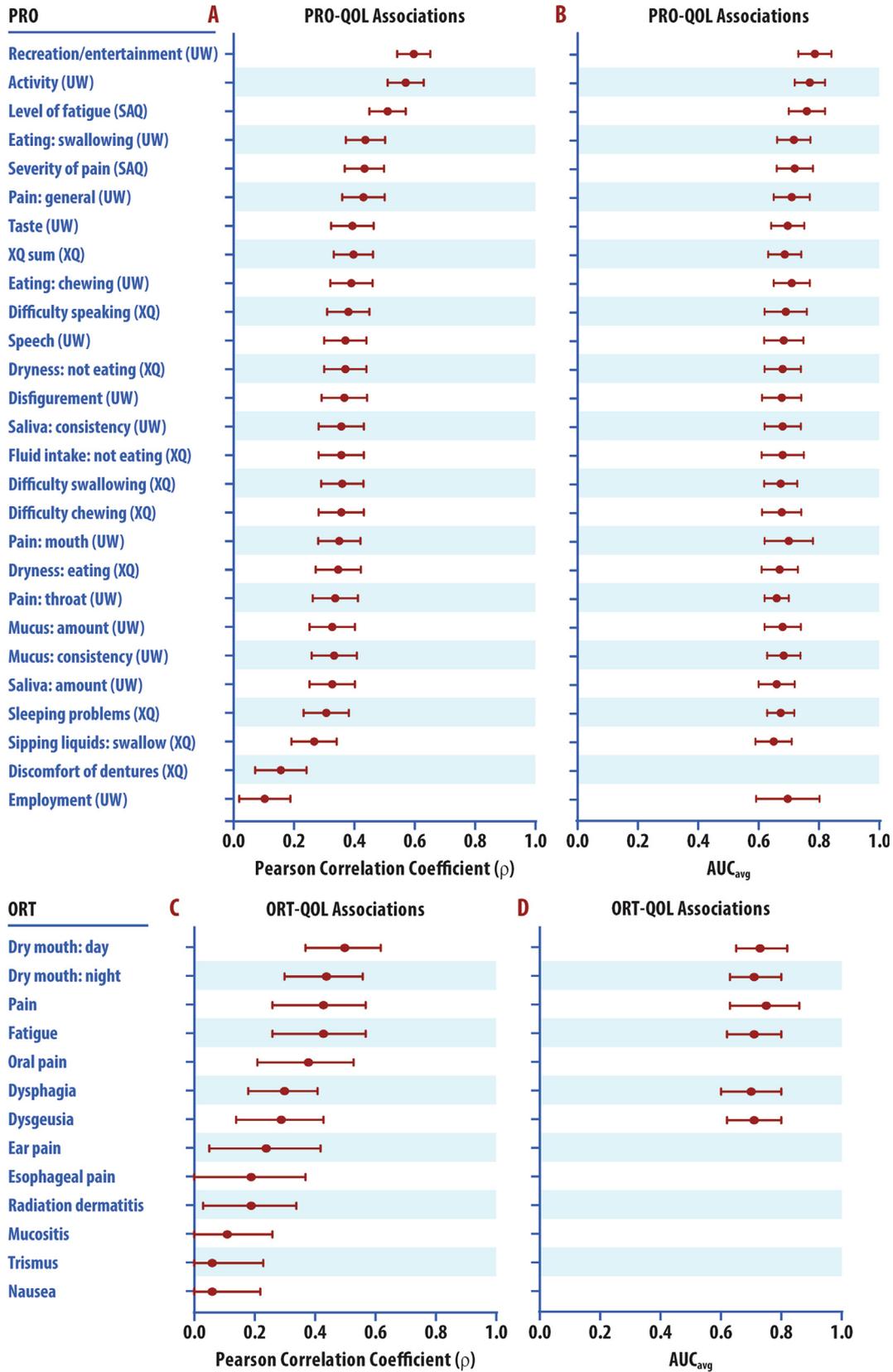


Fig. 3. Associations between QOL and other PROs/ORTs. Forest plots are shown for associations (and 95% confidence intervals) between patient-reported overall quality of life (QOL) from the symptom assessment questionnaire (SAQ) and all other PROs (A and B) and all ORTs (C and D). Pearson's correlation coefficients are shown in (A) and (C), and average AUC values from ROC curves meeting association criteria ($AUC \geq 0.65$, number of true positives ≥ 10 , number of true negatives ≥ 10 , p-value from Fisher's exact test ≤ 0.05) are shown in (B) and (D). No data points are shown for PRO items that did not have any ROC curves meeting these criteria. The questionnaire for each PRO is listed in parentheses: SAQ = symptom assessment questionnaire, XQ = xerostomia questionnaire, UW = University of Washington quality of life questionnaire (UW-QOL). The PRO titles are abbreviated for display purposes.

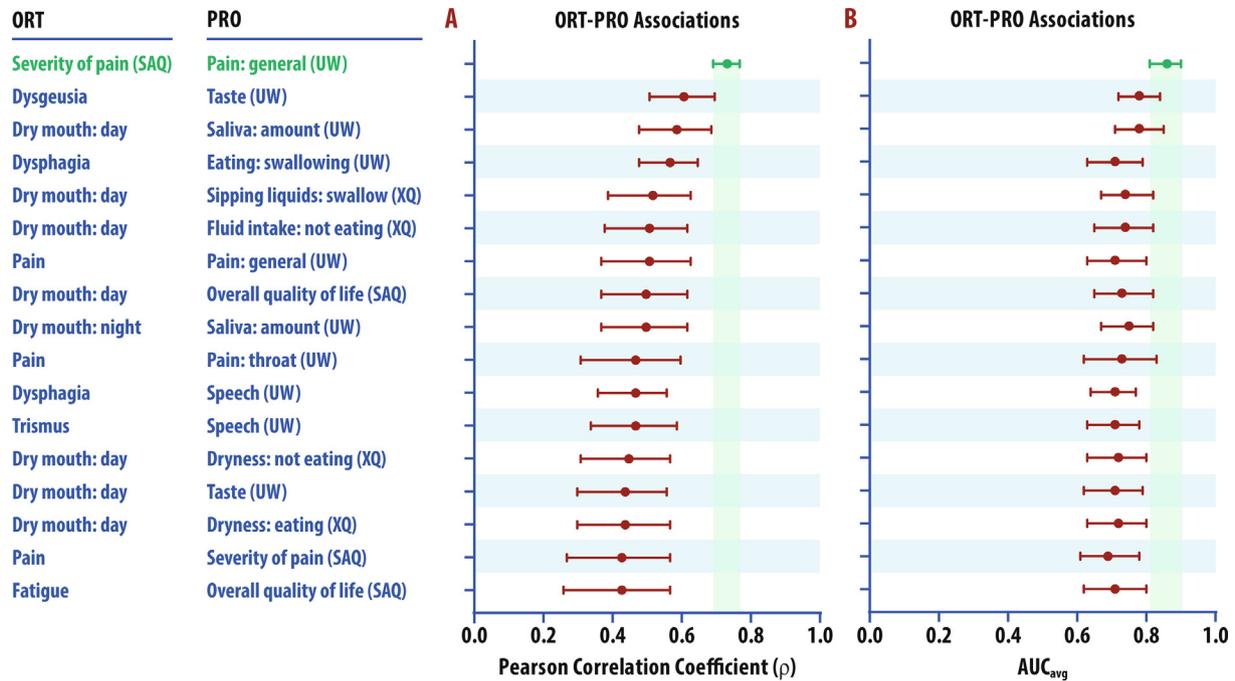


Fig. 4. Associations between ORTs and PROs. Forest plots of ORT-PRO pairs with the highest associations, showing (A) Pearson's correlation coefficients and (B) average AUC values from ROC curves meeting association criteria ($AUC \geq 0.65$, number of true positives ≥ 10 , number of true negatives ≥ 10 , p -value from Fisher's exact test ≤ 0.05), with corresponding 95% confidence intervals. Only ORT-PRO pairs with $\rho \geq 0.4$, $\tau \geq 0.4$, and $AUC_{avg} \geq 0.7$ are shown. The PRO-PRO benchmark is shown (top row, gray column) for comparison. The questionnaire for each PRO is listed in parentheses: SAQ = symptom assessment questionnaire, XQ = xerostomia questionnaire, UW = University of Washington quality of life questionnaire (UW-QOL). The PRO titles are abbreviated for display purposes.

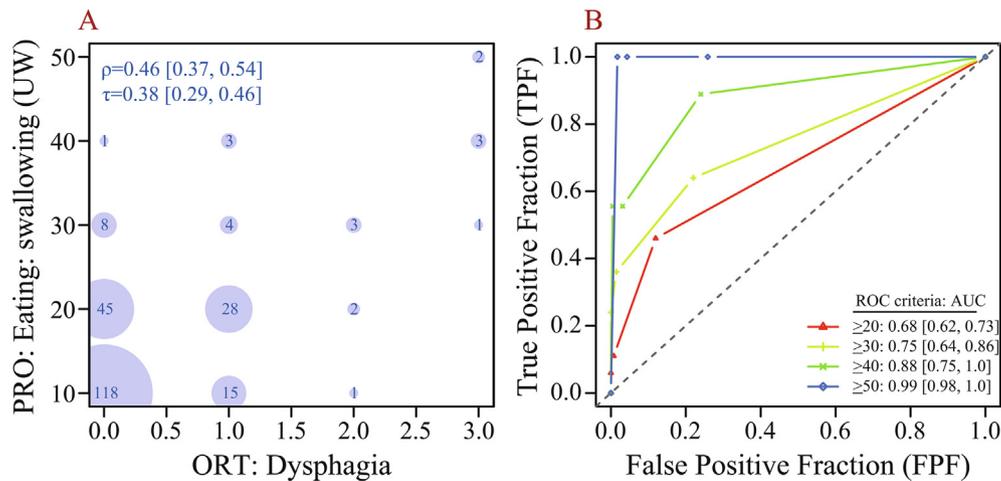


Fig. 5. Sample PRO-ORT relationship. Bubble plot (A) and corresponding ROC curves using all response thresholds (B) for patient reported *eating: swallowing* versus observer-reported *Dysphagia*. The Pearson (ρ) and Kendall (τ) correlation coefficients are listed (A) with 95% confidence intervals in brackets. AUC values from the ROC curves (B) at each response threshold are listed with 95% confidence intervals in brackets. UW = University of Washington quality of life questionnaire (UW-QOL).

entertainment, activity, and fatigue, among a large set of PROs investigated. Pain was also associated, but appeared less important to QOL scores. Associations between PRO items relating to a particular toxicity were strong, both within surveys and across different surveys. ORTs were moderately to strongly associated with PROs in this study, and modestly to moderately associated with patient reported overall QOL. The associations we observed were independent of tumor HPV status, with the single significant ORT-PRO association difference between the HPV+ and HPV- groups most likely due to chance, given the large number of associations tested. Our results show that PROs provide valuable information in addition to ORTs, and imply the potential of capturing pertinent PRO data in fewer items than the 27 included in this study. Moreover,

they imply that questions related to activity, recreation/entertainment and fatigue are at least as important as pain-, dysphagia-, and xerostomia-related questions in capturing the impact of disease and treatment on QOL in our patient population. These PROs are not specific to head and neck cancer, and would be expected to be valuable components of questionnaires for any disease.

Other investigators have shown similar associations between fatigue and QOL or well-being for treated head and neck cancer patients as reported in our study. Sawada and colleagues [46] showed a strong correlation between fatigue and QOL before and during RT. Aguilar and colleagues [16] showed that fatigue was associated with all four QOL domains in the UW-QOL survey after treatment, and Buckwalter and colleagues [47] showed that fatigue

was the most common reason for patients to discontinue employment after radiotherapy. Additionally, van Leeuwen and colleagues [8] recently showed that cancer survivors from many disease sites rated fatigue as more relevant than pain during follow-up. Our results support the notion that fatigue generally has a greater impact on QOL than does pain, but also highlight the importance of activity and recreation/entertainment to patient well-being. Given our results for activity and recreation/entertainment, and prior studies showing a clinically meaningful decrease in social activity during head and neck radiotherapy [25,48,49], we feel that this is an important domain to assess during follow-up, and one that is not assessed in the current CTCAE or PRO-CTCAE.

Several head and neck treatment-specific PROs were also negatively associated with patient reported QOL in our study, including many of those previously recommended for inclusion in PROs for clinical trials [3]. The XQ sum was highly correlated with *saliva amount* from UW-QOL and moderately associated with *overall QOL*, as previously reported at different time points during RT by Lin and colleagues [22]. This suggests that a simplified single symptom PRO is likely sufficient to characterize xerostomia in the clinical environment, as shown by Kamal and colleagues using the single item dry mouth question from the MD Anderson Symptom Inventory-Head and Neck module (MDASI-HN) [50]. Although not specifically included in our PRO questionnaires, it is likely that single item PROs would also be sufficient to characterize other side effects in clinic visits.

ORTs were moderately to strongly associated with PROs in our study, and some were also moderately associated with overall QOL. Previous publications have shown inconsistencies between clinician-reported and patient-reported toxicities [10,12,13,15], with clinicians tending to underestimate the severity of toxicities as reported by patients [11,14]. The relatively poor associations between ORTs and PROs previously reported suggested less value for ORT measures. With the ROC analysis technique described, we were able to be much more specific than simple correlative analysis methods in demonstrating stronger associations when symptoms become more severe. For example, Fig. 5b shows that clinician-reported dysphagia has a higher predictive ability for poor swallowing when the definition of poor swallowing is limited to the worst PRO scores in this category. This demonstrates the ability to use ORT and PRO measurements to reinforce one another. This is an advantage of the ROC method; however, the method is susceptible to having a relatively small number of cases above higher response thresholds, limiting its value in these instances.

Our study has several limitations, some of which stem from the fact that our data were obtained at routine clinic visits rather than as part of a clinical trial with specific follow-up time points at which PRO completion would typically be more rigorously monitored. We also did not include assessments during the course of treatment, which would have provided additional information when side effects are typically at their most severe. In addition, clinician assessments of toxicity during the follow-up period were completed by multiple providers and toxicities were inconsistently assessed, leading to fewer cases available for the ORT-PRO associations. Moreover, our approach required MA involvement, and during busy clinic periods, it is possible that the PRO questionnaires were not administered. It is consequently not possible for us to ascertain how many patients declined completing the surveys versus those who were not asked to complete them. On the other hand, response rates of each question for those administered the questionnaires were very high, likely at least in part due to MA facilitation. Additionally, although MAs were instructed to obtain the patient's response for each question and not to interpret the answers themselves, no additional steps were taken to ensure that no interpretation was done.

We defined “quality of life” in this study by the patient's response to the single item *overall quality of life* from the SAQ. The XQ and UW-QOL instruments have been used over several years at our institution to allow comparison of QOL changes as radiotherapy technologies have evolved. Multiple validated instruments now exist with some suggestion that single questions in a given survey such as the MDASI-HN may perform as well as the aggregate XQ and MDADI instruments [50,51] and may be more broadly applicable to patients without oral feeding. Here, we did not attempt to address the applicability of the many available validated head and neck QOL questionnaires to routine clinical use, but rather to identify particular components of the XQ and UW-QOL that are more likely to be associated with overall QOL. In routine clinic, an appropriate goal is to efficiently ascertain an impression of a patient's side effects and quality of life to help guide the interaction and potential needed interventions. Single items to report side effects such as xerostomia, dysphagia, pain, dysgeusia, etc. appear to be appropriate for this situation. Our study also suggests the importance of including item(s) related to recreation/entertainment and/or activity, and fatigue in questionnaires in the clinic, given their strong associations with QOL that we observed. Our study does not suggest that single items from validated questionnaires can replace the questionnaires themselves when attempting to compare outcome data on an institutional level.

In summary, our study showed associations between patient-reported overall QOL and several general and head and neck-specific PROs recorded at follow-up visits in our radiation oncology clinic. This information can be used to modify PRO questionnaires in order to be more efficient while maintaining similar efficacy in the clinical environment. As a next step towards implementing this system in the clinic, we plan to limit questions to those associated with QOL, and to provide that information to clinicians for use during visits, with a goal of highlighting the most relevant issues to patients in order to optimize their care. We are also investigating whether PROs are associated with dose–volume histogram metrics, and whether this could be used to improve toxicity outcomes from head and neck treatment.

Acknowledgement

Supported in part by research grant AWD010438 from Varian Medical Systems.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2019.04.030>.

References

- [1] Bennett AV, Jensen RE, Basch E. Electronic patient-reported outcome systems in oncology clinical practice. *CA Cancer J Clin* 2012;62:337–47.
- [2] Basch E. Beyond the FDA PRO guidance: steps toward integrating meaningful patient-reported outcomes into regulatory trials and US drug labels. *Value Health* 2012;15:401–3.
- [3] Chera BS, Eisbruch A, Murphy BA, Ridge JA, Gavin P, Reeve BB, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. *J Natl Cancer Inst* 2014;106.
- [4] Cleeland CS, Sloan JA, Cella D, Chen C, Dueck AC, Janjan NA, et al. Recommendations for including multiple symptoms as endpoints in cancer clinical trials: a report from the ASCPRO (Assessing the Symptoms of Cancer Using Patient-Reported Outcomes) Multisymptom Task Force. *Cancer* 2013;119:411–20.
- [5] Dueck AC, Mendoza TR, Mitchell SA, Reeve BB, Castro KM, Rogak LJ, et al. Validity and reliability of the US National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *JAMA Oncol* 2015;1:1051–9.

- [6] Singh JA, Satele D, Pattabasavaiah S, Buckner JC, Sloan JA. Normative data and clinically significant effect sizes for single-item numerical linear analogue self-assessment (LASA) scales. *Health Qual Life Outcomes* 2014;12:187.
- [7] Heutte N, Plisson L, Lange M, Prevost V, Babin E. Quality of life tools in head and neck oncology. *Eur Ann Otorhinolaryngol Head Neck Dis* 2014;131:33–47.
- [8] van Leeuwen M, Husson O, Alberti P, Arraras JL, Chinot OL, Costantini A, et al. Understanding the quality of life (QOL) issues in survivors of cancer: towards the development of an EORTC QOL cancer survivorship questionnaire. *Health Qual Life Outcomes* 2018;16:114.
- [9] (2010, June 14). "National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.". Retrieved September 24, 2018, from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.
- [10] Xiao C, Polomano R, Bruner DW. Comparison between patient-reported and clinician-observed symptoms in oncology. *Cancer Nurs* 2013;36:E1–E16.
- [11] Jensen K, Bonde Jensen A, Grau C. The relationship between observer-based toxicity scoring and patient assessed symptom severity after treatment for head and neck cancer. A correlative cross sectional study of the DAHANCA toxicity scoring system and the EORTC quality of life questionnaires. *Radiother Oncol* 2006;78:298–305.
- [12] Gordon B-BE, Chen RC. Patient-reported outcomes in cancer survivorship. *Acta Oncol* 2017;56:166–73.
- [13] Falchook AD, Green R, Knowles ME, Amdur RJ, Mendenhall W, Hayes DN, et al. Comparison of patient- and practitioner-reported toxic effects associated with chemoradiotherapy for head and neck cancer. *JAMA Otolaryngol Head Neck Surg* 2016;142:517–23.
- [14] Hunter KU, Schipper M, Feng FY, Lyden T, Haxer M, Murdoch-Kinch CA, et al. Toxicities affecting quality of life after chemo-IMRT of oropharyngeal cancer: prospective study of patient-reported, observer-rated, and objective outcomes. *Int J Radiat Oncol Biol Phys* 2013;85:935–40.
- [15] Atkinson TM, Ryan SJ, Bennett AV, Stover AM, Saracino RM, Rogak LJ, et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. *Support Care Cancer* 2016;24:3669–76.
- [16] Aguilari ML, Sandow P, Werning JW, Brennemann L, Psoter WJ. The head and neck cancer patient concern inventory((c)): patient concerns' prevalence, dental concerns' impact, and relationships of concerns with quality of life measures. *J Prosthodont* 2017;26:186–95.
- [17] Chen AM, Daly ME, Farwell DG, Vazquez E, Courquin J, Lau DH, et al. Quality of life among long-term survivors of head and neck cancer treated by intensity-modulated radiotherapy. *JAMA Otolaryngol Head Neck Surg* 2014;140(2):129–33.
- [18] Duman-Lubberding S, van Uden-Kraan CF, Jansen F, Witte BI, Eerenstein SEJ, van Weert S, et al. Durable usage of patient-reported outcome measures in clinical practice to monitor health-related quality of life in head and neck cancer patients. *Support Care Cancer* 2017;25:3775–83.
- [19] Dzioba A, Aalto D, Papadopoulos-Nydam G, Seikaly H, Rieger J, Wolfaardt J, et al. Functional and quality of life outcomes after partial glossectomy: a multi-institutional longitudinal study of the head and neck research network. *J Otolaryngol Head Neck Surg* 2017;46:56.
- [20] Funk GF, Karnell LH, Christensen AJ. Long-term health-related quality of life in survivors of head and neck cancer. *Arch Otolaryngol Head Neck Surg* 2012;138:123–33.
- [21] Hegde JV, Shaverdian N, Daly ME, Felix C, Wong DL, Rosove MH, et al. Patient-reported quality-of-life outcomes after de-escalated chemoradiation for human papillomavirus-positive oropharyngeal carcinoma: findings from a phase 2 trial. *Cancer* 2018;124:521–9.
- [22] Lin SC, Jen YM, Chang YC, Lin CC. Assessment of xerostomia and its impact on quality of life in head and neck cancer patients undergoing radiotherapy, and validation of the Taiwanese version of the xerostomia questionnaire. *J Pain Symptom Manage* 2008;36:141–8.
- [23] Maurer J, Hipp M, Schafer C, Kolbl O. Dysphagia. Impact on quality of life after radio(chemo)therapy of head and neck cancer. *Strahlenther Onkol* 2011;187:744–9.
- [24] Mucke T, Koschinski J, Wolff KD, Kanatas A, Mitchell DA, Loeffelbein DJ, et al. Quality of life after different oncologic interventions in head and neck cancer patients. *J Craniomaxillofac Surg* 2015;43:1895–8.
- [25] Niska JR, Halyard MY, Tan AD, Atherton PJ, Patel SH, Sloan JA. Electronic patient-reported outcomes and toxicities during radiotherapy for head-and-neck cancer. *Qual Life Res* 2017;26:1721–31.
- [26] Rettig EM, D'Souza G, Thompson CB, Koch WM, Eisele DW, Fakhry C. Health-related quality of life before and after head and neck squamous cell carcinoma: analysis of the surveillance, epidemiology, and end results-medicare health outcomes survey linkage. *Cancer* 2016;122:1861–70.
- [27] Reeve BB, Mitchell SA, Dueck AC, Basch E, Cella D, Reilly CM, et al. Recommended patient-reported core set of symptoms to measure in adult cancer treatment trials. *J Natl Cancer Inst* 2014;106:dju129.
- [28] Sloan JA, Halyard M, El Naqa I, Mayo C. Lessons from large-scale collection of patient-reported outcomes: implications for big data aggregation and analytics. *Int J Radiat Oncol Biol Phys* 2016;95:922–9.
- [29] Gotay CC, Kawamoto CT, Bottomley A, Efficace F. The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol* 2008;26(8):1355–63.
- [30] Halyard MY. The use of real-time patient-reported outcomes and quality-of-life data in oncology clinical practice. *Expert Rev Pharmacoecon Outcomes Res* 2011;11:561–70.
- [31] Hubbard JM, Grothey AF, McWilliams RR, Buckner JC, Sloan JA. Physician perspective on incorporation of oncology patient quality-of-life, fatigue, and pain assessment into clinical practice. *J Oncol Pract* 2014;10:248–53.
- [32] Rogers SN, Lowe D, Lowies C, Yeo ST, Allmark C, McAvery D, et al. Improving quality of life through the routine use of the patient concerns inventory for head and neck cancer patients: a cluster preference randomized controlled trial. *BMC Cancer* 2018;18:444.
- [33] Snyder CF, Aaronson NK, Chouair AK, Elliott TE, Greenhalgh J, Halyard MY, et al. Implementing patient-reported outcomes assessment in clinical practice: a review of the options and considerations. *Qual Life Res* 2012;21:1305–14.
- [34] Yang LY, Manhas DS, Howard AF, Olson RA. Patient-reported outcome use in oncology: a systematic review of the impact on patient-clinician communication. *Support Care Cancer* 2018;26:41–60.
- [35] Licitra L, Mesia R, Keilholz U. Individualised quality of life as a measure to guide treatment choices in squamous cell carcinoma of the head and neck. *Oral Oncol* 2016;52:18–23.
- [36] Silveira AP, Goncalves J, Sequeira T, Ribeiro C, Lopes C, Monteiro E, et al. Patient reported outcomes in head and neck cancer: selecting instruments for quality of life integration in clinical protocols. *Head Neck Oncol* 2010;2:32.
- [37] Rolstad S, Adler J, Ryden A. Response burden and questionnaire length: is shorter better? A review and meta-analysis. *Value Health* 2011;14:1101–8.
- [38] Petersen MA, Aaronson NK, Arraras JL, Chie WC, Conroy T, Costantini A, et al. The EORTC CAT Core-The computer adaptive version of the EORTC QLQ-C30 questionnaire. *Eur J Cancer* 2018;100:8–16.
- [39] Langendijk JA, Doornaert P, Verdonck-de Leeuw IM, Leemans CR, Aaronson NK, Slotman BJ. Impact of late treatment-related toxicity on quality of life among patients with head and neck cancer treated with radiotherapy. *J Clin Oncol* 2008;26:3770–6.
- [40] Hassan SJ, Weymuller EA. Assessment of quality of life in head and neck cancer patients. *Head Neck* 1993;15:485–96.
- [41] Weymuller J, Ernest A, Alsarraf R, Yueh B, Deleyiannis FW-B, Coltrera MD. Analysis of the performance characteristics of the university of Washington quality of life instrument and its modification (UW-QOL-R). *Arch Otolaryngol Head Neck Surg* 2001;127:489–93.
- [42] Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, Ship JA. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;50:695–704.
- [43] Mayo CS, Kessler ML, Eisbruch A, Weyburne G, Feng M, Hayman JA, et al. The big data effort in radiation oncology: data mining or data farming? *Adv Radiat Oncol* 2016;1:260–71.
- [44] Mayo CS, Matuszak MM, Schipper MJ, Jolly S, Hayman JA, Ten Haken RK. Big data in designing clinical trials: opportunities and challenges. *Front Oncol* 2017;7:187.
- [45] Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinf* 2011;12:77.
- [46] Sawada NO, de Paula JM, Sonobe HM, Zago MM, Guerrero GP, Nicolussi AC. Depression, fatigue, and health-related quality of life in head and neck cancer patients: a prospective pilot study. *Support Care Cancer* 2012;20:2705–11.
- [47] Buckwalter AE, Karnell LH, Smith RB, Christensen AJ, Funk GF. Patient-reported factors associated with discontinuing employment following head and neck cancer treatment. *Arch Otolaryngol Head Neck Surg* 2007;133:464–70.
- [48] Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS, Leung LH, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. *Int J Radiat Oncol Biol Phys* 2006;66:981–91.
- [49] Rathod S, Gupta T, Ghosh-Laskar S, Murthy V, Budrukkar A, Agarwal J. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. *Oral Oncol* 2013;49:634–42.
- [50] Kamal M, Rosenthal DI, Volpe S, Goepfert RP, Garden AS, Hutcheson KA, et al. Patient reported dry mouth: Instrument comparison and model performance for correlation with quality of life in head and neck cancer survivors. *Radiother Oncol* 2018;126:75–80.
- [51] Grant S, Kamal M, Mohamed ASR, Zaveri J, Barrow MP, Gunn GB, et al. Single-item discrimination of quality-of-life-altering dysphagia among 714 long-term oropharyngeal cancer survivors: comparison of patient-reported outcome measures of swallowing. *Cancer* 2019.