Influence of new late effects on quality of life over time in Hodgkin lymphoma Survivors: a longitudinal survey study

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Background: Long-term Hodgkin lymphoma (HL) survivors are known to have diminished quality of life (QoL). However, limited data are available on temporal changes in QoL and factors associated with the changes.

Methods: In 2010, we conducted a follow-up questionnaire study on 273 HL survivors who participated in a 2003 questionnaire study on late effects after HL. The questionnaire items were limited to new late complications and reassessment of QoL and fatigue level, using the Short Form 36 (SF-36) and the Functional Assessment of Chronic Illness Therapy-Fatigue instruments, respectively. We compared the results from the 2003 and the 2010 questionnaires, and QoL score changes between survivors with and without new late complications during the 7-year period.

Results: There was a significant decline in the SF-36 Physical Component Summary score (median change, −1.8; \( P < 0.0001 \)) over the time period. The decline was significantly greater among survivors with a new cardiac (\( P = 0.005 \)) or pulmonary (\( P < 0.0001 \)) complication, compared with those without any new complications. The survivors reporting new cardiac complications also experienced significantly greater worsening of fatigue scores (\( P = 0.004 \)).

Conclusion: The significant association between the development of new cardiopulmonary complications and decline in QoL and energy level of HL survivors provides further support for current efforts to reduce treatment to limit late effects.

Key words: fatigue, Hodgkin lymphoma, quality of life, survivorship

introduction

Over the last four decades, major advances in the staging and treatment of Hodgkin lymphoma (HL) have transformed the disease from a previously fatal malignancy to a highly curable one [1, 2]. Currently, over three-quarters of all patients presenting with HL will be cured, and the chance of cure among early stage, favorable-prognosis patients, who comprise over half of all cases of HL, is as high as 90% [3, 4]. It is also increasingly recognized that historically treated long-term HL survivors are at elevated risk for the life-threatening late effects including second malignancy and cardiovascular disease [5]. More recently, efforts are focused on exploring treatment reduction in selected patients to limit late effects which may help improve survival outcome [6].

While survival is an important end point, the quality of life (QoL) of survivors of the disease is gaining attention. A number of cross-sectional studies have identified a range of difficulties encountered by survivors of HL [7–20]. Clinically important reduced QoL compared to the normative population, most notably in the physical functioning domain [12, 13, 19, 21, 22], has been documented. In addition, diminished energy level has been consistently demonstrated in several studies, with about one-third of survivors experiencing persistent fatigue years after cure of their HL [7, 9, 14, 20, 23]. Limited data are available on the etiology of the reduced QoL and on changes in QoL over time in this patient population. The impact of late complications of HL therapy on changes in QoL is also unclear.

In this longitudinal survey study, we sought to determine changes in QoL and fatigue level and to document the development of new late effects over a 7-year period in a cohort of long-term HL survivors. Associations between these new late effects and QoL changes over time were explored.

methods

In 2003, 511 survivors of HL, all at least 5 years since diagnosis, participated in a 500-item questionnaire study adapted from the Childhood
The original CCSS instrument was designed to explore a wide range of physical and psychosocial health sequel in childhood cancer survivors. Minor modifications were made to tailor the questionnaire to survivors of HL. In addition, several standardized QoL instruments were added to the questionnaire, including the Short Form 36 (SF-36) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).

In 2010, we conducted a follow-up questionnaire study to assess the development of new late complications and changes in QoL over time in the same population. Those who participated in the original questionnaire study and were known to be alive at the time of the follow-up study were eligible. Potential participants were first mailed an introductory letter describing the follow-up study and were given the opportunity to opt out if they chose not to participate. If the opt-out note was not received by the investigators within 3 weeks, consent for further contact was inferred and the questionnaire was mailed to the potential participant. A reminder letter was sent if the completed questionnaire was not returned after 4 weeks. A reminder telephone call was made if the completed questionnaire was not returned after another 4 weeks. This follow-up questionnaire study was approved by the Institutional Review Board of the Dana-Farber/Harvard Cancer Center.

The follow-up questionnaire was an abbreviated version of the original, limited to items concerning late effects and reassessment of QoL and fatigue level, using the SF-36 and FACIT-F instruments, respectively. The late effects were categorized into cardiac, pulmonary and infectious complications and second malignancies. A participant was considered to have developed a new (i.e. since the original questionnaire was completed) late effect in a category if an affirmative answer was given to one or more items within that category where no affirmative answer was given initially (Table 1).

The SF-36 is a 36-item instrument that assesses eight health concepts: limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health; limitations in usual role activities because of emotional problems; vitality; and general health perceptions. For these eight subscales, linearly transformed scores range from 0 to 100, with higher scores representing higher levels of functioning and health. Scores from the subscales were aggregated into two distinct summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS). Norm-based scoring was used for the two summary scores, computed by the following three-step procedure. First, all eight SF-36 subscales were standardized, using means and standard deviations from the 1990 general US population. Secondly, they were aggregated, using weights (factor score coefficients) from the US general population. Finally, the PCS and MCS summary scores were standardized, using a linear t score transformation with a mean of 50 and a standard deviation of 10 in the general US population.

The FACIT-F scale is a 13-item questionnaire that assesses self-reported fatigue and its impact on daily activities and function. It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit and 4 = very much). As each of the 13 items of the FACIT-F scale ranges from 0 to 4, the range of possible scores is 0–52, with 0 being the worst possible score and 52 the best. To obtain the 0–52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is a good response. All responses are added with equal weight to obtain the total score. Wilcoxon signed-rank test was used to compare the QoL scores from the original 2003 questionnaire and the new questionnaire, and Wilcoxon rank-sum test was used to compare the QoL score changes between participants with and without new late complications during the 7-year period.

### Table 1. Items for the four categories of new late effects since completion of the original 2003 questionnaire

<table>
<thead>
<tr>
<th>Category</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac complications</td>
<td>Congestive heart failure or cardiomyopathy (weak heart muscle)?</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease (hardening or blockage of arteries supplying the heart muscles)?</td>
</tr>
<tr>
<td></td>
<td>A stroke or cerebrovascular accident?</td>
</tr>
<tr>
<td></td>
<td>Angina pectoris (chest pain due to lack of oxygen to heart requiring medication such as nitroglycerine)?</td>
</tr>
<tr>
<td></td>
<td>Heart catheterization (heart cath)?</td>
</tr>
<tr>
<td></td>
<td>Stiff or leaking heart valves?</td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>Chronic cough for greater than 1 month?</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath for greater than 1 month?</td>
</tr>
<tr>
<td></td>
<td>Asthma or bronchitis?</td>
</tr>
<tr>
<td></td>
<td>Lung fibrosis or ‘scarring’ of the lung?</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Infections requiring hospitalization?</td>
</tr>
<tr>
<td></td>
<td>Treatments of infections that are not part of standard medical care?</td>
</tr>
<tr>
<td></td>
<td>Any infections in the past 5 years that were not treated medically?</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Second malignancies</td>
</tr>
<tr>
<td></td>
<td>Cancer, tumors, leukemia</td>
</tr>
</tbody>
</table>

### Results

Of the 511 HL survivors who participated in the original 2003 questionnaire, follow-up questionnaires were sent to 450 survivors who on record were alive and with valid mailing addresses. One hundred and thirty-five patients were not reachable or did not respond, 28 were found to be deceased and 14 opted out. The remaining 273 patients participated in the follow-up questionnaire, resulting in a response rate of 65%, after excluding deceased patients. To assess potential bias introduced by missing data due to nonresponse, the original 2003 QoL scores were compared between those who did and did not participate in the follow-up study. As summarized in Table 2, there were no significant differences in original SF-36 PCS, MCS and FACIT-F scores between participants and nonparticipants in the follow-up study.

The baseline characteristics of the 273 patients who completed both the original and the follow-up questionnaires, and who comprised the study population, are summarized in Table 3. In the 7 years between the original questionnaire in 2003 and the follow-up questionnaire in 2010, there was a significant decline in the SF-36 PCS score, with a median of...
change of −1.8 (P < 0.0001), indicating a decline in physical well-being. However, there were no significant changes in SF-36 MCS (mental well-being) and FACIT-F (fatigue) scores. Details of the comparisons are displayed in Table 4.

A total of 161 participants (59.0%) reported having developed at least one late effect since the 2003 questionnaire. The development of one or more cardiac complications was the most common new late effect, reported by 111 participants (40.7%). In addition, 51 (18.7%), 47 (17.2%) and 25 (9.2%) participants reported new pulmonary complications, second malignancies and infectious complications, respectively.

Among participants who reported new cardiac complications since the 2003 questionnaire, the median change in SF-36 PCS score was −2.7 (P < 0.0001) and the median change in FACIT-F score was −2.0 (P = 0.015) during the time between the two questionnaires. In contrast, among patients without new cardiac complications, the corresponding changes were −0.5 (P = 0.18) and 0.8 (P = 0.24), respectively. The changes in the SF-36 PCS score (P = 0.005) and FACIT-F score (P = 0.004) over time between those who did and did not have new cardiac complications were statistically significant, indicating that those with such complications were more likely to have a lower level of physical well-being and a higher level of fatigue. Note that fatigue scores actually improved slightly to have a lower level of physical well-being and a higher level of mental health functioning [10, 12, 13, 19, 21, 22] and social functioning [10, 13, 22], while mental health functioning appears comparable between the two groups [10, 12, 13, 25]. Factors associated with diminished QoL have also been explored although the results have been inconsistent. More intensive treatment exposures, including high-dose therapy and stem cell transplantation, were associated with poorer QoL scores in several studies [15, 16, 26], while others found no

### discussion

In this longitudinal questionnaire study of long-term survivors of HL, we found that during a 7-year period, over half of the survivors developed one or more new late effects, with the most common one being cardiac complications. In addition, there was a significant decline in the physical component of QoL during this time period. Further analysis revealed that the extent of the decline was significantly greater for survivors who reported a new cardiac or pulmonary complication in the interim, compared with those without a new complication. While there were no significant changes in fatigue level from 2003 to 2010, survivors who developed a new cardiac complication had a significantly greater worsening of fatigue scores compared with those did not report a new cardiac complication. There were no significant changes in the mental component of QoL, and there were also no significant differences in the changes between patients who did or did not experience a new interim late effect.

Prior studies on health-related QoL of HL survivors, using mostly the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 or the SF-36, have shown that survivors, when compared with normal controls, have lower physical functioning [10, 12, 13, 19, 21, 22] and social functioning [10, 13, 22], while mental health functioning appears comparable between the two groups [10, 12, 13, 25]. Factors associated with diminished QoL have also been explored although the results have been inconsistent. More intensive treatment exposures, including high-dose therapy and stem cell transplantation, were associated with poorer QoL scores in several studies [15, 16, 26], while others found no
effect of initial treatment on health-related QoL among survivors [10, 18, 19, 22, 25]. Limited data are available on changes in QoL of HL survivors over time. A number of studies have compared QoL of survivors according to time since diagnosis and treatment. Three studies failed to show a significant effect of length of follow-up time on QoL [10, 12, 26], while one study found better QoL among 10- to 15-year survivors compared with 5- to 9-year survivors [25]. However, these studies are limited by their one-time cross-sectional survey study design, which compared cohorts of patients with different lengths of follow-up time. In contrast, the longitudinal design of our current study allows the evaluation of the trajectory of QoL of the same group of long-term HL survivors over time. The finding of a deterioration in the physical component of QoL in our cohort may be partly related to advancing age [10, 18, 21, 22], but the decline is also clearly associated with development of new cardiopulmonary complications.

Table 4. Quality-of-life comparisons between 2003 and 2010 questionnaires

<table>
<thead>
<tr>
<th>Quality of life</th>
<th>New late effect</th>
<th>N*</th>
<th>2003 Questionnaire</th>
<th>2010 Questionnaire</th>
<th>Differenceb</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Original questionnaire</td>
<td>New questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>Cardiac No 154</td>
<td>51.9 (7.7)</td>
<td>54.6 (23.7, 64.9)</td>
<td>51.9 (6.9)</td>
<td>53.4 (29.4, 62.5)</td>
<td>-0.4 (9.3)</td>
</tr>
<tr>
<td></td>
<td>Yes 109</td>
<td>50.7 (9.0)</td>
<td>53.2 (17.5, 62.5)</td>
<td>51.8 (11.1)</td>
<td>48.4 (17.2, 60.8)</td>
<td>5.2 (10.0)</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>Cardiac No 154</td>
<td>51.6 (8.4)</td>
<td>54.8 (35.6, 64.9)</td>
<td>51.6 (8.5)</td>
<td>53.2 (19.1, 62.5)</td>
<td>1.5 (10.2)</td>
</tr>
<tr>
<td></td>
<td>Yes 109</td>
<td>50.7 (9.0)</td>
<td>52.2 (17.5, 60.9)</td>
<td>50.7 (10.4)</td>
<td>44.5 (17.2, 60.8)</td>
<td>6.2 (10.9)</td>
</tr>
<tr>
<td>FACIT-F Fatigue</td>
<td>Cardiac No 218</td>
<td>51.8 (7.7)</td>
<td>54.4 (20.5, 64.9)</td>
<td>51.9 (9.2)</td>
<td>54.7 (17.3, 66.6)</td>
<td>2.9 (8.2)</td>
</tr>
<tr>
<td></td>
<td>Yes 25</td>
<td>50.8 (9.4)</td>
<td>53.3 (17.5, 60.6)</td>
<td>49.8 (10.5)</td>
<td>50.3 (19.9, 62.5)</td>
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</tr>
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<td>2.4 (8.4)</td>
</tr>
</tbody>
</table>

*Only those who participated in both questionnaires are included (those who did not complete any segment of the questionnaire were excluded from the analysis of that segment).

bDifference = score changes from the 2003 questionnaire to the 2010 questionnaire.

*P value is from two-sided Wilcoxon rank-sum test for comparing participants with and without new late effects with respect to the quality-of-life score changes.

SD, standard deviation; PCS, physical component summary; MCS, mental component summary.
Hjermstad et al. [14] reported longitudinal survey results of 280 HL survivors using the Fatigue Questionnaire. The patients who reported persistent chronic fatigue 8 years after the initial survey were significantly more likely to have had B symptoms at the time of HL diagnosis, compared with patients who had resolution of the chronic fatigue at the 8-year follow-up survey. The impact of late effects of therapy on changes in fatigue level over time, however, was not assessed. The association between the presence of late complications of HL therapy and the increased fatigue has been demonstrated by several one-time cross-sectional studies [20, 23, 27], although the timing of the development of the late complications and its effect on fatigue level are unclear. The finding of the current study of a significant increase in fatigue level limited to only patients with new cardiac disease further consolidates the important contribution of late complications to fatigue symptoms in HL survivors.

The main limitation of this study is the inability to obtain follow-up responses from all original participants, due to interim death, loss to follow-up or patients opting out. However, this likely results in bias toward the null due to nonparticipation of those with a significant decline in health. Accordingly, the true relationship between changes in health and QoL decrement may in fact be underestimated. Another limitation of this study is its reliance on self-reported medical conditions.

The results of this study highlight the importance of continued follow-up of HL survivors, especially in view of the high proportion of patients reporting new late effects during the 7-year period. The results also allow better understanding of temporal changes of QoL in very long-term HL survivors and factors that contribute to these changes. The significant association between the development of new cardiopulmonary complications and the decline in QoL and energy level of HL survivors provides further support for current efforts at treatment reduction to limit late effects. These efforts, in addition to reducing treatment-related mortality, will significantly benefit the QoL of surviving patients.

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disclosures
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references