Review Article

# Patient-reported outcomes in lung and esophageal cancer

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**Abstract:** Carcinomas of the lung and esophagus are associated with significant disease and treatment related morbidity. Measuring patients' self-perceived notion of their health-related quality of life (HRQOL), throughout the course of illness, is central to the delivery of comprehensive, patient-centered care. This article reviews commonly used HRQOL instruments in thoracic surgery and discusses the integral role of patient-reported outcomes (PROs) in comparative effectiveness research and prognostication in the realm of lung and esophageal cancer. We also highlight challenges and future directions for widespread implementation of PROs into clinical and research practice.

**Keywords:** Patient-reported outcome (PRO); health-related quality of life (HRQOL); lung cancer; esophageal cancer; thoracic surgery

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## Introduction

The delivery of patient-centered care hinges on the ability to measure and implement into clinical practice what is of greatest concern to patients. Objective data regarding perioperative complications and survival must be complemented with patient-reported outcomes (PROs) to contextualize therapy and outcomes for individual patients. This is of utmost importance in patients with disorders of the lung and esophagus, which carry significant morbidity, in part due to a high burden of symptoms affecting health-related quality of life (HRQOL) (1). This review will focus on the topic of PROs in malignant thoracic disease, including lung and esophageal carcinoma, and highlight key issues regarding integration of PROs in to clinical thoracic surgery research.

### *Utility of PROs in surgery*

PROs are measures of HRQOL, including physical, emotional and mental well-being obtained by patient self-report, without interpretation of their response by clinicians (2). The addition of PROs to traditionally collected outcome measures (i.e., morbidity, mortality, overall survival) can offer a comprehensive overview of the patient experience around the time of surgery.

The patient's account of his or her health is also crucial in understanding the effect of an intervention and measuring the quality of care being delivered. The impact of an intervention on disability, symptoms and HRQOL is an important outcome, which only patients can assess. As such, patient-centric measures of health status can add meaningfully to the results of prospective studies of comparative effectiveness research involving different treatments and outcomes, and can aid in guideline development (2). In addition, there is a positive relationship between improved HRQOL scores and long-term survival in cancer patients (3). Using PROs to develop better prognostic estimates can inform shared decision making and

**Table 1** Commonly used patient-reported outcomes instruments in thoracic surgery

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| Generic instruments |
| Medical Outcomes Study Short Form 36 (SF-36) |
| Patient-Reported Outcomes Measurement Information System (PROMIS) |
| MD Anderson Symptom Inventory |
| Edmonton Symptom Assessment Score (ESAS) |
| Rotterdam Symptom Checklist |
| Depression, Anxiety, and Stress Scale 21 (DASS-21) |
| Nottingham Health Profile |
| Disease-specific instruments |
| European Organization for Research and Treatment of Cancer (EORTC) Modules |
| Quality of Life Questionnaire Core 30 (QLQ C-30) |
| QLQ Lung Module 13 (LC13) |
| QLQ Esophagus Module 18 (OES18) |
| Functional Assessment of Cancer Therapy (FACT) Oncologic and Organ Specific Modules |
| Lung Module (FACT-L) |
| Esophagus Module (FACT-E) |
| Gastroesophageal Reflux Disease Health Related Quality of Life Questionnaire |
| Gastrointestinal Quality of Life Questionnaire |
| Dyspnea Index |

further accelerate patient-centered care (4). The benefits of PROs also include superior response rates as the onus lies on individual patients as opposed to clinicians that look after multiple patients (2). Additional advantages include reduced observer bias and increased public accountability of health services and health care professionals (2). PROs, therefore, can also play a role in performance measurement and quality improvement (2,5).

## Available instruments

Both generic and disease-specific PRO measures (PROMs) are available for use in thoracic surgery. They are often administered concomitantly and can provide complementary information about the patient experience (*Table 1*). The most commonly used tools in thoracic surgery include the Medical Outcomes Study Short Form 36 (SF-36), the European Organization for Research and Treatment of Cancer (EORTC), and Functional Assessment of Cancer Therapy (FACT) Oncologic and Organ Specific Modules.

SF-36 is a well-validated and widely used generic outcome measure (6). The questionnaire consists of 36 items and is grouped into eight scales: physical functioning, social functioning, role limitations caused by physical problems, role limitations caused by emotional problems, mental health, energy/vitality, bodily pain, and general health and a single item concerning health change. These can be further classified into two higher order domains representing the physical and mental aspects of HRQOL (6). EORTC modules consist of a generic Quality of Life Core Questionnaire (QLQ C-30) as well as the disease-specific QLQ Lung Module 13 (LC13) and QLQ Esophagus Module 18 (OES18) (7). The 30-item core questionnaire explores five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, pain, nausea and vomiting), and a global HRQOL scale. The remainder of the questions cover additional symptoms commonly reported by cancer patients (i.e., dyspnea, sleep disturbance, etc.), and the financial impact of the disease and treatment (7). The modular supplements include both multi-item and single-item measures of lung cancer-associated (i.e., coughing, hemoptysis, dyspnea and pain) and esophageal cancer-associated symptoms (i.e., dysphagia, early satiety and heartburn), as well as side-effects from conventional chemo- and radiotherapy (i.e., hair loss, neuropathy, sore mouth and dysphagia) (8,9). Similarly, the general version of the FACT questionnaire (FACT-G) applies to a variety of chronic illnesses and cancers. It consists of 27 items that explore various facets of HRQOL over 4 subscales: physical, social, emotional and functional well-being (10). The lung and esophageal cancer specific modules (FACT-L and FACT-E, respectively) explore disease specific symptoms including chest pain, cough, xerostomia, weight loss and voice quality (11,12). Domain comparisons of the EORTC and FACT questionnaires have shown discordance among tools, particularly with respect to emotional, social and overall QOL, as well as disease-specific symptomatology. For instance, the social function scale of the EORTC QLQ-C30 has items that differ in content to those within the social function scale of the FACT-G. Although the disease-specific modules contain similar items, differences in scoring systems preclude any meaningful comparisons of results. While both tools have acceptable feasibility and validity, they are

 

not interchangeable and their variable emphasis on different aspects of QOL has affected their clinical utility in patients with lung and esophageal cancer (13). Also of note, the EORTC QLQ-C30 and LC13 modules were validated in a cohort of patients with inoperable lung cancer (7,8); their use therefore, may be limited amongst resectable lung cancer patients and must be guided by the specific aims of the research question at hand.

The recently developed Patient-Reported Outcome Measurement Information System (PROMIS) is another well-validated system of PROMs that includes a variety of questionnaires spanning physical, mental and social health domains (14). PROMIS surveys can be tailored to any patient population and are based on item response theory to adapt to the specific symptoms of a patient (14). PROMIS is now recommended by the Center for Medical Technology Policy—an independent non-profit organization established to improve the quality of healthcare research—as a preferred PRO measure for clinical research and has been used in a variety of fields including thoracic surgery (14,15).

## PROs in lung carcinoma

There is a large body of literature on the topic of PROs and HRQOL in lung cancer (15-22). The majority of studies, however, are retrospective or prospective observational studies of limited sample sizes. Despite variations in quality, most reports describe an initial decline in HRQOL, with eventual recovery within 6–12 months of surgery. For instance, in a longitudinal study of PROs using the MD Anderson Symptom Inventory, Fagundes *et al.* demonstrated that fatigue, pain, dyspnea and disturbed sleep peaked 3–5 days after surgery, with recovery within 3 months of surgery (17). Likewise, in their prospective study of PROs amongst 127 patients undergoing lung cancer surgery, Khullar *et al.* reported that nearly all QOL scores, including physical function, pain, sleep and fatigue, demonstrated resolution within 6 months of surgery (15). This study also examined the role of PROs as end points of comparative effectiveness research in lung cancer. Patients undergoing video-assisted thoracic surgery (VATS) experienced superior levels of physical function and ability to participate in social activities, as well as less pain intensity and fatigue in relation to those undergoing thoracotomies. No group differences in PROs were identified amongst patients treated with lobectomy *vs.* sublobar resection (15). These findings were in keeping with previous SF-36 studies by Zhao *et al.* (19) and Fernando *et al.* (20), in which minimally invasive thoracoscopy was associated with improved QOL outcomes (including dyspnea, pain, energy and physical role functioning) compared to thoracotomy. In the latter study, segmentectomy was associated with a detriment in dyspnea scores at 2 years from surgery compared to wedge resection (20). The impact of extent of resection on HRQOL is well-documented in the literature. In Balduyck *et al.*'s study of 30 patients using EORTC questionnaires, sleeve lobectomy was associated with a smaller impairment in physical, role and cognitive functioning, compared to pneumonectomy (21). This finding was later corroborated in a larger population-based study by Sartipy *et al.* using the SF-36 survey in 117 patients, where lobectomy also had less of a negative impact on physical aspects of HRQOL than pneumonectomy at 6 months (22).

The predictive value of QOL for survival was first demonstrated by Ganz *et al.* in a sample of 40 patients with advanced metastatic lung cancer, where patients with higher scores had better mortality, and vice versa (23). Since then, numerous studies (24-27) have explored QOL as a prognostic marker in lung cancer, including a large study of 809 patients using the EORTC QLQ-C30 and QLQ-LC13 questionnaires. After adjusting for demographic and clinical predictors of survival, QOL measures of postoperative anxiety, strength, dyspnea and physical function were all found to be independent predictors of long-term overall survival (27). The abovementioned studies demonstrate the feasibility of measuring PROs and their utility as valuable end points in the evaluation and treatment of lung cancer.

## PROs in esophageal carcinoma

While historically the surgical esophageal cancer literature has focused on traditional outcomes such as perioperative morbidity and mortality, there has been an increase in the inclusion of PROs as study endpoints in more recent years. PROs and HRQOL are being used in research at all stages of the patient journey, from diagnosis, to treatment response, to long-term survival (28).

At diagnosis, esophageal cancer patients are often symptomatic with dysphagia, weight loss, or chest pain. Because of this late presentation, cancer stage is often advanced. Studying the hypothesis that patient quality of life may be associated with clinical stage, a multi-institutional Canadian study of 135 esophageal cancer patients found that pre-treatment FACT-E scores could distinguish lower and higher clinical T-stage patients (29). Current treatment decisions rely significantly on cancer stage; as the

 

reproducibility and reliability of PROs in determining stage is confirmed, they can become an important adjunct for patients and physicians when planning treatment.

As in lung cancer, PROs are being used to compare interventions in esophageal cancer research. For example, in the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial which established current standard of care tri-modality therapy (30) for patients with locally advanced esophageal cancer, HRQOL was included as a secondary endpoint to compare scores in those who received chemoradiotherapy and surgery versus surgery alone. The investigators found HRQOL dropped immediately following chemoradiotherapy, but there was no difference in scores postoperatively, suggesting that preoperative therapy does not impact recovery following surgery (31). This example illustrates how PRO data created a more compelling case to treat patients with tri-modality therapy. Of note, survey response rates were 54% or 76% (31), which highlights the challenge of incorporating HRQOL assessment in clinical and research practice.

The prognostic value of quality of life scores in esophageal cancer has been demonstrated from as early as 2001 (32). Several studies since then have shown both pre- and postoperative HRQOL scores to be associated with survival (33-37); however, no prognostic tools currently available for survival prediction in esophageal cancer incorporate these measures (38).

Other areas of investigation with PROs in esophageal cancer include change in scores during therapy and time to return to baseline following treatment (39). Many opportunities exist to enhance research with the addition of this outcome, and research groups around the world are moving toward routine collection of PRO data in esophageal cancer databases and studies.

## Future directions—challenges and opportunities

The numerous advantages of PROs are balanced by several challenges, which may limit their rapid integration in to clinical practice. First, most PROMs are designed by physicians, leading to subjective variability in the content and scoring systems. For this reason, the US Food and Drug Administration (FDA) now mandates open-ended patient input in the development of all PROMs (40). Second, accurate measurement of QOL hinges on highly variable patient factors, including language and culture. Further, the poor survival of thoracic malignancies and rapid deterioration of performance status due to disease and treatment related symptoms poses a challenge for long-term follow-up and serial HRQOL measurement (41). However, high morbidity and short survival is precisely why the inclusion of PROs is crucial in studies evaluating treatments for lung and esophageal cancer. Numerous national societies, including the American College of Chest Physicians (ACCP) and the FDA, now endorse the routine use of PROs to inform clinical guidelines and as end points in clinical trials (1). Global interest in PROMs has encouraged national agencies to standardize approaches to collecting and reporting PROs. This includes the Canadian Institute for Health Information's (CIHI) PROMs program, launched to support the development of PROMs data collection standards and reporting in priority topics (42). The US National Institutes of Health-sponsored PROMIS tool is another example of a national platform for the measurement of patient-reported symptoms and other health outcomes, and is available online. Linkage of PRO data with clinical registry data (i.e., Society of Thoracic Surgeons' National Database) has been tested successfully in thoracic surgery, allowing for more research with patient-centric outcomes (15). To further enhance the uptake of value-based health care, the International Consortium for Health Outcomes Measurement (ICHOM) has proposed a core set of health outcomes, gathered using the expert opinion of clinicians and patient representatives, for collection in routine clinical practice internationally. This includes recommendations for lung cancer, which focus on 5 overarching themes including degree of health, survival and quality of death (43).

## Conclusions

PROs are central to the delivery of high-quality patient-centered care. Patients with lung and esophageal cancer are vulnerable to significant detriments in HRQOL as a result of disease and treatment, which underscores the importance of including PROs as important outcomes in research. There is a paucity of high-quality studies focusing on PROs in malignant thoracic disease. Incorporation of PROs into outcomes research is expected to facilitate the delivery of value-based surgical care for patients with lung and esophageal cancer.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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