Electronic patient-reported outcomes monitoring during lung cancer chemotherapy: A nested cohort within the PRO-TECT pragmatic trial (AFT-39)

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ABSTRACT

Objectives: Patients with lung cancer have high symptom burden and diminished quality of life. Electronic patient-reported outcome (PRO) platforms deliver repeated longitudinal surveys via web or telephone to patients and alert clinicians about concerning symptoms. This study aims to determine feasibility of electronic PRO monitoring in lung cancer patients receiving treatment in community settings.

Methods: Adults receiving treatment for advanced or metastatic lung cancer at 26 community sites were invited to participate in a prospective trial of weekly electronic PRO symptom monitoring for 12 months (NCT03249090). Surveys assessing patients' satisfaction with the electronic PRO system were administered at 3 months. Descriptive statistics were generated for demographics, survey completion rates, symptom occurrence, and provider PRO alert management approaches. Pairwise relationships between symptom items were evaluated using intra-individual repeated-measures correlation coefficients.

Results: Lung cancer patients (n = 118) participating in electronic PROs were older (mean 64.4 vs 61.9 years, p = 0.03), had worse performance status (p = 0.002), more comorbidities (p = 0.02), and less technology experience than patients with other cancers. Of delivered weekly PRO surveys over 12 months, 91% were completed. Nearly all (97%) patients reported concerning (i.e., severe or worsening) symptoms during participation, with 33% of surveys including concerning symptoms. Pain was the most frequent and longest lasting symptom and was associated with reduced activity level. More than half of alerts to clinicians for concerning symptoms led to intervention. The majority (87%) would recommend using electronic PRO monitoring to other lung cancer patients.

Conclusions: Remote longitudinal weekly monitoring of patients with lung cancer using validated electronic PRO surveys was feasible in a multicenter, community-based pragmatic study. A high symptom burden specific to lung cancer was detected and clinician outreach in response to alerts was frequent, suggesting electronic PROs may be a beneficial strategy for identifying actionable symptoms and allow opportunities to optimize well-being in this population.

Abbreviations: **PROs**, patient-reported outcomes; **EORTC QLQ-C30**, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

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1. Introduction

Lung cancer is the third most commonly diagnosed cancer with more than 200,000 cases and the leading cause of cancer death with more than 130,000 fatalities nationally estimated for 2020 [1,2]. Despite increasing survival rates [1], more than 90% of lung cancer patients still report uncontrolled symptoms (e.g. dyspnea, cough, pain), which negatively impact their quality of life [3]. However, symptoms are commonly missed or underestimated by providers caring for cancer patients [4]. Therefore, systems to remotely monitor patient-reported outcomes (PROs) have been developed, with studies demonstrating improved detection of disease progression and reduced healthcare costs [5,6]. While collection of web-based electronic PROs (PROs) have been used in controlled trials and as part of survivorship databases [7], their feasibility in routine care settings for detection of and management of treatment intolerance in lung cancer patients is unknown.

Electronic PRO software platforms can be used to deliver web-based or telephonic surveys to ambulatory patients. These platforms utilize algorithms that automatically alert clinicians at predetermined thresholds for concerning symptoms, which may require further testing or treatment. Electronic PRO platforms have been demonstrated to reduce emergency room visits and improve health-related quality of life and overall survival in cancer patients in prospective and population-based research [8,9]. A ongoing multi-site cluster-randomized trial ("PRO-TECT" (AFT-39), ClinicalTrials.gov NCT03249090) is investigating the clinical utility of electronic PRO implementation in community oncology practices for patients receiving treatment of advanced or metastatic cancer. The feasibility and acceptability of PROs for monitoring symptoms during treatment in the community setting of advanced or metastatic lung cancer patients, who are expected to be have significant functional limitations and other potential barriers to electronic PRO use, has not been determined. Therefore, the objective of this work was to examine PRO survey completion rates, provider management strategies of PRO alerts, and patient satisfaction with electronic PRO monitoring in a cohort of patients with lung cancer nested within the PRO-TECT pragmatic clinical trial.

2. Methods

2.1. Study population and setting

The PRO-TECT trial enrolled adult patients with advanced or metastatic cancer of any type (except leukemia or indolent lymphoma) (Table 1) receiving systemic therapy (including chemotherapy, immunotherapy, and/or targeted therapies). Participants were randomized to report PRO symptoms weekly at 26 US community oncology sites for up to one year versus use of patient- and clinician-level educational materials for symptom management in a control arm. Institutional Review Board (IRB) approval was obtained at each participating site prior to enrolling subjects at that site. The subset of patient participants with lung cancer and using the PRO system was included in this analysis. Electronic PRO symptom surveys were delivered via a stand-alone electronic PRO platform that was not tethered to patient portals or an electronic health record (EHR) system. Participants received an electronic prompt by email or automated telephone call each week reminding them to complete a brief symptom survey either via web/smartphone or the automated telephone system called Interactive Voice Recording (IVR). The delivery method was a patient choice up-front. Missed surveys led to an automated reminder message (at 24 h) and subsequently a reminder (phone call, email, or in-person) from the trial research assistant at the treating clinic, if needed (Fig. 1).

2.2. Electronic PRO

Symptoms were assessed using the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [10–13] items for pain, nausea, vomiting, constipation, diarrhea, appetite, dyspnea, insomnia, and depression and their key attributes of frequency, severity, and interference with functioning [14]. PRO-CTCAE items are scored using a 5-point ordinal verbal descriptor scale (never to almost constantly for frequency, none to very severe for severity, and not at all to very much for interference with functioning) [15]. Skip pattern logic was used whereby if frequency was reported as "never," the severity and interference items for that symptom were skipped. PRO questions about physical function (patient-reported Eastern Cooperative Oncology Group [ECOG] performance status [16]), falls, and financial toxicity were also asked. Free text boxes allowed patients to optionally write in symptoms and comments. Provider alerts were sent to a practice nurse or provider at their treating site when a symptom item response was concerning (i.e. was graded as severe or very severe, the worst two response options for frequency, severity, or interference); worsened by 2 levels from the prior survey (i.e. was graded none and increased to moderate the following week); or free text was entered by the patient or caregiver. For a symptom measured on multiple attributes (e.g., pain frequency/severity/ interference), only one alert was sent if the alert-triggering criteria for a concerning symptom was satisfied by more than one of the attributes related to that symptom.

Table 1
PRO participants by cancer type.

Cancer Type	N (%)
Bladder/Urothelial	17 (2.9%)
Brain	0 (0%)
Breast	97 (16.4%)
Cervical	5 (0.8%)
Colorectal	100 (16.9%)
Gastro-Esophageal/ Stomach	25 (4.2%)
Gallbladder/Bile Duct	8 (1.3%)
Head and Neck	2 (0.3%)
Kidney	19 (3.2%)
Liver	3 (0.5%)
Lung	118 (19.9%)
Lymphoma	3 (0.5%)
Melanoma	11 (1.9%)
Myeloma	28 (4.7%)
Neuroendocrine/Carcinoid	7 (1.2%)
Non-Hodgkin's Lymphoma	0 (0%)
Ovarian	40 (6.7%)
Pancreatic	37 (6.2%)
Prostate	33 (5.6%)
Sarcoma/GIST	10 (1.7%)
Skin	0 (0%)
Testicular	0 (0%)
Thyroid	1 (0.2%)
Uterine	19 (3.2%)
Unknown (cancer of unknown primary)	9 (1.5%)
Other	1 (0.2%)
Total	593

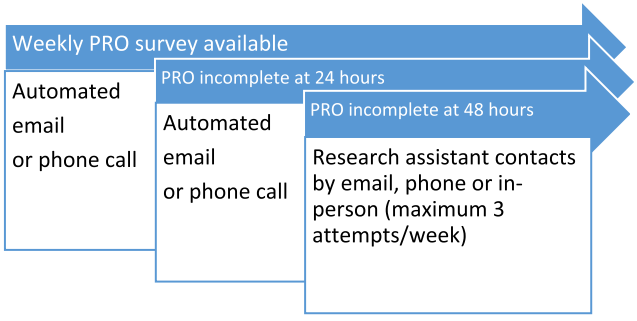


Fig. 1. Weekly electronic PRO survey delivery and reminder schedule.

2.3. Additional surveys

Additional surveys were delivered throughout the study period. Quality of Life (QOL) was measured at enrollment and every 3 months [using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)] [17]. At 3 months, patients completed a survey assessing their satisfaction with the remote electronic PRO system using a 5-point ordinal verbal descriptor scale for agreement with the item (strongly disagree to strongly agree). In response to each alert for concerning symptoms, the practice nurse or research assistant completed a form in real-time recording what clinical actions were taken in response to the alert.

2.4. Analysis

Prior to analyses, all weekly surveys distributed after a patient went off study (e.g., death) were discarded. PRO survey responses and clinician management strategies were examined. Frequencies and proportions were used to describe categorical variables and median (ranges) and means (standard deviations) were used to describe continuous variables. Student's *t*-test was used for comparing means and chi-squared test for comparing frequencies. For determining frequency of alerts for concerning symptoms, only one alert was tabulated for each symptom type even if multiple attributes met alert-triggering criteria. Pairwise relationships between co-occurring dichotomous symptom alert items per weekly survey with each other were evaluated using intra-individual repeated-measures correlations after accounting for the clustered nature of the weekly data [18]. Close to medium effect sizes ($r_{rm} > 0.2$) were reported.

Free text responses were analyzed for frequency after typos were corrected and similar words (e.g. coughing and cough) were recoded. Words related to the side of the body affected by the symptom (e.g. left side), time course, and common descriptors were excluded; words related to location (e.g. back) were retained. The remaining words in the responses were ranked by frequency of occurrence across entries and per patient. Average duration of symptoms was calculated as a mean based on the average number of consecutive weeks a concerning symptom was reported, per patient, and as the total number of weekly records a concerning symptom was reported, averaged over the number of patients who reported such a symptom.

Patient feedback responses were summarized as the percentage of patients agreeing or strongly agreeing with each satisfaction survey question. Missing responses for two patient feedback survey questions added after study start were removed. Patient satisfaction was operationalized as ≥75% of patients recommending the remote electronic PRO system to other patients and feasibility was operationalized as ≥75% completion of surveys a priori, based on prior work [19].

3. Results

3.1. Parent study enrollment

For the parent PRO-TECT study, 1444 patients were assessed for eligibility with 1351 identified as eligible including 597 patients enrolled to the PRO arm, 600 patients enrolled in the control arm, and 154 refusals (11.4%). For the ineligible patients (n = 93; 6.4%), reasons included cognitive issues (n = 18; 19.4%), language other than English, Mandarin, or Spanish (n = 4; 4.3%), and otherwise not meeting inclusion criteria due to disease stage or treatment characteristics (n = 71; 76.3%). Refusal reasons included not interesting/willing to complete surveys (n = 41; 26.6%), survey time requirements (n = 36; 23.4%); not wanting to be contacted between visits (n = 4; 2.6%), too sick/physically impaired (n = 13; 8.4%), and other/missing (n = 60; 38.9%). Of enrolled patients, all had metastatic cancer except one (an advanced lung cancer patient in the control arm). Six patients (n = 4 in the PRO arm and n = 2 in the control arm) were excluded after enrolment due to not receiving systemic therapy. The remaining retained 593 PRO participants were analyzed here.

3.2. Demographics

Analysis of the 118 lung cancer patients enrolled to PRO use from 22 sites between October 2017 and May 2020 was done. All lung cancer patients enrolled to PRO use had metastatic disease. Mean time from lung cancer diagnosis was 1.84 (sd 2.69) years and time from being found to have metastatic lung cancer was 1.32 (sd 2.27) years. The majority of lung cancer patients received chemotherapy (recorded at enrollment, n = 64; 54%). Systemic treatments at enrollment included chemotherapy only (n = 34; 28.8%), immunotherapy only (n = 44; 37.3%), targeted therapy only (n = 10; 8.5%), chemotherapy plus immunotherapy (n = 29; 24.6%), and all three modalities (n = 1; 0.8%). Baseline demographic characteristics as well as survey mode and prior technology use are presented in Table 2 for participants with lung cancer compared to all other cancer type participants. Lung cancer patients were older (mean 64.4 vs 61.9 years, p = 0.03), had worse performance status (p = 0.002), more comorbidities (p = 0.02), and less technology experience than other cancer patients. Individual EORTC QLQ-C30 items at baseline also were examined for differences from other cancer patients. Patients with lung cancer reported difficulty with taking a long walk (p = 0.02), shortness of breath (p < 0.001), remembering (p = 0.005), worrying (p < 0.001), and concentrating (p = 0.02) more frequently than patients with other types of cancer. Fewer lung cancer patients reported problems with diarrhea compared to other cancer patients (p 0.02). Characteristic of lung cancer patients who opted for IVR were compared to lung cancer patients who chose web-based electronic PRO completion (Table 3). There was no difference in mean age (65.3 vs. 63.9 years, p = 0.45) amongst IVR versus web-based PRO completion users. Education levels and technology experience were lower in the IVR than the web-based group (p = 0.009).

3.3. Follow-up

At time of this analysis (July 2021), endpoints were available for all (n = 118) lung cancer patients enrolled to PROs. The median study participation time was 44.5 weeks (interquartile range from 25 to 52 weeks). The final status for participants were as follows: 44% (n = 52) had completed study follow-up of 1 year, 15% (n = 18) had died, 20% (n = 23) went to hospice, 18% (n = 21) had gone off study due to change in oncology practice or discontinuation of treatment plan, and 3.4% (n = 4) voluntarily withdrawn from the study.

3.4. Survey completion

The majority of expected weekly PRO surveys (91% [3988/4396], ranging from 85% to 97% at each weekly PRO survey timepoint) were completed by the participating lung cancer patients (Fig. 2). Survey completion rate per patient was a median of 96.2% (IQR 87–100%). The research assistants made 669 reminders to complete surveys to lung cancer PRO participants (15.2% of delivered surveys). Of the 4396 weekly PRO symptom surveys, 33% (n = 1470) triggered at least one alert to clinicians for a concerning symptom (i.e. PRO-CTCAE item was graded severe/very severe, or worsening by two points from prior response, free text response entered), which included 3305 individual symptom alerts (5.4% of the total survey items). On average, 0.75 (SD 1.42) alerts were generated per patient per week with a range of 0 to 11 alerts per patient per week. The frequency of patients with alerts during the study period is shown in Fig. 3, with the highest proportion of patients generating an alert in their second week on study (58%). 86% (n = 101/118) of patients reported 3 or more different types of symptoms that triggered alerts. Only 3 patients (3/118, 2.5%) reported no concerning symptoms at all.

Table 2
Baseline characteristics of patients with lung cancer compared to patients with other cancer types participating in PROs.

	Lung cancer (n = 118)	Other cancers (n = 475)	p value
Age (mean, sd)	64.4 (9.9)	61.9 (11.9)	0.03
ECOG score (n, %)			0.002
0	41 (34.7%)	211 (44.5%)	
1	59 (50.0%)	218 (46.0%)	
2	14 (11.9%)	44 (9.3%)	
3	4 (3.4%)	1 (0.2%)	
Comorbidities^ (n,%)			0.02
0–1	67 (56.8%)	323 (68.0%)	
2–4	51 (43.2%)	152 (32.0%)	
EORTC Score (mean, sd)*			
EORTC QLQ-C30 Summary Score	76.6 (15.0)	78.35 (14.73)	0.24
EORTC QLQ-C30 Global Health Status	63.98 (21.01)	66.68 (21.30)	0.22
EORTC QLQ-C30 Physical Function	71.12 (21.83)	75.17 (20.87)	0.06
Gender (n, %)			0.61
Male	49 (42%)	185 (38.9%)	
Female	69 (58%)	290 (61.1%)	
Self-reported race (n, %)			0.19
American Indian or Alaskan Native	3 (2.6%)	8 (1.7%)	
Asian	0 (0%)	2 (0.4%)	
Black	11 (9.4%)	88 (18.7%)	
Pacific Islander	0 (0%)	2 (0.4%)	
Multiple	0 (0.0%)	1 (0.2%)	
White	103 (88%)	370 (78.6%)	
Self-reported ethnicity (n,%)			0.89
Hispanic	3 (2.5%)	11 (2.3%)	
Education			0.06
Up to 8th	2 (2%)	8 (1.7%)	
9th to 11th	12 (10%)	23 (4.9%)	
High School/GED	39 (33%)	134 (28.8%)	
Some College	39 (33%)	131 (28.2%)	
Associates Degree	5 (4%)	34 (7.3%)	
College Degree	12 (10%)	79 (17.0%)	
Advanced Degree	8 (7%)	56 (12.0%)	
Employment			0.07
Full-time	11 (9.3%)	83 (17.5%)	
Part-time	13 (11.0%)	59 (12.4%)	
Not currently working	94 (79.7%)	332 (70.0%)	
Marital Status			0.96
Single	11 (9.3%)	47 (9.9%)	
Married/Partnered	75 (63.6%)	310 (65.3%)	
Separated/Divorced	18 (15.3%)	64 (13.5%)	
Widowed	14 (11.9%)	54 (11.4%)	
Prior computer/device use			0.03
Never	19 (16%)	43 (9.1%)	
Ever (once a week to daily)	99 (83.9%)	432 (90.9%)	
Prior email use			0.03
Never	31 (26%)	83 (17.5%)	
Ever (once a week to daily)	87 (73.7%)	392 (82.5%)	
Prior internet use			0.1
Never	23 (19%)	64 (13.5%)	
Ever (once a week to daily)	95 (80.5%)	411 (86.5%)	
PRO method			0.35
IVR	47 (39.8%)	167 (35.2%)	
Web-based	71 (60.2%)	307 (64.8%)	

^number of comorbidities of arthritis, lung disease, heart disease and/or diabetes by patient self-report.

* Quality of Life (QOL) was measured with European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C30)[16].

3.5. Symptom burden

Table 4 shows the frequency of lung cancer patients reporting concerning PRO-CTCAE symptoms. Pain was the most frequently reported concerning symptom and was noted by 83.1% of patients with episodes lasting 2.87 weeks on average and reported during the study period for 8.3 weeks overall on average. Other symptoms with the longest episode duration across patients were dyspnea (mean duration 2.02 weeks) and reduced activity (1.98 weeks). Close to moderate correlations were found between pain and reduced activity level ($r_{rm} = 0.29$), and between vomiting and nausea ($r_{rm} = 0.3$). The correlations between appetite and reduced activity level ($r_{rm} = 0.25$) and between appetite and nausea ($r_{rm} = 0.25$) were also noticeably higher than the other pairwise correlations.

The symptoms that most commonly rapidly increased in score (i.e. from none/mild to severe/very severe in a single week) across patients were frequency of diarrhea (n = 75 weekly surveys), changes in appetite (n = 58), frequency of nausea (n = 57), severity of insomnia (n = 52), frequency of pain (n = 51), and severity of constipation (n = 53). 49% (n = 58) of patients completing PROs reported "other symptoms" in free text entries among 252 weekly reports over the course of the study. The most common of these write-in free-text symptoms were pain (n = 38), cough (n = 18), shortness of breath (n = 17) and back pain (n = 13).

Table 3
Characteristics of patients with lung cancer choosing IVR for PRO completion compared to patients choosing web-based.

	IVR (n = 47)	Web-based (n = 71)	p value
Age (mean, sd)	65.28 (9.59)	63.87 (10.13)	0.45
Gender (n, %)			0.563
Male	18 (38.3%)	31 (43.7%)	
Female	29 (61.7%)	40 (56.3%)	
Education*			0.009
Up to 8th	1 (2.2%)	1 (1.4%)	
9th to 11th	8 (17.4%)	4 (5.6%)	
High School/GED	21 (45.7%)	18 (25.4%)	
Some College	12 (26.1%)	27 (38.0%)	
Associates Degree	2 (4.3%)	3 (4.2%)	
College Degree	0 (0.0%)	12 (16.9%)	
Advanced Degree	2 (4.3%)	6 (8.5%)	
Prior computer/device use			< 0.001
Never	17 (36.2%)	2 (2.8%)	
Ever (once a week to daily)	30 (63.8%)	69 (97.2%)	
Prior email use			< 0.001
Never	26 (55.3%)	5 (7.0%)	
Ever (once a week to daily)	21 (44.7%)	66 (93.0%)	
Prior internet use			< 0.001
Never	21 (44.7%)	2 (2.8%)	
Ever (once a week to daily)	26 (55.3%)	69 (97.2%)	

* 1 missing response.

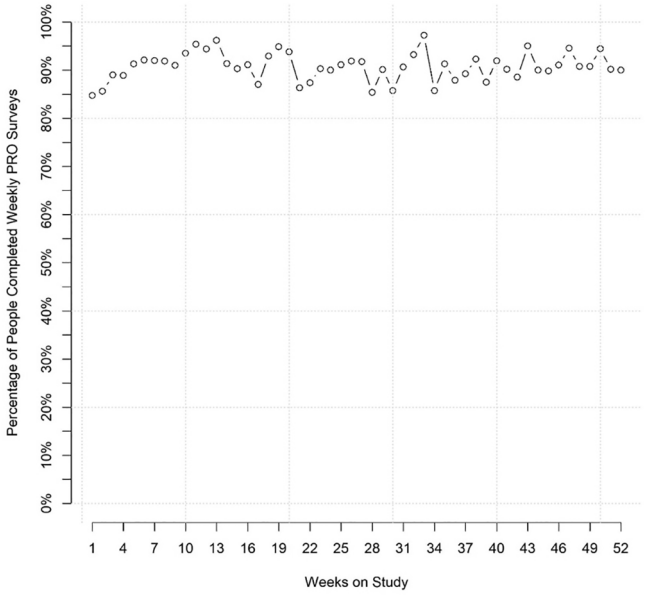


Fig. 2. Electronic PRO survey completion rates by lung cancer patients over 12 months on study.

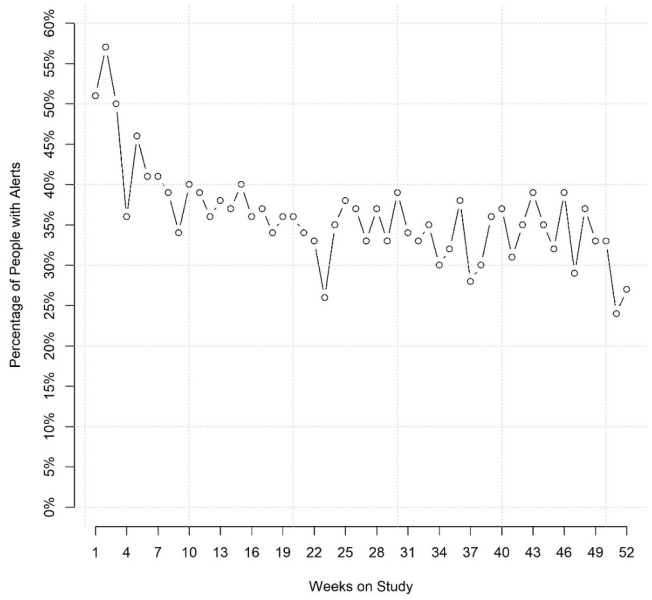


Fig. 3. Frequency of patients with alerts for concerning symptoms during study period.

Table 4
Frequency of metastatic lung cancer patients reporting concerning symptoms by type and their mean duration.

Symptom Type	% (n = 118)	Mean continuous duration (weeks)*	Mean reported weeks**
Pain	83.1%	2.87	8.3
Reduced Activity	58.5%	1.98	4.99
Diarrhea	51.7%	1.34	3.51
Reduced Appetite	51.7%	1.16	2.28
Dyspnea	50.8%	2.02	5.28
Constipation	47.5%	1.07	2.20
Nausea	48.3%	1.28	3.65
Fallen	43.2%	1.23	2.55
Insomnia	39.0%	1.29	3.89
Depression	37.3%	1.58	4.93
Vomiting	22.0%	1.06	2.27
Financial Toxicity***	15.3%	n/a	n/a

* Mean continuous duration is calculated as the average number of consecutive weeks a concerning symptom was reported, per patient.

** Mean reported weeks is calculated as the total number of weekly records a concerning symptom was reported, averaged over the number of patients who reported such a symptom.

*** Financial Toxicity was collected every 4 weeks.

Fig. 4 shows more commonly written in symptoms with increased density in the word cloud.

3.6. Alert management

Management by physicians and nurses in response to the 1470 alerts generated for concerning PROs during the study period is presented in Table 5. An alert may have had more than one management strategy. Overall, 55.9% (n = 822) of alerts received resulted in a provider contacting a patient and/or delivering an intervention. The most common management strategies were planned discussion of the PRO alert at the next visit (19.1%) and coaching on self-management or over the counter treatments (18.4%). For 18.3% of alerts (n = 269), the treating clinician reported changing the care plan due to the alert, including prescribing medications and expediting evaluation through the clinic, emergency department, and/or by imaging.

Fig. 4. Most common words per patient written in "other symptoms" survey item.

Table 5
Nursing interventions for concerning symptom alerts.

Intervention	n	% (n = 1470)*
Coached patient to self-manage or treat symptoms	270	18.4%
Prescribed or changed medications (supportive drugs and/or cancer treatment)	162	11%
Expedited a clinic appointment	68	4.6%
Ordered imaging and/or laboratory test(s)	28	1.9%
Referred to the emergency department	11	0.7%
Planned to address concern at next clinic visit	281	19.1%

* More than one intervention may have been taken per alert.

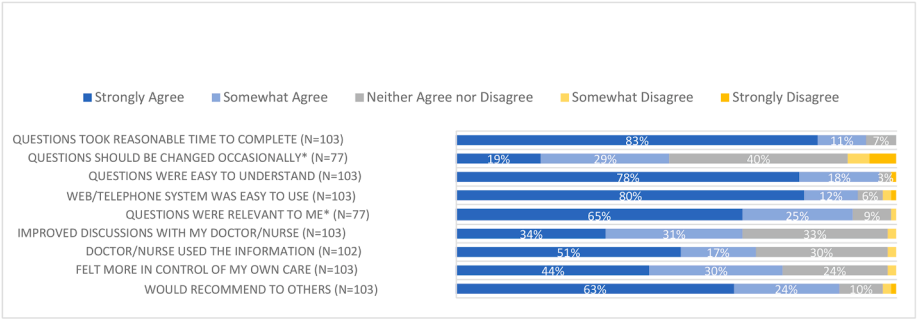
3.7. Participant feedback

Results of 103 available patient feedback surveys are presented in Fig. 5. The majority of patients provided positive feedback, with 87% (n = 90/103) who would recommend the system to other patients and 89% (n = 69/77) who felt the symptom questions were relevant. Patients answered that the PRO data improved discussions with their provider 65% (n = 67/103) of the time and that the provider used the information 67% (n = 69/102) of the time. Patients also reported that using PROs increased control of their care (74%, n = 76/103).

4. Discussion

4.1. Remote electronic PRO monitoring in lung cancer patients

The findings of this study demonstrate the potential utility of automated electronic PRO surveys for long-term monitoring of symptoms remotely in lung cancer patients. Based on the excellent overall consent rate in the parent PRO-TECT study (88.6%), lung cancer patients were willing to participate in using electronic PROs. As expected, lung cancer patients were older, had worse performance status and were more symptomatic at baseline than patients with other cancer types participating in electronic PROs. Yet, this study demonstrates the feasibility, relevancy, and satisfaction with weekly remote electronic PRO monitoring in lung cancer patients. Electronic PRO symptom surveys sent to lung cancer patients had high completion rates throughout the 52 week follow up period (average 91% of all delivered surveys were completed, and this ranged from 85% to 97% completion at each weekly survey time point), which is comparable to other PRO studies [8,20]. This high



* questions added after study start

Fig. 5. Lung cancer patient feedback on weekly PRO survey.

survey completion rate is notable despite the real-world community setting of this trial and the long duration of remote weekly monitoring (median 44 weeks). There was only a 3.4% withdrawal rate, demonstrating the perceived utility of participating in electronic PROs by lung cancer patients. While reminders were provided by the trial research assistants for incomplete surveys 48 h after initial survey delivery, 85% of surveys were completed by lung cancer PRO participants without the research assistant needing to provide a reminder or assistance. The use of IVR appears to be very important to PRO participation for lung cancer patients, as 40% chose the telephonic platform for PRO survey completion.

Electronic PROs appeared to detect relevant symptom burden in lung cancer patients, as alerts to clinicians were generated on one-third of weekly PRO surveys, and 97% of patients provided survey responses that generated at least one symptom alert during the study. Electronic PROs also appeared to provide valuable and actionable information to clinicians as more than half of alerts resulted in a provider action and importantly, 18% of alerts resulted in a change in clinical management, suggesting electronic PROs may serve as an early warning system for patients who require assessment prior to the next planned clinic visit. Overall, lung cancer patients reported high satisfaction with the electronic PRO system. Importantly, the majority of lung cancer patients reported that PROs were used by their clinician, increased their control over their care, and would recommend use of the system to other patients.

4.2. Clinical application of electronic PROs in lung cancer patients

This study also describes the longitudinal patient-reported symptom burden and its management in patients with metastatic lung cancer as detected by use of an electronic PRO system. The majority of existing knowledge on symptom burden during lung cancer treatment is derived from adverse event reports of clinical trials of therapeutic drugs [21], cross-sectional studies in similar patient groups [3,22–25], and reports from the FDA's Center for Drug Evaluation and Research Patient-Focused Drug Development Program [26]. Reporting of PROs from trials in lung cancer patients has largely focused on earlier stage patients after operative or medical treatments [5,27,28], and this study in metastatic lung cancer patients lends support to findings from these prior trials. This study demonstrates that by using a brief symptom survey for oncology patients with the ability to include "other" symptoms as write-ins, electronic PROs were able to alert clinicians for the most important symptoms in lung cancer patients including pain, cough, and shortness of breath [25], and that clinicians were able to respond to these alerts.

These findings suggest the potential role of electronic PROs for routine clinical care improvement in lung cancer patients [29,30]. Poorly controlled symptoms such as pain and dyspnea can be drivers of downstream complications such as emergency room visits and hospitalization, pointing to the value of electronic PROs to identify and allow management of these issues early before they worsen and lead to potentially avoidable admission [8]. Other common symptoms found by this electronic PRO were more episodic (diarrhea/constipation, reduced appetite, nausea) and presumably related to receipt of chemotherapy, suggesting prophylaxis and symptom self-management strategies could be more routinely applied earlier.

4.3. Future directions of electronic PROs in lung cancer patients

Several areas for improvement in a lung cancer specific electronic PRO questionnaire for real-world symptom monitoring were identified by this work. Analysis of write-in symptoms shows cough and the specific location of pain (e.g. back pain) were commonly reported by lung cancer patients. Future systems should incorporate the ability to capture "other" symptoms telephonically, as this was a very commonly chosen electronic PRO completion method (40%) by lung cancer patients. As electronic PRO completion by IVR was associated with less experience and access to technology than in participants who chose web-based PRO completion, IVR may allow increased access to electronic PRO use by these patient groups. IVR should be considered a routine platform option for PRO administration in similar patient populations. Future electronic PRO systems could include a mechanism for mapping "write-in" symptoms to a validated symptom library in order to be capture all patients' experiences without increasing the survey question item burden [31].

5. Limitations

There are several limitations of this study. First, patient selection to the parent trial may bias the results and so the findings from this feasibility study may not be generalizable to other oncology practices. However, the pragmatic trial design and community-based setting for participant recruitment does enable assessment of realistic refusal rates and survey completion rates for informing a future real-world study of electronic PRO use in lung cancer patients. Both the low participation refusal rate and high survey completion rates point to the feasibility and relevancy of electronic PROs for clinical remote symptom monitoring. Next, the study did rely on trial research assistants to identify participants and provide reminders for incomplete surveys after 48 h. However, non-automated reminders were used in relatively few instances of survey delivery (15%) to lung cancer patients over the 12 month follow-up period. Further, this study was not designed to evaluate barriers to electronic PRO use that have been described in minority or socioeconomically disadvantaged patient populations, which does require future investigation to increase the reach of electronic PROs to potential target populations [32]. Finally, the implementation outcomes and strategies required for increased adoption of electronic PRO monitoring use in routine practice for clinical care improvement is not answered by this work and will need to addressed in future studies. Central to this future work will be examining clinician needs for alert thresholds and their

management including whether electronic PRO platforms should be fully integrated into the EHR.

6. Summary

The use of PROs has evolved from measurement of end points in clinical trials to health information technology driven tools that can enable remote monitoring of patients and improve their symptoms [33]. Electronic PROs have increasing utility in the context of the global pandemic and the associated rise of telemedicine and may serve as valuable adjuncts to virtual care for rural or less-resourced patients or practices [34–36]. Most importantly, the findings of this study suggest that electronic PRO monitoring can empower lung cancer patients to communicate more effectively with their clinicians and enhance existing care processes. These results may improve the appropriateness of remote electronic PROs for lung cancer patients and therefore impact lung cancer specific clinical outcomes.

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CRediT authorship contribution statement

Gita N. Mody: Conceptualization, Methodology, Writing– original draft, Formal analysis. **Angela M. Stover:** Conceptualization, Methodology, Writing – review & editing. **Mian Wang:** Formal analysis, Writing – review & editing. **Bellinda L. King-Kallimanis:** Writing – review & editing. **Jennifer Jansen:** Project administration, Writing – review & editing. **Sydney Henson:** Project administration. **Arlene E. Chung:** Methodology. **Mattias Jonsson:** Methodology. **Antonia Bennett:** Methodology. **Angela B. Smith:** Writing – review & editing. **William A. Wood:** Writing – review & editing. **Alison Deal:** Formal analysis. **Brenda Ginos:** Data curation, Formal analysis. **Amylou C. Dueck:** Data curation, Formal analysis. **Deborah Schrag:** Writing – review & editing. **Ethan Basch:** Conceptualization, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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