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Research Article

The Discordance between Patient- and Clinician Reported Outcomes during (Chemo-) Radiation Therapy for Lung Cancer

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Abstract

Purpose Capturing information on toxicity in lung cancer patients during and after (chemo-)radiation is crucial for optimal symptom management. Patient Reported Outcomes (PRO) potentially improve toxicity detection by providing information directly from the patient's perspective. The aim of this study is to examine the prevalence of, and agreement between patient and clinician reported toxicity during (chemo-)radiation for lung cancer in a real world setting.

Methods An observational study was performed in lung cancer patients (n=110) treated with (chemo-)radiation with curative intent. Commonly occurring symptoms were scored at the end of treatment using EORTC QLQ-C30 and EORTC LC-13 questionnaires. Clinicians (CRO) prospectively scored these symptoms with the maximum toxicity grade at each clinical appointment during and at the end of treatment using the Common Toxicity Criteria for Adverse Events version 4.0. Symptom prevalence based on both patient and clinician data was described, as well as (dis)agreement between patient and clinician scoring ($p<0,05$).

Results Patients most often scored fatigue (n=66/110). Four of six symptoms (i.e. dysphagia, cough, dyspnea and anorexia) showed significant difference in the proportions of PRO versus CRO scores ($p<0,05$) indicating a discordance between patient and clinician report. Symptoms in most cases reported only by patients with the exception of dysphagia which was more often scored only by the clinician (12%) compared to only by the patient (6%).

Conclusion This study showed that clinician reported toxicities during (chemo-)radiation are often discordant, with most substantial underreporting of fatigue. These results emphasize the need to use patient reported outcomes in radiotherapy lung cancer care.

Keywords: Lung cancer; Toxicity; Patient reported outcomes; Radiotherapy; Symptom management

Introduction

Radiotherapy (with or without additional chemotherapy) is an important treatment option for patients diagnosed with lung cancer. Because of these treatments, patients can experience both acute and late toxicities, symptoms of which significantly impact treatment tolerance and health related quality of life (HRQoL) [1-3]. Effective symptom management is therefore essential during the intensive, often multidisciplinary lung cancer treatment. The prevalence and grade of treatment related toxicity symptoms are typically scored and monitored by clinicians using the Common Toxicity Criteria for Adverse Events (CTCAE) [4]. Moreover, these CTCAE scores are the main indicator for the currently used prediction models for toxicities such as radiation induced esophagitis and radiation pneumonitis [5].

In recent years, it has become increasingly evident that adding the patient's perspective by means of Patient Reported Outcomes (PRO) can be beneficial to improve patient centered healthcare, predicting clinical outcomes and treatment evaluation, including symptom management [6] PRO are measured using Patient Reporting Outcome Measures (PROM's), questionnaires in which a patient reports on symptoms and other aspects of their well-being [7,8].

Several studies have assessed the relationship between clinician reported outcomes (CRO) and PRO, showing that solely clinical reporting of symptoms using the CTCAE has a limited reliability and does not accurately reflect the complete patient's experience [9-11]. Few studies have researched the use of PRO in a curative radiotherapy (RT) setting. A study among 116 lung cancer patients undergoing thoracic (chemo-)radiation reported PRO showed a greater severity of symptoms compared to that reported by the clinician, and that there was only a fair to moderate agreement between the CRO and PRO symptom data [12]. Several studies have been performed among lung cancer patients treated with other types of therapy. A study among lung and genitourinary cancer patients treated with mostly targeted therapy or chemotherapy showed that there was relatively high agreement between PRO and CRO data in case of objectively observable symptoms, while more subjective symptoms such as fatigue and dyspnea showed lower agreement [13]. Another longitudinal study by Basch, et al. showed that among lung cancer patients receiving chemotherapy, patients report their symptoms earlier and more frequently, compared to their clinicians [14]. Moreover, research has shown that the use of PROMS for symptom monitoring leads to improved Health related Quality of Life (HRQoL) and overall survival [15,16]. The knowledge of this discordance in lung cancer patients treated with curative intent (chemo)radiotherapy is limited. Besides, while most of the evidence of PRO and CRO data was derived from clinical trials, few studies have examined the relationship between PRO and CRO data in a setting that reflects routine clinical practice for lung cancer patients receiving (chemo-) radiation in a real-world setting. This study aims to analyze the concordance of prospectively scored symptoms during and after curative (chemo-)radiation routine clinical care treatment in lung cancer patients and their treating radiation oncologists.

Materials and methods

Patient sample

An observational study was performed in an unselected random cohort of patients diagnosed with lung cancer and treated with (chemo-)radiation with curative intent. Patient data was routinely collected during treatment with the possibility of opting out of data collection (pursuant to Dutch national legislation prior to 25 May 2018). Patients were treated within the Netherlands Cancer Institute /Antoni van Leeuwenhoek between June 2016 and January 2018.

Patient self-reported symptoms

Patients were asked to, electronically or in paper form, complete the Dutch version of the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) version 3.0 and the Lung Cancer C-13 (EORTC LC-13) module as part of routine clinical care at the end of radiotherapy or chemo-radiation treatment [17]. The EORTC-QLQ-C30 consists of thirty items that can be analyzed as six functional scales, three symptoms scales and six single items symptoms. The EORTC LC-13 is a lung cancer specific questionnaire comprised out of multi- and single-item lung cancer associated symptoms{Bergman, 1994 #526}. The patient reports their symptoms over de past month. In this study only a selection of the symptoms' scales were used for the analysis. The patients addressed the items within a timeframe described as 'during the last week' and scored the items on a four-point Likert scale ('1=not at all', '2= a little', '3=quite a bit' and '4=very much'). For the symptom items and scales a higher score reflects a greater intensity of the symptoms.

Clinician reported symptoms

Clinicians (radiation oncologists) prospectively scored the symptoms in a toxicity report electronically weekly during and at the end of the five to six weeks treatment using the CTCAE version 4.0. A predefined list of common thoracic toxicities in the Electronic Health Record (EHR) was used that included the following symptoms: chest wall pain, cough, dysphagia, dyspnea, anorexia, dermatitis, fatigue, nausea, pneumonitis, and weight loss. Besides these common toxicities, there was a possibly to score an additional elaborate list of less common toxicities available. The

CTCAE grades the severity of adverse events on a scale from 1 to 5 in which grade 1 reflects asymptomatic or mild symptoms, and grade 5 reflects death related to the adverse event [4]. For this analysis, we used the maximum CTCAE score that was recorded up until the end of treatment for each symptom. The data was extracted automatically from the EHR.

Analysis

Patient characteristics are presented as number and percentage of the total sample. To calculate the patient reported symptom score using the EORTC questionnaires we defined a cut-off point with a score of 3 or higher. The PRO prevalence score was compared with CRO data using a CTCAE cut-off score of grade 2 or higher to reflect clinically relevant symptoms. This approach has been used in previous research [18,19]. For sensitivity reasons the clinician scored symptoms with a cut-off score of ≥1 grade, and PRO symptoms with a cut-off of ≥2 and a cut-off of 4 were also calculated. The prevalence of the symptoms was obtained by dividing the total number of cases by the total sample used for this analysis (n=110). The prevalence rates were calculated for both the PRO and CRO reported symptoms based on the previously decided cut-off scores.

At last, the agreement between the scoring of patients and clinicians was defined for each symptom. We calculated the proportion of patients with a symptom present and reported by 1) both the patient and their clinician, 2) the patient only, 3) the clinician only, as well as the proportion of absent symptoms (reported by both PRO and CRO). Lastly the proportions of present/absent symptoms of the PRO and CRO data were compared using the Pearson chi-squared (in case of <20% of the cells with expected frequencies <5) and Fisher´s exact test (in case of >20% of the cells having expected frequencies <5). A p-value of <0.05 was considered statistically significant.

Results

Sample

Between June 2016 and January 2018, 432 consecutive lung cancer patients were treated with (chemo-)radiation. 114 patients (32%) were not willing/able to receive the questionnaires. Of the 318 patients that received it, 196 patients (60%) returned the questionnaire. 56 patients (18%) were excluded because of incomplete questionnaires and 30 patients (9%) because of incomplete CRO data (less than two data points during data collection). The final study population included 110 patients (35%) (Figure 1).

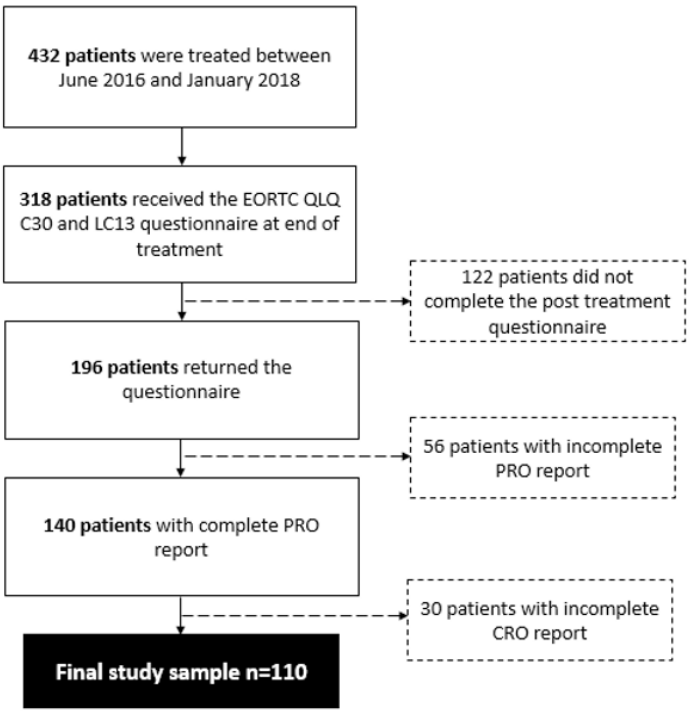


Figure 1: Flowchart of patient inclusion.

Patient sample

Most of the patients had non-small cell lung cancer (n=98, 89%) (Table 1), with the majority having stage III disease (n=78, 71%). About half of the patients were treated with concurrent chemo-radiation (n=56, 51%), the other patients were treated with either sequential chemo-radiation (n=21, 19%) or conventional radiotherapy (n=33, 30%). Most patients were older than 65 years (n=73, 66%) and had a good performance status (WHO of zero or one) (n=88, 80%).

Characteristic	n	(%)
Diagnosis		
Non-Small Cell Lung Cancer	98	(89)
Small Cell Lung cancer	12	(11)
Received treatment		
Concurrent chemo-radiation	56	(51)
Sequential chemo-radiation	21	(19)
Radiotherapy only	33	(30)
Age		
< 65 years	37	(34)
≥ 65 years	73	(66)
Gender		
Male	56	(51)
Female	54	(49)
WHO Performance status		
0	29	(26)
1	59	(54)
2	13	(12)
3	1	(1)
4	0	(0)
Missing	8	(7)
Clinical Stage		
I	1	(1)
II	13	(12)
III (NOS)	9	(8)
III	69	(63)
IV	9	(8)
Received dose (Gy)		
17x 3	11	(10)
21x 2.75	1	(1)
24x 2.4–3,3	80	(73)
25x 2–2.75	7	(6)
30x 1.5–2	10	(9)
33x 2	1	(1)
Abbreviations; WHO, World Health Organization; NOS, not otherwise specified; Gy, Gray		

Table 1 Patient and treatment characteristics (n= 110)

Patient and clinician reported symptoms

Overall, 80% (n=88) of the patients reported one or more symptoms (score of 3 or higher). The prevalence of patients' reported symptoms was higher compared to the number of clinician reported symptoms (Figure 2). There was an exception for dysphagia which was reported in 36% (n=40) of patients by the clinicians and 31% by the patients themselves (n=34). Fatigue was most often reported by patients (n=66, 60%) and showed the largest discrepancy between PRO and CRO data (n=66, 60% versus n=15, 14% respectively).

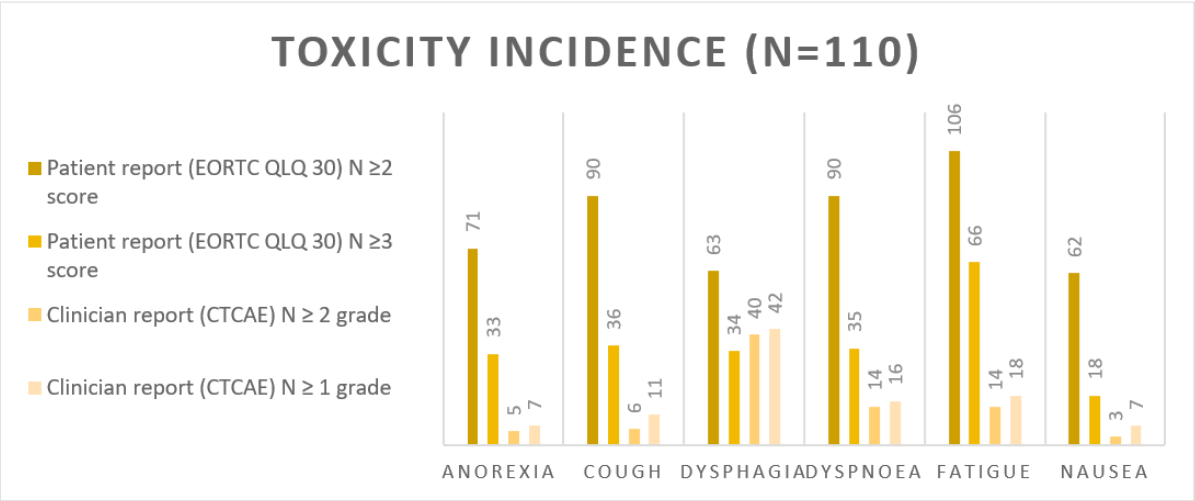


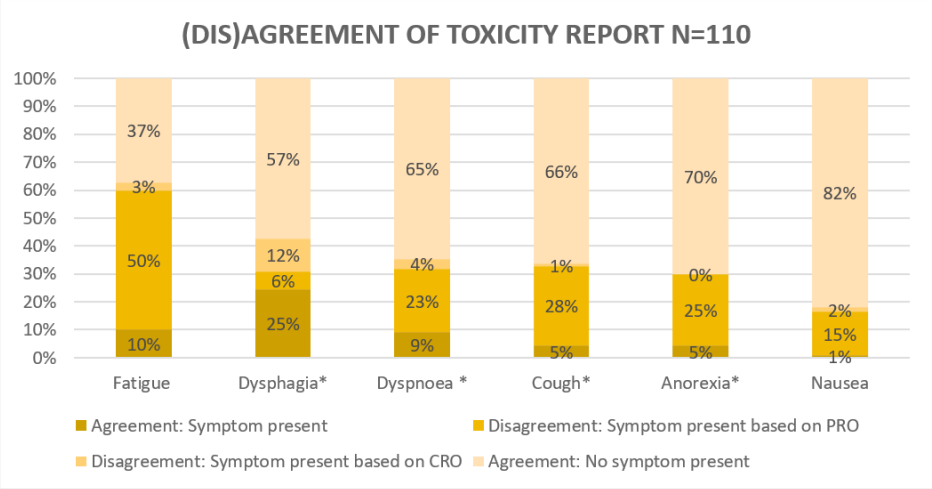
Figure 2: The prevalence of the analyzed toxicities scored by the patients and clinicians at the end of treatment (based on two different cut-offs).

In the sensitivity analyses, we applied two other cut-off points for the PRO data. Firstly, we applied a lower cut-off (≥ 2). Using this cut-off an increase was observed for all symptoms, especially for cough, going from 33 patients (30%) to 90 patients (82%), and for dyspnea going from 35 patients (32%) to 90 patients (82%). Since this cut-off also includes the reporting of mild symptoms, this indicates a relatively large proportion of patients experience mild cough and dyspnea. Moreover, using this cut-off, almost all patients (n=106, 96%) reported fatigue.

Secondly, when applying the higher cut-off of 4 we observed the following decreases in prevalence numbers (compared to our standard cut-off) for each symptom; anorexia report decreased from 33 (30%) to 15 patients (14%), cough report from 36 (33%) to 12 patients (11%), dysphagia report from 34 (31%) to 13 patients (12%), dyspnea report from 35 (32%) to 8 patients (7%), fatigue report from 66 (60%) to 25 patients (23%) and nausea report from 18 (16 %) to 6 patients (5%). When comparing these numbers with the CRO prevalence (≥ grade 2), as well as dysphagia, dyspnea was scored more often by the clinicians compared to the patients (CRO: n=14 (13%), PRO n=8 (7%). With the sensitivity analyses for the CRO data (CRO cut-off score of n ≥1 grade) the CRO reported only slightly increased symptoms (two to five additional patients per symptom) compared to the original cut-off (n ≥2 grade).

Patient and clinician agreement

Four out of six symptoms showed a significant difference in proportions (symptom present/symptom absent) between PRO report and CRO report (i.e. dysphagia p=0.00; cough, p=0.01; Dyspnea, p=0.00; anorexia, p=0.00). No significant difference was found for fatigue and nausea. Overall, the PRO and CRO agreement in case of an observed symptom was low (figure 3). For most symptoms this was 10% or less, with one exception of dysphagia with a proportion of 25% (n=27) agreement. In cases of an absent symptom the agreement was relatively high, ranging from 37% for fatigue (n=41) to 82% for nausea (n=90). The proportion of cases in where the patients reported a symptom while this was not reciprocated by the clinician, were especially high for fatigue (50%, n=55), cough (28%, n=31) and anorexia (25%, n=31). There was only a minority of cases in which the clinician reported the symptoms, while the patient did not (ranging from 1-12%). Dysphagia was the only exception with more cases of solely CRO (12%, n=13) report compared to the cases solely reported by PRO (6%, n=7).



* Significance level p<0,005

Abbreviations; PRO: Patient reported outcomes; CRO: clinician reported outcomes

Figure 3: The proportions of (dis)agreement between patient report (PRO) and clinician report (CRO) per toxicity.

Discussion

A vast discrepancy between PRO and CRO reported symptoms was found in this real world observational study among lung cancer patients treated with (chemo) radiation. Patients reported more symptoms compared to their clinicians (independent of the cut-off score). Next, there was only minor agreement between patients and clinician report in case of an observed symptom. The sensitivity analyses also showed that when looking at mild symptoms, there is an even larger number of symptoms (e.g. cough, dyspnea) that are missed by the clinician.

This study, as well as previously reported literature among lung cancer patients [13,16,20], emphasizes the unique and essential property of PROMs: giving access to symptoms from the patient perspective that could otherwise be missed. Given these substantial discordances, the use of PROMs in clinical health care is essential to reflect the patients' health status in the best possible manner. Moreover, PROMs can be used to improve symptom monitoring during clinical cancer care, which in turn leads to improved clinical outcomes such as improved HRQoL and overall survival by mechanisms of early intervention or dose modifications [15,16].

Another important finding was the high prevalence of fatigue reported by the patients and the low prevalence of clinician reported fatigue. Previous research shows that fatigue indeed is a major burden for lung cancer patients and their HRQoL during, as well as after treatment [21-23]. It has previously been reported that more subjective symptoms such as fatigue, show higher levels of disagreement between patients and clinicians [13,23]. A reason for the underreporting of fatigue by clinicians could be the fact that they consider fatigue as a treatment side effect that is difficult to treat [24]. This may be the cause of the lower perceived treatability or urgency to inquire and report fatigue [24,25]. Nonetheless, research shows that exercise, lifestyle, as well as cognitive behavioral options can be potentially beneficial for cancer patients [26-28]. Research should therefore focus on how to improve fatigue counselling and referral for lung cancer patients.

This study showed that the observed discordance between PRO and CRO data does not apply to all symptoms. This phenomenon has also been reported in other tumor sites [29]. For example, a meta-analysis comparing PRO and CRO data on radiation dermatitis in breast cancer patients found overall high levels of agreement, while for some symptoms (e.g. acute breast pain) a discordance was reported [30]. In our study, dysphagia showed a substantial higher level of agreement compared to the other symptoms. Dysphagia is caused by (chemo) radiation-induced esophagitis and, along with fatigue, is the most common acute toxicity in patients during radiotherapy or chemo-radiation [31]. Dysphagia is potentially dose-limiting and is generally treated with medication and a dietary advice [32]. Due to these implications, clinicians might be more alert to recognize and report dysphagia, which could explain the high reported prevalence.

A key strength of the present study was the representation of weekly electronic scored data in clinical radiotherapy practice by the treating clinicians. Few studies have focused on the PRO and CRO relationship within a clinical radiotherapy setting for lung cancer. Moreover, the patient population included a real-world sample of lung cancer patients treated with curative intent (chemo) radiotherapy.

Several limitations of this study need to be acknowledged. Firstly, the study has a relatively small sample size, instigating lower generalizability. Thereby, our analysis was performed with 35% of the total group of patients treated at the hospital during data collection. This could have potentially caused a selection of patients who were in a generally better condition, willing to fill out the questionnaires. However, since this effect over CRO and PRO disagreement has also been shown in groups of palliative patients [12,33], we do not expect this selection to have major influence on this result. Furthermore, we should consider that even though we used comparable cut-off scores to calculate the prevalence numbers, the EORTC QLQ C30 (PRO data) and the CTCAE grading system (CRO data) are not directly comparable. Both instruments were designed with a different goal, and there is no evidence-based consensus on how to effectively compare the outcomes. However, the method used in this study was in line with previous research attempting to compare these instruments [18, 19, 34]. A solution to have a more aligned system could be implementing the use of the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) that includes an algorithm that translates PRO report into existing CTCAE grades [35]. Recently, a subset of this PRO-CTCAE was developed specifically for use in lung cancer [36]. The effect of the PRO-CTCAE based symptom monitoring is currently being tested in a Dutch multicenter trial [37].

This study revealed that clinician reported symptoms during (chemo-)radiation treatment with curative intent is largely discordant compared to PRO reported symptoms. Only dysphagia showed relatively good agreement, while for the other symptoms the discrepancies were substantial. The results of this study highlight the strong benefits of implementing PRO data in clinical lung cancer care.

Disclosures: The authors declare no conflicts of interest

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