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Xerostomia-related quality of life for patients with oropharyngeal carcinoma treated with proton therapy

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Abstract

Purpose: We report longitudinal patient-reported quality-of-life (QoL) outcomes related to xerostomia in patients with oropharyngeal cancer treated with intensity-modulated proton therapy (IMPT).

Materials and methods: Patients treated from May 2012 through December 2016 at a single institution for AJCC7 stage III-IV, M0 oropharyngeal cancer were given the 15-item Xerostomia-Related QoL Scale (XeQoLS) before, during, and for up to 2 years after treatment. We evaluated the evolution of xerostomia-related QoL over that time, and examined potential associations between those measures with clinical characteristics.

Results: Sixty-nine patients had XeQoLS scores at baseline and at least once either during or after treatment. The mean ($\pm$ SD) XeQoLS score (0–4) was 0.24 ± 0.57 at baseline. Subsequent scores were 2.00 ± 1.01 at 6 weeks on treatment, and 1.03 ± 0.76 , 0.97 ± 0.78 , 0.82 ± 0.69 , and 0.70 ± 0.75 at 10 weeks, 6 months, 1 year, and 2 years after treatment, respectively. All were statistically different from baseline ($p < 0.001$). Univariate analyses demonstrated associations between XeQoLS score and time ($p < 0.0001$ for each interval), baseline XeQoLS score ($p < 0.0001$), stage ($p = 0.008$), N status ($p = 0.006$), and mean oral cavity dose ($p = 0.038$), but not

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Declaration of Competing Interest
None.

Appendix A. Supplementary data

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for age, sex, T status, receipt of chemotherapy, smoking history, disease site, laterality of neck irradiation, mean parotid dose, or mean submandibular dose. Multivariate analysis suggested that baseline XeQoLS scores, phase of treatment, and N status were associated with XeQoLS scores measured during treatment and recovery.

Conclusions: Patients receiving IMPT reported the greatest xerostomia-related QoL impairment at 6 weeks on treatment, with a 49% improvement by 10 weeks after treatment; however, XeQoLS scores remained above baseline after 2 years. As we aim to establish the value of IMPT in oropharyngeal tumors to de-intensify treatment over conventional therapy, these data help inform discussions about xerostomia-related quality of life for patients with oropharyngeal cancer treated with IMPT.

Proton therapy has an important role in the management of head and neck cancer, where the dosimetric characteristics of proton particles are advantageous for treating tumors in complex anatomic areas. In addition to highly targeted dose depositions owing to the Bragg peak and superior lateral dose distribution of proton therapy, the introduction of spot-scanning techniques that allow intensity-modulated proton therapy (IMPT) further improve dose distributions and normal-tissue sparing relative to intensity-modulated (photon) radiation therapy (IMRT), a finding that has been validated in case-matched analyses showing lower doses to the oral cavity, palate, larynx, mandible, and esophagus [1]. From a clinical standpoint, the potential reduction in treatment-related morbidity with proton therapy is of particular interest for patients with oropharyngeal cancer. Patients with HPV-positive disease have favorable prognoses but have a modest frequency of acute and late adverse effects such as xerostomia, dysgeusia, odynophagia, dysphagia, and radiation dermatitis. This has led to recent efforts to de-intensify both local and systemic therapies in attempts to maintain high cure rates while reducing toxicities. Modern proton therapy offers an opportunity to reduce normal-tissue toxicity and thereby improve quality of life (QoL) while maintaining excellent disease control.

Validated patient-reported outcomes (PRO) instruments are essential for gaining insight into both symptom burden and overall QoL effects experienced by patients and for benchmarking the effects and outcomes of novel treatment approaches [2–6]. For xerostomia-related QoL, the Xerostomia-Related Quality of Life Scale (XeQoLS) has been correlated with physical symptom burden instruments including the xerostomia-specific questionnaire (XQ) and salivary flow rates [7]. Prior studies have used the XeQoLS to demonstrate the benefit of parotid-sparing bilateral neck irradiation compared with standard approaches [7,8]. In a prospective study examining QoL after parotid-sparing IMRT, QoL scores were correlated with symptom burden, with each improving significantly during the first year after radiation therapy [9]. Recent investigations have demonstrated that reduced radiation doses to the bilateral parotid glands, contralateral submandibular gland, and oral cavity are correlated with improved xerostomia-related QoL metrics [10,11]. Direct PRO comparisons between IMRT and IMPT for oropharyngeal cancer, both in terms of QoL and symptom burden, are more limited. Improved symptom burden during the subacute recovery phase with IMPT versus IMRT has been reported, but how this relates to longer-term QoL outcomes is uncertain and the subject of an ongoing prospective, randomized phase II/III trial [4,12,13].

In this study, we provide a retrospective analysis of prospectively acquired, long-term QoL outcomes related to xerostomia in patients with oropharyngeal cancer treated with IMPT. We describe clinical and treatment-specific factors that influence how patients experience xerostomia, including tumor category, baseline xerostomia-related QoL, receipt of chemotherapy, laterality of neck irradiation, and salivary gland doses. We also report individual subdomain scores to study how IMPT affects specific QoL domains during treatment, acute recovery, and chronic recovery phases.

Materials and methods

Eligibility and design

In this institutional review board–approved protocol, we analyzed xerostomia-related QoL in patients who received proton therapy for oropharyngeal carcinoma from May 1, 2012 through December 31, 2016 at The University of Texas MD Anderson Cancer Center. Inclusion criteria included patients having stage III/IV, M0 oropharyngeal cancer (per the 7th edition of the American Joint Committee on Cancer staging manual) who were treated with proton therapy and had documented scores on the Xerostomia-Related Quality of Life Scale (XeQoLS) [7] at baseline and at least once thereafter (during treatment or at 10 weeks, 6 months, 12 months, or 24 months after treatment). Questionnaires were completed in person or by mail, phone, or secure electronic methods.

Xerostomia-related quality of life instrument

The XeQoLS questionnaire measures the effects of salivary gland dysfunction and xerostomia on the four major domains of oral health-related quality of life: physical, pain, personal, and social. The questionnaire consists of 15 items, each rated on a 0-to-4 point Likert scale, with higher scores indicating more severe symptom burden. Questionnaires were completed before treatment (baseline), during treatment, and at the following time points: 2, 4, 6, 8, 10 weeks, 6, 12, 16, 20 months, and at 2, 2.5, 3, 3.5, and 4 years after treatment, with analysis limited to include baseline, 6 weeks on-treatment, and follow-up visits at 10 weeks and at 6, 12, and 24 months. For each available time point, the mean XeQoLS scores were calculated for the global and individual subdomains as the average of the 15 individual items, with each item scored on a 0-to-4 scale.

Statistical methods

The demographic and clinical characteristics of patients and the XeQoLS scores were summarized with descriptive statistics. Paired *t* tests were used to compare the XeQoLS global scores between time points. Bonferroni corrections were applied to account for multiple comparisons. Piecewise linear mixed effects modeling was used to analyze changes in the mean XeQoLS global score over time. The piecewise linear mixed effects models were fitted with three time splines, which were during treatment and during the acute and chronic recovery phases. The knot locations were fixed at 6 weeks on-treatment (corresponding to the approximate end of treatment), and at 10 weeks after treatment. Associations with XeQoLS global score trajectories were explored with univariate and multivariate models. Baseline records were excluded from the multivariate analysis when the

models were adjusted for the baseline score. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC) data analysis software.

Results

Patient and treatment characteristics

Sixty-nine patients met the inclusion criteria for this analysis. Mean patient age was 62.4 years and 87% were men. Fourteen patients (20%) had stage III disease, and 55 (80%) had stage IV disease. The tumor status distribution was as follows: 32% T1, 46% T2, 9% T3, 12% T4a, and 1% T4b. The nodal status distribution was: 4% N0, 19% N1, 73% N2, and 4% N3. The primary tumor sites were base of tongue and glossopharyngeal sulcus (59%) and tonsil (41%). HPV p16-positive disease was present in 84% of patients. Thirty-eight patients (55%) were current or former smokers, and twenty-nine patients (42%) had never smoked.

All patients received IMPT with a median dose of 69.3 Gy(RBE) (range 60–70 Gy(RBE)). Five patients (7%) received a total dose of 60–64 Gy(RBE), twenty-five patients (36%) received 65–68 Gy (RBE), and thirty-nine patients (57%) received 69–70 Gy(RBE). The mean parotid dose was 27.8 ± 5.7 Gy(RBE), the mean submandibular dose was 51.5 ± 15.1 Gy(RBE), the mean contralateral parotid dose was 17.5 ± 9.0 Gy(RBE), the mean contralateral submandibular dose was 39.2 ± 21.9 Gy(RBE), and the mean oral cavity dose was 22.4 ± 10.6 Gy(RBE). Fifty-seven patients (83%) received bilateral neck irradiation and twelve patients (17%) received unilateral neck irradiation. Fifty-four patients (78%) received chemotherapy (38 [55%] with concurrent chemotherapy, 5 (7%) with induction chemotherapy, and 11 (16%) with both induction and concurrent chemotherapy). Thirty-six patients (56%) did not have documented xerostomia-directed treatments, twelve patients (18%) received medical therapy, twelve patients (18%) received acupuncture, and eight patients (12%) received both medical therapy and acupuncture. Additional patient, treatment, and disease characteristics are included in Table 1.

Global and subdomain XeQoLS scores

Of the 69 patients included in this analysis, 59 had XeQoLS data at 6 weeks on-treatment, 44 at 10 weeks after treatment, 51 at 6 months after treatment, 34 at 12 months after treatment, and 26 at 24 months after treatment. Mean and median global XeQoLS scores from pretreatment baseline through 24 months after treatment are shown in Fig. 1. The mean ($\pm$ SD) XeQoLS score was 0.24 ± 0.57 at baseline and was highest at 6 weeks during treatment (mean 2.00 ± 1.01 , $+1.74$ relative to baseline, $p < 0.0001$). At 10 weeks after treatment, the mean XeQoLS score was significantly lower than the peak score at 6 weeks during treatment (mean 1.03 ± 0.76 , -0.81 relative to week 6 during treatment, $p < 0.0001$); the score at 10 weeks after treatment remained significantly higher than the baseline score ($+0.91$ relative to baseline, $p < 0.0001$). The mean XeQoLS score at 24 months was 0.70 ± 0.75 and remained significantly higher than baseline values ($+0.65$ relative to baseline, $p < 0.0001$), and no change was noted between 12 months after treatment and 24 months after treatment (-0.04 relative to 12 months after treatment, $p = 0.772$). Median (interquartile range) XeQoLS scores were 0.0 (0.0–0.2) at baseline, 2.0 (1.3–2.8) at 6 weeks on-treatment, 0.9 (0.4–1.6) at 10 weeks after treatment, 0.9 (0.3–1.3) at

6 months after treatment, 0.7 (0.3–1.1) at 12 months after treatment, and 0.4 (0.1–0.9) at 24 months after treatment.

Mean subdomain XeQoLS scores (physical, personal, pain, and social domains) are shown in Fig. 2. Overall, the trajectory of the individual subdomains followed the general trend of the global XeQoLS mean scores. Peak subdomain scores occurred at 6 weeks during treatment, with decreased scores by 10 weeks after treatment and mean scores remaining higher than baseline at 24 months after treatment. The physical, personal, and pain subdomains demonstrated similar score profiles, whereas the social subdomain had a lower mean score relative to the other three subdomains.

Patients were also stratified by baseline median XeQoLS score into those above and those at the baseline score (Fig. 3). Patients with baseline XeQoLS scores above the median recorded higher peak global XeQoLS scores at 6 weeks during treatment and more persistently elevated XeQoLS scores up to 24 months after treatment. In addition to there being an absolute difference, the longitudinal difference between baseline scores and subsequent scores for patients with baseline XeQoLS scores above the median was higher than for those with baseline scores at the median ($p < 0.0001$).

Univariate and multivariate analyses

Univariate and multivariate analyses to identify potential associations between global XeQoLS score and patient, disease, and treatment-specific characteristics are shown in Table 2. On univariate analysis, XeQoLS score was significantly correlated with the phase of treatment, with estimates of +0.328, -0.427, and +0.095 during the periods of treatment, acute recovery, and chronic recovery, respectively ($p < 0.0001$ for each phase). Significant associations on univariate analysis were also observed for baseline XeQoLS score ($p < 0.0001$), N status ($p = 0.006$), overall stage ($p = 0.008$), and mean oral cavity dose ($p = 0.038$). No associations were found between XeQoLS score and age at diagnosis ($p = 0.22$), sex ($p = 0.659$), receipt of chemotherapy ($p = 0.751$), smoking history ($p = 0.543$), primary disease site ($p = 0.620$), ipsilateral versus bilateral of neck irradiation ($p = 0.170$), mean parotid dose ($p = 0.997$), or mean submandibular dose ($p = 0.477$). Results from the mixed effects multivariate model suggested that elevated baseline global XeQoLS score was significantly associated with global XeQoLS scores measured during treatment, acute recovery, and chronic recovery phases ($p < 0.0001$ for each phase). Nodal status (N0 or N1) was independently associated with greater XeQoLS scores on multivariate analysis ($p = 0.013$), and mean oral cavity dose was not significantly associated with XeQoLS score on multivariate analysis ($p = 0.373$). We did not observe significant correlations between mean salivary gland doses and change in global XeQoLS score between baseline and 6 weeks on treatment as shown in Table 3.

Discussion

Key findings from this retrospective analysis of prospectively acquired xerostomia-related QoL outcomes in patients with oropharyngeal cancer treated with IMPT are as follows. The highest scores (reflecting worse QoL) were reported at 6 weeks during treatment, with significant improvement by 10 weeks after treatment; XeQoLS scores remained significantly

above baseline levels at 2 years after treatment, though on a Likert scale of 0–4 the mean difference was only 0.46. On univariate and multivariate analysis, XeQoLS scores were significantly associated with phase of treatment or recovery, baseline XeQoLS score, and nodal status.

Our findings provide guidance for counseling patients about xerostomia-related QoL during and after receipt of IMPT. Although considerable variation was noted in the magnitude of individual XeQoLS scores, the general trend across all subgroups was that xerostomia-related QoL was worst at 6 weeks with significant improvement by 10 weeks after treatment, although XeQoLS scores remained above baseline levels for up to 2 years after treatment. These data also suggest that patients reporting worse xerostomia-related QoL before beginning treatment may be more likely to report persistently impaired QoL due to xerostomia during the treatment, acute recovery, and chronic recovery phases for up to 2 years after completing treatment. Patients with lower baseline QoL impairment may have more robust improvement in their QoL measurements after treatment, whereas those with worse baseline QoL may exhibit prolonged QoL impairment, particularly in the chronic recovery phase. However, this observation requires confirmation in well-balanced, larger populations and should be correlated with physical symptom burden. Measures to preserve or improve salivary gland function may be particularly beneficial for patients reporting worse xerostomia-related QoL at baseline.

As head and neck cancer clinical trials assess IMPT relative to traditional approaches, instruments such as XeQoLS illustrate how receipt of IMPT translates to patient-reported outcomes both during and after treatment [4]. The XeQoLS instrument used in our study is an effective and validated tool to reliably, efficiently, affordably, and consistently assess xerostomia-related QoL from the patient perspective [4].

Previous studies for salivary gland sparing IMRT have measured xerostomia-related QoL up to 5 years after treatment. Hawkins et al. observed improvement in QoL until 18 months followed by a stabilization in QoL scores up to 5 years after treatment [10]. Other studies have generally reported improvement in xerostomia-related QoL until 1 year after completion of treatment, without significant improvement beyond 1 year [14–18]. Interestingly, a recent study of de-intensified chemoradiation in which patients with oropharyngeal patients received 60 Gy using IMRT with dose-reduced cisplatin reported that xerostomia-related QoL scores improved between 1 and 2 years after treatment; in that study, patients receiving unilateral irradiation had QoL scores return to baseline, whereas others had QoL scores that remained above baseline [19]. This suggests that de-intensification, either through lower absolute dose or radiation techniques to better spare salivary glands, can permit more significant improvements in QoL after treatment. Because one of the advantages of proton therapy is improved sparing of the oral cavity, our finding that mean oral cavity dose was associated with XeQoLS score on univariate, but not multivariate, analysis warrants further study in larger populations. We did not observe a significantly different QoL outcome for patients receiving unilateral versus bilateral neck irradiation in the current study. Our data from patients treated with IMPT is consistent with the trends observed for patients receiving standard radiation doses of IMRT, as we observed

improvement in xerostomia-related QoL to 12 months after completion of IMPT, followed by stability in XeQoLS scores through 2 years after treatment.

This study had several limitations. The instrument used in this study (XeQoLS) describes xerostomia-related QoL from the patient's perspective; however, these measurements are not correlated with more objective tools to measure symptom burden or salivary gland function. In previous studies of IMRT, correlations have been documented between PRO instruments such as the XeQoLS and objective salivary function and dosimetric measurements [7,11,20]. The follow-up duration of 2 years includes the acute and chronic recovery phases, but the continued evolution of xerostomia-related QoL beyond 2 years is not captured in the current study as it has been described for other studies up to 5 years [10]. The degree of study attrition is relevant particularly at later time points, which is attributed to either patients not completing questionnaires at certain visits or patients not attending the later follow-up visits. For patients with oropharyngeal cancer, long-term survival is anticipated, so longer follow-up with larger patient populations is necessary to demonstrate the extent of recovery and associated effects on QoL after IMPT. Of particular interest will be comparing the severity of late effects between IMPT and IMRT at time points beyond 2 years after treatment. Lastly, the results from this single-institution analysis may differ from results obtained at other institutions offering IMPT owing to differences in the patient populations, radiation planning, treatment delivery, and available resources for multidisciplinary management of symptoms.

In conclusion, nearly all patients treated with IMPT for oropharyngeal cancer experienced xerostomia-related QoL to some extent that was at its worst during treatment but significantly improved at 10 weeks after IMPT, with continued improvement throughout and particularly in the first year after treatment. Those patients with high baseline XeQoLS scores were more likely to continue to report prolonged effects of xerostomia on QoL. An ongoing randomized clinical trial comparing IMPT with IMRT will provide further insight on the potential functional advantages of proton therapy for patients with oropharyngeal cancer, as well as relevant prognostic factors that influence symptom severity. Because HPV-associated oropharyngeal cancer has a more favorable prognosis, de-intensification strategies are being actively explored to reduce treatment-related toxicity, and proton therapy is anticipated to play an increasing role in these efforts. In this context, these data provide a framework for understanding how xerostomia-related QoL evolves during and after receipt of proton therapy for patients with oropharyngeal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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	Baseline	6 wk during treatment	10 wk after treatment	6 mo after treatment	12 mo after treatment	2 y after treatment
No. of patients	69	59	44	51	34	26
Mean XeQoLS global score (SD)	0.24 (0.57)	2.00 (1.01)	1.03 (0.76)	0.97 (0.78)	0.82 (0.69)	0.70 (0.75)
Median XeQoLS global score	0.0	2.0	0.9	0.9	0.7	0.4
Interquartile range (IQR)	0.0 – 0.2	1.3 – 2.8	0.4 – 1.6	0.3 – 1.3	0.3 – 1.1	0.1 – 0.9
vs. 6 wk during treatment	-1.74 ($p < 0.0001$)	—	—	—	—	—
vs. 10 wk after treatment	-0.91 ($p < 0.0001$)	+ 0.81 ($p < 0.0001$)	—	—	—	—
vs. 6 mo after treatment	-0.82 ($p < 0.0001$)	+ 0.97 ($p < 0.0001$)	+ 0.11 ($p = 0.323$)	—	—	—
vs. 12 mo after treatment	-0.67 ($p < 0.0001$)	+ 1.34 ($p < 0.0001$)	+ 0.46 ($p = 0.002$)	+ 0.23 ($p = 0.031$)	—	—
vs. 2 yr after treatment	-0.65 ($p < 0.0001$)	+ 1.28 ($p < 0.0001$)	+ 0.42 ($p = 0.007$)	+ 0.32 ($p = 0.016$)	+ 0.04 ($p = 0.772$)	—

Fig. 1.

Global scores on the Xerostomia-Related Quality of Life Scale (XeQoLS). Box-and-whisker plots for patient-reported outcomes as measured by the XeQoLS score. T, on treatment; AR, acute recovery phase (up to 10 weeks after completing radiation); CR, chronic recovery phase (up to 2 years after treatment).

Fig. 2.

Individual subdomain scores from the XeQoLS including effects on the physical, personal, pain, and social domains. T, on treatment; AR, acute recovery phase (up to 10 weeks after completing radiation); CR, chronic recovery phase (up to 2 years after treatment).

Fig. 3. Mean XeQoLS global scores stratified by baseline median XeQoLS score. Patients were categorized by baseline XeQoLS score as being either at or above the median. T, on treatment; AR, acute recovery phase (up to 10 weeks after completing radiation); CR, chronic recovery phase (up to 2 years after treatment).

Table 1

Patient and treatment characteristics.

Characteristic	No. of patients (%)
Sex	
Female	9 (13)
Male	60 (87)
Age	
Mean (SD)	62.4 (10)
Median (range)	64 (37–84)
Disease site	
Base of tongue	37 (54)
Glossopharyngeal sulcus	4 (6)
Tonsil	28 (41)
Stage	
III	14 (20)
IV	55 (80)
T category	
T1	22 (32)
T2	32 (46)
T3	6 (9)
T4a	8 (12)
T4b	1 (1)
N category	
N0	3 (4)
N1	13 (19)
N2a	6 (9)
N2b	32 (48)
N2c	11 (16)
N3	3 (4)
HPV P16 status	
Negative	1 (1)
Positive	58 (84)
Unknown	10 (14)
Smoking history	
Current	2 (3)
Former	36 (52)
Never smoked	29 (42)
Unknown	2 (3)
Chemotherapy	
Induction	5 (7)
Concurrent	38 (55)
Induction + concurrent	11 (16)

Characteristic	No. of patients (%)
None	15 (22)
Radiation dose	
60–64 Gy(RBE)	5 (7)
65–68 Gy(RBE)	25 (36)
69–70 Gy(RBE)	39 (57)
Laterality of neck irradiation	
Unilateral	12 (17)
Bilateral	57 (83)
Xerostomia treatment	
None	36 (56)
Medical therapy	12 (18)
Acupuncture	12 (18)
Medical and acupuncture	8 (12)

Table 2 Univariate and multivariate regression analyses for factors associated with global XeQoLS score^{*}

Characteristic	Global XeQoLS Score		
	Univariate Estimate	P	Multivariate Estimate P
Phase of treatment			
On treatment	0.328	<0.0001	0.343 <0.0001
Acute recovery	-0.427	<0.0001	-0.445 <0.0001
Chronic recovery	0.095	<0.0001	0.098 <0.0001
Intercept	0.177	0.039	-0.251 0.138
Baseline XeQoLS Score	0.661	<0.0001	0.593 <0.0001
Age	0.01	0.223	NI -
Sex			
Female	-0.098	0.659	NI -
Male	-		
Stage			
III	-		
IV	-0.48	0.008	NI -
T category			
T1/T2	-		
T3/T4	-0.333	0.064	NI -
N category			
N0/N1	0.476	0.006	0.394 0.013
N2/N3	-		
Concurrent chemotherapy			
Yes	-0.052	0.751	NI -
No	-		
Smoking history			
Current			
Former	0.092	0.543	NI -
Never	-		

Global XeqQLS Score				
Characteristic	Univariate		Multivariate	
	Estimate	P	Estimate	P
Disease site				
Base of tongue	-0.078	0.620	NI	-
Tonsil	-			
Laterality of neck irradiation				
Bilateral	-0.25	0.170	NI	-
Unilateral	-			
Salivary gland doses (mean)				
Parotid	5.1E-7	0.997	NI	-
Submandibular	4.0E-5	0.477	NI	-
Oral cavity	0.016	0.038	0.006	0.373

NI, not included.

* A piecewise linear mixed effects model was used for multivariate analyses.

Table 3

Correlation of mean salivary gland and oral cavity doses with change in global XeQoLS score.*

	Parotid	Submandibular	Oral cavity
Dose	27.8 (5.7)	51.5 (15.1)	22.4 (10.6)
<i>R</i>	−0.075	−0.009	−0.060
<i>p</i>	0.57	0.95	0.67
<i>n</i>	58	54	62

Abbreviations/definitions: Dose, includes standard deviation, in Gy(RBE); *R*, Pearson correlation coefficient; *p*, *p*-value for $p > |r|$, $H_0: r = 0$; *n*, number of patients analyzed.

* Change in global XeQoLS score defined as difference between ‘On Treatment week 6’ and baseline scores.