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CLINICAL INVESTIGATION

Association Between Physician- and Patient-Reported Symptoms in Patients Treated With Definitive Radiation Therapy for Locally Advanced Lung Cancer in a Statewide Consortium

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Purpose: Little data have been reported about the patient experience during curative radiation therapy (RT) for lung cancer in routine clinical practice or how this relates to treatment toxicity as reported by clinicians. The purpose of this study was to compare clinician-reported adverse events (AEs) with patient-reported outcomes (PROs), including both specific symptoms/side effects, as well as overall quality of life (QoL) during and after definitive RT for locally advanced lung cancer (LALC) in a large statewide cohort.

Methods and Materials: PROs were prospectively collected from patients treated with definitive RT for LALC at 24 institutions within the Michigan Radiation Oncology Quality Consortium between 2012 and 2018 using the Functional Assessment of Cancer Therapy trial outcome index. Physicians prospectively recorded AEs using the Common Terminology Criteria for Adverse Events, version 4.0. Patient-reported QoL changes from baseline were assessed during and after RT using the

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The authors are not authorized to share Michigan Radiation Oncology Quality Consortium data. The data are individually owned by the member institutions of the Michigan Radiation Oncology Quality Consortium.

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Functional Assessment of Cancer Therapy trial outcome index. Spearman correlation coefficients were calculated for AEs and similar PROs, and a multivariable analysis was used to assess associations with QoL.

Results: A total 1361 patients were included in the study, and 53% of respondents reported clinically meaningful declines in QoL at the end of RT. The correlation between clinician-reported esophagitis and patient-reported trouble swallowing was moderate (R = .67), but correlations between clinician-reported pneumonitis and patient-reported shortness of breath (R = .13) and cough (R = .09) were weak. Clinician-reported AEs were significantly associated with clinically meaningful declines in patient-reported QoL (R = − .46 for summary AE score). QoL was more strongly associated with fatigue (R = − .41) than lung-specific AEs.

Conclusions: AEs are associated with clinically meaningful declines in QoL during and after RT for LALC, but associations between AEs and QoL are only modest. This highlights the importance of PRO data, and future research should assess whether earlier detection of PRO changes could allow for interventions that reduce the frequency of treatment-related clinically meaningful declines in QoL.

Introduction

Patient-reported outcomes (PROs) have become an important component of cancer therapy assessment.[1-4] They provide a measure of the impact of cancer and its treatment on patient well-being directly from the patient's perspective. Clinician-reported adverse events (AEs) directly assess the toxicity of a given treatment on an objective scale; however, PROs allow for a more subjective interpretation of the treatment effect on an individual patient level. This is important when clinicians prepare patients for the anticipated effects of therapy, both in terms of specific treatment-related toxicities and overall quality of life (QoL). Because QoL has been shown to be associated with overall survival in patients with cancer,[5-9] PROs can also play an important role in treatment decisions and/or the frequency of on-treatment monitoring of higher-risk patients.

PROs are now routinely acquired as part of clinical trials, along with AEs, and PROs have been recommended to be used as endpoints for clinical trials in oncology.[2] Several trials have reported on changes in QoL based on PROs collected during and after treatment for lung cancer,[10-19] but typically focused on PROs to assess various treatment regimens for different stages of disease in the clinical trial setting. However, less has been reported on QoL outside of clinical trials and in the routine clinical environment,[20] particularly for the definitive treatment of lung cancer involving radiation therapy (RT). Moreover, the association between clinician-reported treatment toxicities and patient-reported QoL is not well established in this population.[19,21] Clinician understanding of the patient experience during and after treatment is especially important for this group, because the majority of patients with locally advanced lung cancer (LALC) are not treated as part of a clinical trial and may not be reflective of the typical trial population.

In this study, we assessed PROs and AEs during and after definitive treatment for LALC using conventionally fractionated RT with or without chemotherapy in a variety of clinical settings across the state of Michigan. This was accomplished through the Michigan Radiation Oncology Quality Consortium, a statewide collaborative consortium working on quality improvement projects to improve the radiation treatment experience. We aimed to quantify changes in QoL during treatment and follow up to identify patient and clinical factors associated with clinically meaningful declines in QoL, and measure correlations between PROs and AEs.

Methods and Materials

Patients and data collection

Patients with locally advanced (stage II or III) non-small or small cell lung cancer treated with definitive RT with or without chemotherapy between 2012 to 2018 at 24 Michigan Radiation Oncology Quality Consortium centers were included in this study. Data were prospectively collected at the start of RT, weekly during RT, and at 1, 3, and 6 months after completing RT. Paper surveys were provided to patients and clinicians at the time of clinic visits, and written responses were manually entered into an electronic database by research coordinators on site at each institution. Surveys were collected for research purposes and not intended for clinical utilization by the clinicians. This effort was approved by an institutional review board as a quality initiative. Clinical assessments and treatment information on all eligible patients were entered into the database, but patient participation in surveys was voluntary (with written consent documentation waived).

Outcomes

PROs and QoL were assessed using the Functional Assessment of Cancer Therapy trial outcome index (TOI).[22,23] This index is a validated survey for patients with lung cancer and includes 3 QoL components: Physical well-being, functional well-being, and lung cancer subscale. There are a total of 22 items in this survey, with 7 contributing to physical well-being, 7 to functional well-being, and 8 to the lung cancer subscale. Patients completed the Functional Assessment of Cancer Therapy TOI surveys at the start of RT, during the final week of RT, and at each follow-up visit. Patients also rated their swallowing ability on a 5-point scale at each weekly on-treatment visit. Changes in the overall TOI score

of ≥5 points were considered clinically meaningful, and changes of ≥2 points in any of the subscales were considered clinically meaningful.[24]

Clinicians graded AEs during weekly on-treatment visits and all follow-up visits using the Common Terminology Criteria for Adverse Events (CTCAE), version 4. Esophagitis, esophageal pain, fatigue, and cough were recorded during weekly on-treatment visits and at each follow-up visit. Dyspnea, pleuritic pain, and pneumonitis were recorded during the first and last week of RT and at each follow-up visit. Substantial treatment-related toxicities were defined as any grade ≥2 AE that was also worse than the pretreatment grade. To quantify the overall treatment toxicity, an AE summary score (AE score) was also generated as the sum of the grades of all AEs at each time of evaluation, using equal weighting for the burden of each individual AE.[25]

Statistical methods

PROs were summarized and analyzed as continuous variables and as the binary indicator for a clinically meaningful change using previously published thresholds.[24] Generalized linear mixed effects models were used to evaluate the association between grade ≥2 toxicity and the odds of clinically meaningful declines in TOI while controlling for other baseline clinical factors. Patient-level random intercept terms were included to account for within-patient (between multiple timepoints) correlation. For pneumonitis and fatigue, associations were assessed at each postbaseline timepoint after controlling for time of evaluation as a categorical covariate. For esophagitis, the association was assessed during and at the end of treatment.

Associations between AEs and PROs were measured using Spearman's rank correlation coefficients and included data from all available follow-up times. Correlations were also computed for pairs of individual AEs and similar side effects reported by the patient at the same visit (cough—cough, dyspnea—shortness of breath, pneumonitis—cough, pneumonitis—shortness of breath, pleuritic pain—cough, pleuritic pain—shortness of breath, esophagitis—trouble swallowing, esophageal pain—trouble swallowing, fatigue—lack of energy) and overall using the patient-reported "I am bothered by the side effects of treatment" question and AEs. Spearman coefficients were also calculated between AEs and changes in TOI (and each subset) to assess associations between toxicities and QoL.

To understand the potential impact of missing data, baseline characteristics and QoL at the end of treatment were summarized and compared between patients who did and did not complete QoL forms at 6 months. R, version 4.0.0, was used for all statistical analyses.

Results

A total of 1361 patients treated at 24 radiation oncology centers throughout the state of Michigan were included in the study. Patient, tumor, and treatment variables are summarized in Table 1. Most patients had American Joint Committee on Cancer (7th edition) stage IIIA or IIIB disease, and 84% had non-small cell lung cancer. The median age was 67 years, and most patients were Eastern Cooperative Oncology Group performance status score 0 or 1. Most

Table 1 Patient, tumor, and treatment characteristics

Characteristic	Overall (N = 1361)
Age, years (IQR)	
Median	67 (60-74)
Sex, n (%)	
Female	639 (47.0)
Male	722 (53.0)
Race, n (%)	
White	1076 (79.1)
Black	222 (16.3)
Other	63 (4.6)
Eastern Cooperative Oncology Group performance status score, n (%)	
0	667 (49.0)
1	352 (25.9)
2	98 (7.2)
3	23 (1.7)
4	3 (0.2)
Number of Comorbidities, n (IQR)	
Median	2.0 (1.0-3.0)
Stage, n (%)	
IIA	115 (8.4)
IIB	104 (7.6)
IIIA	780 (57.3)
IIIB	362 (26.6)
D95 to planning target volume, Gy (IQR)	
Median	60 (54-63)
Mean lung dose, Gy (IQR)	
Median	15 (12-18)
Concurrent chemotherapy, n (%)	
No	475 (34.9)
Yes	886 (65.1)
Neoadjuvant chemotherapy, n (%)	
No	1281 (94.1)
Yes	80 (5.9)
Adjuvant chemotherapy, n (%)	
No	1218 (89.5)
Yes	143 (10.5)

Abbreviations: IQR = interquartile range

patients (86%) had at least 1 major medical comorbidity, as summarized in Supplemental Table 1.

Physician assessed toxicity

Esophagitis and fatigue were the most commonly reported grade ≥2 toxicities, occurring in 52% and 41% of patients, respectively (Suppl. Table 2). A total of 111 patients were observed to have grade ≥2 pneumonitis (crude rate of 8.2%) at some point during the 6 months of follow up after RT. Accounting for the incomplete follow up on many patients, this corresponds to an estimated rate of 14.2% if all patients had been seen at 1, 3, and 6 months. The mean AE score (sum of grades of all CTCAE toxicities) increased from 1.9 at baseline to 4.4 at the end of RT, then decreased to 3.2, 3.0, and 2.7 at 1, 3, and 6 months of follow up (Suppl. Fig. 1).

Patient-reported outcomes

The number of patients providing PROs (TOI) at the start of RT (baseline), end of RT, as well as 1, 3, and 6 months after RT were 885 (65%), 847 (62%), 707 (52%), 504 (37%), and 370 (27%), respectively. Of the 885 patients who completed PROs at baseline, 749 (85%), 630 (71%), 445 (50%), and 325 (37%) also completed them at the end of RT, and 1, 3, and 6 months after RT, respectively. Patients who were missing QoL information were similar to those completing the QoL survey in terms of age, sex, race, and disease stage (Table 2). Patients missing QoL information at 6 months were slightly less likely to have Eastern Cooperative Oncology Group performance status score 0/1 (87% vs 92%) and less likely to have been treated with concurrent chemotherapy (57% vs 74%). Similarly, differences in mean TOI at the end of treatment were small, although statistically significant (mean TOI = 54 vs 52 in patients with vs without missing QoL at 6 months).

Average TOI scores and each component (lung cancer subscale, physical well-being, and functional well-being) declined significantly during RT, but then improved so that by 6 months the mean values were near baseline values (Suppl. Fig. 2). A majority of patients (53%) reported clinically meaningful worsening of TOI from baseline to the end of treatment compared with 37% of patients at 6 months (Fig. 1). Of the 395 patients with declines in TOI at the end of RT, 182 (46%) still reported declines at 1 month while 147 (37%) did not (17% missing). These numbers were 108 (27%) and 134 (34%) at 3 months (39% missing), and 73 (18%) and 92 (23%) at 6 months (59% missing).

Among the 3 subscales, clinically meaningful declines were the most common for physical well-being, and clinically meaningful improvements were more common for functional well-being and the lung cancer subscale. At 6 months after RT, 42.5% of patients reported clinically meaningful improvements in functional well-being, and 40.8% reported clinically meaningful improvements in the lung cancer subscale.

Predictors of patient-reported outcomes

To assess whether common clinician-reported grade ≥2 toxicities were associated with declines in patient-reported

Table 2 Distribution of missing QoL data at 6 months of follow up based on patient and tumor characteristics

Variable	Level	Missing QoL at 6 months	Not missing QoL at 6 months	*P*-value
		n (%) or mean (SD)	n (%) or mean (SD)	
Age, years		67.8 (9.74)	67.0 (9.77)	.136
Sex	Female	342 (46.5)	359 (49.2)	.312
	Male	394 (53.5)	370 (50.8)	
Race	Black and other	153 (20.8)	155 (21.3)	.874
	White	583 (79.2)	574 (78.7)	
Number of comorbidities		2.03 (1.40)	1.92 (1.35)	.124
Eastern Cooperative Oncology Group score	0/1	574 (87.0)	516 (92.0)	.006
	≥2	86 (13.0)	45 (8.0)	
Stage	IIA	57 (7.74)	69 (9.47)	.613
	IIB	58 (7.88)	50 (6.86)	
	IIIA	425 (57.7)	416 (57.1)	
	IIIB	196 (26.6)	194 (26.6)	
Concurrent chemotherapy	Yes	419 (56.9)	536 (73.5)	< .001
Trial outcome index at end of treatment		54.4 (14.9)	51.9 (14.1)	.011

Abbreviations: QoL = quality of life; SD = standard deviation

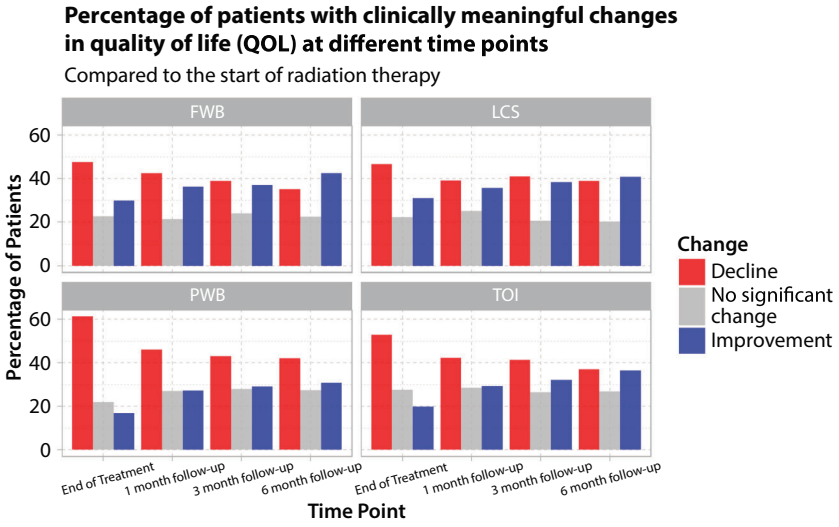

Fig. 1. Bar charts showing the percentage of patients with clinically meaningful declines, clinically meaningful improvements, and no clinically meaningful changes in quality of life at different timepoints compared with the start of radiation therapy. *Abbreviations:* FWB = functional well-being; LCS = lung cancer subscale; PWB = physical well-being; TOI = trial outcome index.

QoL, generalized linear mixed models were fit and adjusted for many baseline patient factors (Table 3). Clinically meaningful declines in patient-reported TOI were associated with clinician-reported grade ≥2 pneumonitis (odds ratio [OR]: 4.39; 95% confidence interval [CI], 1.98-9.81; Model A), fatigue (OR: 3.76; 95% CI, 2.46-5.73; Model B), and esophagitis (OR: 2.69; 95% CI, 1.78-4.11; Model D) after controlling for clinical and treatment characteristics. Pneumonitis and fatigue remained significant when both were included (Model C). Time of evaluation was also significant in the models with a reduced likelihood of TOI declines with increasing time. Stage was marginally significant in the multivariable model ($P = .07$), with an increased stage associated with higher odds of a decline in TOI.

Correlation of patient-reported outcomes with CTCAE toxicity

Correlations between clinician and patient scores were weak for several outcomes as measured by both clinicians and patients: Cough (R = .34), dyspnea versus shortness of breath (R = .36), and fatigue versus lack of energy (R = .33; Table 4). Stronger but still moderate correlations were observed between clinician-reported esophagitis and patient-reported trouble swallowing (R = .67). The lowest correlations were seen between clinician-reported pneumonitis and patient-reported cough (R = .09) and shortness of breath (R = .13). Correlations were still low when using the change from baseline in the PROs (R = .12 for cough; R = .16 for shortness of breath). To further characterize this correlation, pneumonitis grade was plotted versus patient-reported cough and shortness of breath in Figure 2 using data at 1, 3, and 6 months after RT. Many patients with grade ≥2 pneumonitis reported stable or improved shortness of breath and cough. Conversely, there were also patients with grade 0/1 pneumonitis who reported substantial worsening of cough and shortness of breath.

Correlation coefficients between clinician-reported AEs and overall patient-reported QoL (TOI and subscales) are also listed in Table 4. The AE score had a stronger association with these QoL metrics than any individual AE, with a maximum negative correlation of −0.46 for TOI and −0.47 for physical well-being. Among individual AEs, fatigue had the strongest negative associations with QoL, with a maximum negative correlation coefficient of −0.43 for physical well-being.

The PRO "I am bothered by the side effect of treatment" was weak-to-moderately associated with clinician-reported AE score. Fatigue, esophagitis, and esophageal pain had poorer associations for pneumonitis, cough, dyspnea, and pleuritic pain (Suppl. Table 3).

Discussion

To our knowledge, this is the largest study reporting longitudinal PROs and AEs for patients with LALC treated with definitive RT or chemotherapy in routine clinical practice. A majority of patients reported clinically meaningful declines in QoL during RT with or without concurrent chemotherapy. A substantial fraction of patients continued to report poorer QoL even at 6 months after RT, particularly for physical well-being. Conversely, a substantial percentage of patients reported clinically meaningful improvements in QoL after treatment, most notably for functional well-being and the lung cancer subscale. Clinician-reported AEs were significantly associated with clinically meaningful declines in QoL during and after RT, but associations between AEs

Table 3 Generalized linear mixed effects models for associations between grade ≥2 toxicities and clinically meaningful declines in TOI for all timepoints for pneumonitis (model A), fatigue (model B), and both pneumonitis and fatigue (model C), and associations are limited to during and at the end of treatment for esophagitis (model D)

	Model A		Model B	
Predictor	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Baseline TOI	1.07 (1.05-1.08)	< .001	1.07 (1.06-1.09)	< .001
Time* − 1-month follow up	0.69 (0.50-0.95)	.02	0.77 (0.55-1.07)	.12
Time* − 3-month follow up	0.63 (0.44-0.92)	.02	0.79 (0.54-1.14)	.21
Time* − 6-month follow up	0.37 (0.24-0.56)	< .001	0.45 (0.29-0.68)	< .001
Age (years)	0.99 (0.97-1.01)	.26	0.99 (0.97-1.01)	.15
Sex (male)	0.87 (0.61-1.23)	.41	0.90 (0.63-1.28)	.56
Number of comorbidities	1.05 (0.92-1.20)	.46	1.03 (0.91-1.18)	.61
Eastern Cooperative Oncology Group score	1.18 (0.92-1.53)	.20	1.10 (0.85-1.43)	.47
Planning target volume (per 100 cc increase)	1.00 (0.94-1.06)	.99	1.00 (0.94-1.06)	.99
Neoadjuvant chemotherapy (present vs absent)	0.69 (0.34-1.43)	.32	0.77 (0.37-1.57)	.47
Adjuvant chemotherapy (present vs absent)	0.72 (0.41-1.27)	.26	0.79 (0.45-1.40)	.43
Concurrent chemotherapy (present vs absent)	1.32 (0.85-2.05)	.21	1.24 (0.80-1.93)	.33
Stage (Reference level IIA)				
IIB	0.34 (0.13-0.86)	.02	0.31 (0.12-0.79)	.01
IIIA	1.31 (0.71-2.42)	.38	1.35 (0.73-2.48)	.34
IIIB	1.26 (0.64-2.50)	.50	1.32 (0.67-2.61)	.43
Histology (small cell vs non-small cell lung cancer)	1.08 (0.68-1.71)	.76	1.01 (0.64-1.62)	.95
Pneumonitis grade ≥2	**4.39 (1.98-9.81)**	**< .001**		
Fatigue grade ≥2			**3.76 (2.46-5.73)**	**< .001**

	Model C		Model D	
Predictor	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Baseline TOI	1.07 (1.06-1.09)	< .001	1.06 (1.04, 1.08)	< .001
Time* − 1-month follow up	0.74 (0.53-1.03)	.07		
Time* − 3-month follow up	0.70 (0.48-1.03)	.07		
Time* − 6-month follow up	0.40 (0.26-0.62)	< .001		
Age (years)	0.99 (0.97-1.01)	.15	1.01 (0.98, 1.03)	.64
Sex (male)	0.92 (0.65-1.29)	.62	1.01 (0.67, 1.52)	.96
Number of comorbidities	1.04 (0.91-1.18)	.59	1.06 (0.92, 1.23)	.40
Eastern Cooperative Oncology Group score	1.10 (0.85-1.41)	.47	1.15 (0.85, 1.54)	.36
Planning target volume (per 100 cc increase)	1.00 (0.94-1.06)	.96	1.01 (0.94, 1.08)	.75
Neoadjuvant chemotherapy (present vs absent)	0.69 (0.34-1.40)	.30	0.51 (0.21, 1.17)	.12
Adjuvant chemotherapy (present vs absent)	0.74 (0.42-1.29)	.29	0.84 (0.44, 1.59)	.59
Concurrent chemotherapy (present vs absent)	1.27 (0.83-1.95)	.28	1.07 (0.64, 1.78)	.80
Stage (vs. IIA)				
IIB	0.31 (0.13-0.79)	.01	0.23 (0.07-0.67)	.009
IIIA	1.34 (0.73-2.44)	.34	0.92 (0.45-1.88)	.81
IIIB	1.32 (0.68-2.58)	.41	0.97 (0.44-2.16)	.94
Histology (non-small vs small cell lung cancer)	1.04 (0.66-1.64)	.87	0.94 (0.55-1.60)	.81
Pneumonitis grade ≥2	**3.56 (2.34-5.43)**	**< .001**		
Fatigue grade ≥2	**3.87 (1.71-8.75)**	**.001**		
Any esophagitis grade ≥2 during radiation therapy or end of treatment			**2.69 (1.78-4.11)**	**< .001**

Abbreviations: CI = confidence interval; OR = odds ratio; SD = standard deviation

* Reference time is end of treatment

Table 4 Spearman correlation coefficients between PROs and clinician-reported AEs

	PRO (specific symptom)				PRO (quality of life)			
AE	Cough	Shortness of breath	Trouble swallowing	Lack of energy	Trial outcome index	Physical well-being	Functional well-being	Lung cancer subscale
Cough	0.34				−0.21	−0.16	−0.13	−0.26
Dyspnea		0.36			−0.31	−0.26	−0.22	−0.33
Pneumonitis	0.09	0.13			−0.07	−0.07	−0.04	−0.10
Pleuritic pain	0.07	0.09			−0.13	−0.14	−0.07	−0.13
Esophagitis			0.67		−0.29	−0.33	−0.19	−0.19
Esophageal pain			0.65		−0.25	−0.31	−0.16	−0.16
Fatigue				0.33	−0.41	−0.43	−0.32	−0.29
AE score					−0.46	−0.47	−0.31	−0.39

Abbreviations: AE = adverse event; PRO = patient-reported outcome

and PROs (including QoL) were weak to moderate, and pneumonitis was only minimally associated with patient-reported cough and shortness of breath.

Our QoL findings compare favorably with those of other studies in which average declines in QoL tended to be longer lasting.[10,12,14] Both Radiation Therapy Oncology Group study 0617 and the pooled results of 2 prospective clinical trials comparing concurrent chemotherapy or cetuximab showed significant declines in overall QoL and physical functioning that remained at 3 months after RT.[10,12] We found clinically meaningful declines in TOI and physical well-being at the end of RT, but neither of these remained meaningful 3 months later. Only 65% of patients in our study received concurrent chemotherapy, and the details of this use are not completely known so the utility of direct comparisons with these research trials that included concurrent chemotherapy for all patients is limited. However, we found that a substantial percentage of patients had clinically

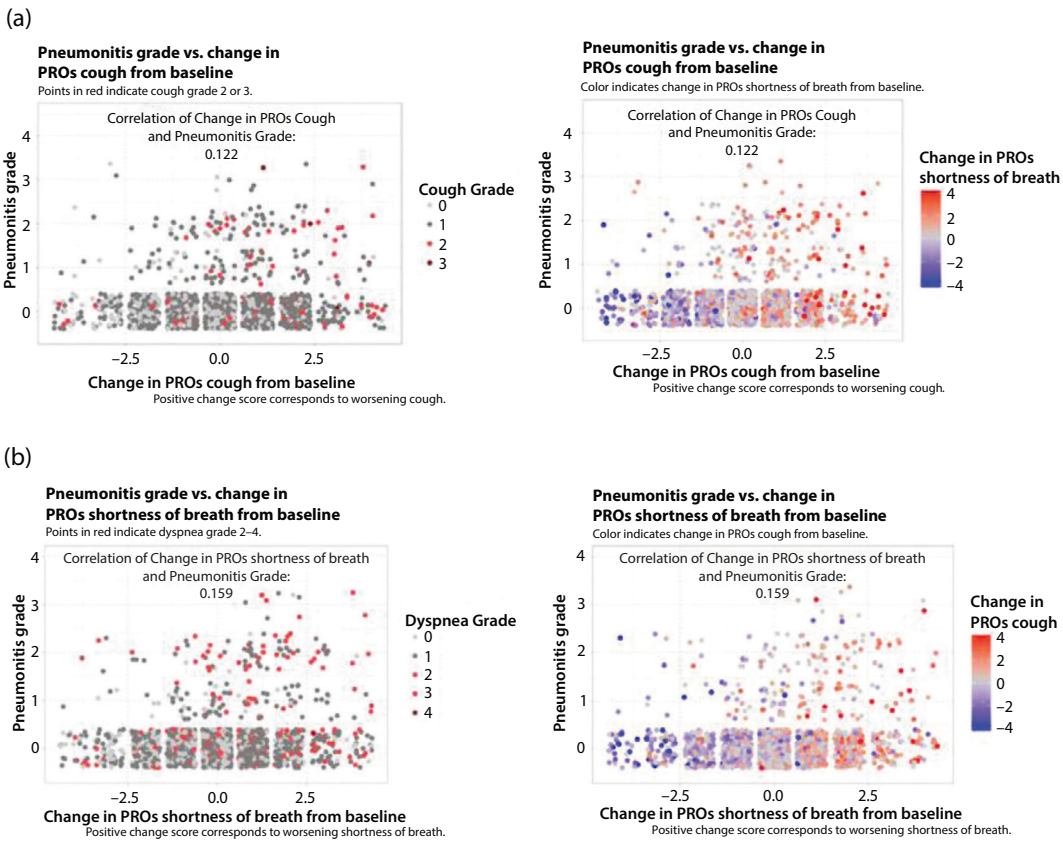

Fig. 2. Scatter plot of pneumonitis grade versus (A) change in patient-reported cough from baseline, and (B) change in patient-reported shortness of breath from baseline.

meaningful improvements in QoL during and after RT, which explains why the mean changes in QoL are not more pronounced in our cohort. Moreover, we did not find statistically significant differences in QoL changes for those patients who did or did not receive chemotherapy with RT.

AEs in our study were significantly associated with clinically meaningful declines in QoL, with ORs ranging from 2.70 to 4.39 for esophagitis, pneumonitis, and fatigue. However, correlations between AEs and PROs (including QoL) were weak to moderate. Other investigators have similarly found fair or moderate associations between PROs and AEs across a range of cancers.[7,19,21,26-29] Specifically for lung cancer, Atherton et al.[19] found more substantial declines in QoL for patients who had higher grade toxicities during treatment, but a low correlation between PROs and AEs. We also found that the overall AE score had a stronger negative correlation with QoL than any individual AE, and that fatigue had a stronger association with QoL than any of the more lung-specific AEs. This agrees with the results of a recent single-institution analysis of patients treated with RT for head and neck cancer[28] and a survey of patients with lung cancer who rated global symptoms as more important than more specific disease symptoms or side effects.[30]

Our results underscore the importance of PRO data in evaluating the effect of treatment on patient well-being. AEs have a clearly defined scale, but their relatively weak associations with QoL suggest that they are unable to capture the overall impact of treatment. This is further underscored by the low-moderate correlation between AE score and the general PRO "I am bothered by the side effects of treatment" (R = .37), which has previously been investigated as a single-item measure of overall treatment toxicity.[27] Patient input is clearly needed to assess the impact of toxicity, even if only a single item is used for efficiency. This is likely to become increasingly more important as we shift to providing more virtual care, an environment in which some AEs are more difficult to capture.

Our study also highlights the challenges for clinicians in grading toxicities for patients with lung cancer, especially those that are common at baseline in this patient population. Associations between clinician and patient reports for cough, dyspnea, and fatigue were moderate at best, with correlation coefficients of 0.34, 0.36, and 0.33, respectively. On the other hand, the association between esophagitis and trouble swallowing, which is typically not present at baseline, was much stronger with a correlation coefficient of 0.67. This may be because esophagitis is easier to quantify than more subjective toxicities[31] that are more easily attributable to RT or because medications are readily available to treat this side effect during RT.

The reasons for the very weak associations between pneumonitis and both cough and shortness of breath are less clear, because these are typically symptoms for this toxicity. This is more complicated because a single toxicity typically causes multiple symptoms, including low-grade fever, which is not a PRO in our study. However, some patients with grade 2 or 3 pneumonitis surprisingly reported improved cough and/or shortness of breath. One possible explanation for these results is that pneumonitis generally occurs several weeks after RT when patients are not seen weekly. Conceivably, treatment of pneumonitis with steroids would improve symptoms by the next follow-up visit when PROs are provided, but still recorded as a toxicity requiring intervention at that time. Regardless of the reasons, this discrepancy is a clear example of the utility of recording AE grades in addition to PROs to monitor toxicity.

The major strengths of this study are the number of patients included and its applicability to the routine clinical environment. Patients were treated at 24 institutions throughout the state of Michigan, ranging from smaller community practice settings to large academic institutions. The quality consortium also facilitated prospective data collection, which undoubtedly improved the response rate. However, the major limitation remains missing data, particularly at the later follow-up times. The response rate at the end of RT was similar to the rate before treatment, and decreased by 20%, 43%, and 60% at 1, 3, and 6 months after RT. Although some of this attrition was likely due to patient mortality, there also could be other nonrandom factors contributing. However, the response rates in our study are reasonable for LALC, particularly for patients not treated as part of a clinical trial.[10,12] Another limitation of our study was that recurrence rates were not collected and could not be incorporated into our analysis.

Conclusions

Patients treated with definitive RT or chemotherapy for LALC in a statewide consortium experienced clinically meaningful declines in QoL that peaked at the end of treatment when AEs were also at a maximum. On average, recovery or improvement was rapid and by 6 months after treatment, an equal number of patients had clinically meaningful improvements as declines in QoL. Clinician-reported AEs were associated with clinically meaningful declines in patient-reported QoL, but correlations between AEs and QoL (and other PROs) were only weak to moderate. This suggests that treatment-related AEs account for only a portion of QoL changes that patients experience, and reinforces the importance of PRO data to better understand the effect of cancer treatment on patient well-being. Future research should assess whether earlier detection of PRO changes could allow for interventions that reduce the frequency of treatment-related clinically meaningful declines in QoL.

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