Patient-reported outcome measures in definitive chemoradiation for non-small cell lung cancer

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Patient-reported outcome measure (PROM) is an umbrella term that refers to any report on a health status measure that is reported directly from the patient, without the influence of clinicians (1). Heath status measures assessed by PROMs broadly include 3 categories: (I) overall measures of health-related quality of life (HR-QOL); (II) functional measures that may include but are not limited to physical, emotional, social, or cognitive well-being outcomes; (III) symptom-specific outcomes measures that may be disease-related or treatment-related (2). PROMs are of particular interest as physician-reported measures are known to under report important symptoms and toxicities from therapy and its associated level of burden on patients (3). Furthermore, PROMs have been shown to more closely associate with cancer patients' overall well-being and function when compared to physician-reported treatment measures (4).

Lung cancer is the leading common cause of cancer death in the United States, with a majority of the patients presenting with unresectable locally-advanced or advanced disease (5). With the advances in immunotherapy for NSCLC, in targeted agents for oncogene-driven NSCLC and in radiotherapy delivery, definitive-intent radiation is increasingly being offered in concert with systemic therapy for patients with locally-advanced disease and with limited-metastatic burden (6-12). However, these therapies are not without risk. In a systematic review of 19 randomized trials of NSCLC patients receiving chemoradiation compared to radiation alone, treatment-related deaths were rare, but non-trivial in both NSCLC patients who received chemoradiation (n=11/1,109) as well radiation alone (n=6/966) (13). Furthermore, the rates of acute esophagitis (RR 1.8, 95% CI: 1.3–2.3), neutropenia (RR 3.53, 95% CI: 1.8–6.7), and grade 3 to 4 anemia significantly increased with chemoradiation as compared to radiation alone (RR: 3.5, 95% CI: 1.8–6.8) (13). Given the older age of lung cancer patients at presentation, competing medical comorbidities and frailty, and the types of potential risks with therapy, the ability to predict tolerability, toxicity, and outcomes at initial presentation prior to aggressive chemoradiation remains crucial.

PROMs in NSCLC offer insights into the how the disease and its treatment affect the patients' sense of well-being from baseline through treatment and to surveillance. In published literature on PROMs in NSCLC patients receiving chemoradiation, baseline PROMs can be used to identify patients at risk for worse outcome after chemoradiation. In secondary QOL analyses of phase III trials of chemoradiation for NSCLC patients, for every 10-point decrease in baseline QOL measure there was an additional 9–10% increase in risk of death (RTOG 9801: HR 0.99 using the EORTC QLQ-C30 summary score, P<0.004; RTOG 0617: HR 0.9 using FACT-TOI score, P<0.046, respectively) (14,15). Moreover, PROMs

are commonly used to describe changes in functional measures and symptoms with treatment. Movsas *et al.* also demonstrated a clinically meaningful decrease in evaluated physical well-being, functional well-being, and lung cancer specific symptoms 3 months post-treatment using FACT-TOI scores (15). PROMs have also been used as an intervention tool to improve symptom management and hence outcomes in patients with advanced lung cancer. A phase III study of electronic patient report-based symptom surveillance versus standard computed tomography-based surveillance in patients with advanced lung cancer demonstrated that PROM-based routine surveillance was associated with an increase in median survival (19 *vs.* 12 months), which resulted improved cost-effectiveness of cancer care during the follow-up period (a savings of 362 euros per year per patient) (16). If physicians can accurately identify who is at risk of tolerating definitive chemoradiation poorly, unnecessarily treatment, treatment-related morbidity, and potential costs may be averted.

In the article by Vogel *et al.* that accompanies this editorial, the primary aim of the analysis was to evaluate associations between baseline clinical characteristics of patients with NSCLC and poor HR-QOL following the receipt of definitive chemoradiation (17). In this article, 43 NSCLC patients who enrolled in an institutional clinical trial from 2009 to 2012, received definitive chemoradiation, and completed a set of HR-QOL assessments at ≥1 time point were included in the analysis. Assessments collected at baseline, during chemoradiation, or at 3-month post-treatment included: EuroQol (EQ-5D), MD Anderson Symptom Inventory (MDASI), and Functional Assessment of Cancer Therapy-General (FACT-G). All patients had stage II–III NSCLC, treated with platinum-doublet chemotherapy delivered concurrently with radiation (median 66.6Gy, range: 45–79.2 Gy). The patients were predominantly men (60%), Caucasian (91%), partnered (70%), and were able to read and understand English. The median age of the patient population was younger (median 65 years) with a low comorbidity index (median Charlson Comorbidity Index; CCI: 0, range 0–5). The cohort in this study reflects a more selected population of patients than those patients typically diagnosed with NSCLC: median age 75 years, with similar incidence rate between white and black patience (57 per 100,000 people) (18).

Exploratory testing showed potential associations between baseline clinical characteristics and individual and overall HRQOL scores, in the pre- and post-treatment time periods. Potential baseline clinical characteristics found to be significantly associated with poor HRQOL measures on univariate analyses included: female gender, African American ethnicity, older age >60 years, receipt of carboplatin-based chemotherapy type, baseline hemoglobin <12, and higher CCI. On adjusted analysis, baseline CCI was associated with severe post-treatment individual symptom and overall MDASI scores as well as worse EQ-5D index scores.

Clinicians at this point are unable to consistently and accurately identify which NSCLC patients will do poorly with chemoradiation, but have found that baseline functional status as determined by poor baseline performance status, high burden of co-morbid disease, and worse baseline quality of life are associated with worse outcomes in patients with lung cancer (14,15,19,20). This article by Vogel *et al.* adds to the currently literature by taking a small first step towards exploring how PROMs may be incorporated to the decision-making process for selecting patients with locally-advanced NSCLC to receive definitive chemoradiation. This analysis also underscores that there may be barriers to the collection of PROMs and integration into clinical care, as 44% of patients had completed only baseline assessments.

Considerations in this study design include limitations of a single institution exploratory analysis of a small cohort of NSCLC patients, subject to multiple testing. Future work in this area is needed to properly collect data (I) from a larger multi-institutional "real-world" patient population that is reflective of the patients diagnosed with locally-advanced NSCLC, (II) using common validated lung-cancer specific PROMs that reflect the questions and symptoms of interest, (III) along with well-selected clinical measures including baseline clinical, laboratory, and tumor measures, treatment details, and objective chemoradiation-related toxicity outcomes. Future efforts must also evaluate and limit any perceived barriers to PROM collection in order to ensure enough power to elucidate the value of PROMs in this population. Robust associations between baseline clinical, treatment, and patient reported measures and increased risk of poor-tolerance to definitive chemoradiation can then be incorporated into clinical prediction algorithms that would help clinicians best identify the NSCLC patients at high, intermediate, or low risk of treatment toxicity.

In summary, Vogel and colleagues are to be congratulated for beginning to explore associations between baseline clinical measures that may be associated with worse patient reported outcomes after receipt of definitive chemoradiation. Given the importance of appropriately

selecting NSCLC patients best suited for aggressive definitive chemoradiation, incorporating PROMs that better report the overall well-being and symptoms important to the patient into the clinical decision-making process may better identify patients that may benefit from chemoradiation.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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