editorials

Longitudinal Assessment of Health-Related Quality of Life Among Survivors of Hodgkin Lymphoma: It Is About Time!

Susan K. Parsons, MD, MRP[1]

For more than half a century, curative therapy has been available for patients with Hodgkin lymphoma (HL) as radiotherapy, multiagent chemotherapy, or combined modality. Although survival rates vary considerably by patient and disease factors, such as age, fitness or frailty, and extent of disease,[1] the majority of patients are cured. Despite this considerable success, survivors of HL face potential late effects of treatment, which translate to premature mortality or considerable morbidity and diminished health-related quality of life (HRQoL).

Research to date on how HL and its treatment affect HRQoL has been limited to generally small study samples and cross-sectional design, which have hampered generalizability and interpretability of these key outcomes.[2] In the 2016 systematic review by Linendoll et al,[2] only two prospective, longitudinal studies were identified, both focusing only on early-stage disease in adults.[3,4] Strikingly, there have been no similar studies for treated patients with advanced-stage disease or any formal evaluation of HRQoL in children and adolescents. The first longitudinal study of HRQoL in 300 children and adolescents with high-risk HL met study accrual in 2019 (NCTN 02166463); preliminary results demonstrated marked diminution in HRQoL at diagnosis and before treatment initiation, along with persistence throughout the first year after treatment.[5]

Researchers have faced many challenges in assessing HRQoL. Until relatively recently, there were no validated measures with sufficient normative data for understanding how HRQoL domain scores or HRQoL trajectories compared with other populations. Over time, cultural and linguistic cross-validation has also occurred, which allows measures to be used across populations and languages. Concerns about potential burden of assessment to both the participating sites and patients have been addressed by the use of multidimensional profile measures, encompassing several domains, and the emergence of short forms or computer-adaptive testing that allow for briefer assessments with higher precision of measurement.

HRQoL assessment alongside clinical trials has faced other unique issues. First, typical follow-up during and after clinical trials is relatively short compared with decades of anticipated survival, which is when the majority of late effects occur. Thus, a full appreciation of the impacts on HRQoL over the disease course is limited. Second, studies have been hampered by attrition at more distal time points, resulting in missing data, which introduces bias in findings. Reasons for missing data have not been routinely collected, making it difficult to discern whether the missing data are ignorable or not. Missing data are ignorable if the cause is not related to the outcome. For example, if an assessment was missed because the patient had to work instead of going to the clinic, the data may be ignorable (ie, random) because the missed visit likely would not result in lower HRQoL. In contrast, if the assessment was missed because the patient felt too ill to visit the clinic, the worsened health would likely be related to lower HRQoL; thus, the data would be nonignorable and nonrandom. Statistical methods have been developed to address missing data by type, such as multiple imputation for data missing at random or pattern mixture models for missing data that are nonrandom. Despite these advancements, the best approach to missing data is to avoid it. Strategies for avoiding missing data include selecting HRQoL batteries that are salient to both clinicians and patients, aligning HRQoL assessment with planned clinical assessments, establishing infrastructure to track the timing of assessments with reminders sent to sites and/or participants, and allowing for collecting data using remote modes, such as telephones or Web-based forms for completion. Long-term follow-up studies, adequate resources to optimize data completion at later time points, including formal tracking and remote data collection, are sorely needed. Engaging participants directly through the use of virtual data portal and regular reminder systems (eg, text messaging), may enhance the salience of the data collection, particularly as patients move from initial treatment to survivorship.

In the article that accompanies this editorial, Kreissl et al,[6] reporting on behalf of the German Hodgkin Study Group, have provided a comprehensive evaluation of HRQoL in more than 4,000 HL patients treated in three clinical trials, HD13, HD14, and HD15

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(ISRCTN63474366, ISRCTN04761296, and ISRCTN32443041, respectively). These three trials included patients with early-stage favorable disease (HD13), early-stage unfavorable disease (HD14), and advanced-stage disease (HD15) who were treated from 2003 to 2009. Across the trials, patients completed the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 20 questionnaire, a multidimensional profile measure that encompasses five functioning scales, three multi-item symptom scales, and six single-item symptom scales.[7] Data were collected serially before treatment was initiated, during treatment, at the end of treatment, and annually up to 5 years of survivorship.

Several key findings emerged. First, participation levels were high across all three studies (83% to 88%). However, males and younger patients were less likely to participate than females or older patients. Second, baseline assessments demonstrated that HRQoL was impaired, even before the start of treatment, across most of the domains of HRQoL and across all disease stages. Greater impairment was noted among patients with more advanced disease and for those who were older (defined as age 50 to 60 years). Notably, fatigue was also the most affected in advanced-stage patients, as has been previously reported. Throughout treatment, impaired HRQoL persisted. By 1 year off treatment, improvement in HRQoL was noted across all patients, a pattern that continued to 2 years off treatment and then leveled off. Older patients had less HRQoL recovery compared with younger patients.

Kreissl et al[6] note that financial problems were the most affected domain of HRQoL in the first year off treatment across all three trials; the magnitude of impairment reached 30 points compared with normative data, for which a difference of 10 points is considered to be clinically meaningful. Financial problems have been shown to be strongly associated with other domains of HRQoL such as fatigue.

Strikingly, although treatment approaches differed by study, their influence on HRQoL for patients who were off treatment was not apparent. Previous reports by Ganz et al[3] and Heutte et al[4] similarly showed little difference by treatment arms in the first 1 to 2 years off treatment. What can we make of these patterns? First, early assessments seem to be influenced by the extent of disease burden and the impact of associated symptoms, such as pain, dyspnea, and loss of appetite. In the period after initial treatment has been completed, patients primarily experience resolution of somatic impairments. However, as survivors begin to resume normal roles and responsibilities, other areas of health and well-being become unmasked, such as the above-mentioned financial problems and persistent fatigue. From an assessment perspective, what may be important to the patient may shift over time and may require additions to the measurement battery to more robustly capture such domains. For example, survivors may be ready to address the impact of HL and its treatment on sexual functioning, relationship building, or family formation only after they have completed initial treatment. Similarly, although the intensity of acute toxicity may wane, functional limitations or consequences may be more apparent to survivors when they resume normal activities. Chronic low-grade peripheral neuropathy, for example, may compromise the survivor's self-care and fine and gross motor functioning, and it may also increase the risk of falls and accidents, even as the clinical grade improves. Chronic fatigue is likely to be experienced similarly.

As noted above, the Kreissl et al[6] study also had to contend with missing data, particularly after the second to fifth years off treatment. By the fifth year, assessment completion rates across all three trials fell to 40% or lower. Although disease factors, such as International Prognostic Score and stage did not differ among those with missing assessments and those with complete data, patients with a higher number of relapses or early death were more likely to have missing data. Interestingly, males and younger patients also were more likely to have missing assessments in later years of survivorship, although the reasons for this are not known. Sex differences in initial participation, as well as in later follow-up, warrant closer study to ensure that the findings are generalizable across women and men. It would be interesting to determine whether medical follow-up after initial treatment also fell off for males and younger patients, suggesting that more active strategies to keep them in care are needed.

Finally, the interpretation of longitudinal data across multiple domains, time points, and clinical trials is complex. Kreissl et al[6] display these data graphically with heat maps. An alternative strategy would be to include an overall appraisal of HRQoL in which the respondent internally integrates across domains. This could take the form of a closed response item answered on a Likert-type scale, or it could be a very brief utility scale, such as the EuroQoL five-dimension instrument (EQ-5D) or the Patient-Reported Outcomes Measurement Information System 29+2 (PROMIS 29+2), in which the "+2" refers to a two-item utility scale, scored from 0 to 1 in which 0 is the worst health and 1 is the best health.

In summary, despite decades of successful HL treatment, our understanding of the short- and long-term effects of this disease on HRQoL is limited. The Kreissl et al study team should be congratulated for their painstaking data collection and analysis across three clinical trials and disease groups. These results reinforce the importance of baseline assessment and the contributions of the disease itself to HRQoL appraisal, the transient effects of treatment, and the longstanding impacts of HL and its treatment on psychosocial and related functioning.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the author and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.20.01585.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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