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Quality of Life is Similar between Long-term Survivors of Indolent and Aggressive Non-Hodgkin Lymphoma

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Abstract

Differences in quality of life (QOL) of long-term survivors of aggressive or indolent subtypes of non-Hodgkin lymphoma (NHL) have not been frequently evaluated. We assessed these differences by analyzing results of a large QOL survey of long-term NHL survivors. We hypothesized that the incurable nature of indolent NHL would relate to worse QOL in long-term survivors while the potentially cured long-term survivors of aggressive lymphoma would have better QOL. We found that QOL was similar between the two groups. Results suggest that patients with indolent NHL are coping well with their disease, yet experience some overall feelings of life threat.

INTRODUCTION

The quality of life (QOL) of survivors of non-Hodgkin lymphoma (NHL) is inferior to age and sex matched normative controls[1,2]. However, there is little information about differences in QOL between survivors of different subtypes of NHL[3,4]. The QOL for survivors of aggressive and indolent NHL may differ because of the distinct prognosis and life expectancy for these two groups. Individuals with aggressive lymphoma are very sick at the time of initial diagnosis and may die quickly from complications, but, if in remission after 5 years, they are considered “cured.” In contrast, indolent lymphomas are often found incidentally in asymptomatic individuals (i.e., enlarged lymph nodes) and may not require treatment for years after their diagnosis; however, with a few exceptions, there is no cure. Therefore, even during periods of remission survivors of advanced stage indolent lymphoma are living with the knowledge that their lymphoma will, in all likelihood, eventually come back.

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DECLARATION of INTEREST STATEMENT

The authors report no declarations of interest.

The natural history of these lymphoma types could lead to different life attitudes and concerns, but little is known about differences in their QOL outcomes and the psychosocial impact of cancer. Prior studies have not found a significant difference between the QOL of survivors of indolent and aggressive NHL; however, none of these reports have examined very long term survivors of lymphoma{Mols, 2007 #1}{Blaes, 2011 #4}{Oerlemans, 2013 #3}. To assess the differences between those with aggressive and indolent NHL, we analyzed the results of a large QOL survey of long-term survivors of NHL[5–11].

Another important consideration between these two groups is the matter of time since diagnosis; as more time passed since diagnosis, many of those with aggressive lymphoma would be considered cured, while those with indolent lymphoma would continue to have a high likelihood of relapse. Therefore, we hypothesized that the differences in QOL between these two populations would be greater in the group that was further out from diagnosis since the subgroup with indolent lymphoma would continue to live with active disease. The results of this work and previously published analyses of the QOL of survivors of lymphoma will help target the areas of need and lead to development of new interventions to improve the QOL in long-term and short term survivors of indolent lymphoma.

MATERIALS and METHODS

Participants and Procedures

This analysis used data from a cross-sectional study of adult NHL survivors from two academic medical settings (Duke University and the University of North Carolina) who were ≥ 2 years post-diagnosis. Following Institutional Review Board approval at both sites, 886 survivors (74% response rate) were identified through the Tumor Registries and returned a signed consent form and questionnaire that included items related to QOL and impact of cancer. Full details about the methods used to administer the surveys have been previously described[10]. Clinical data such as histology, treatment status, and disease stage were collected via self-report and the Tumor Registry databases. NHL histology was characterized as indolent or aggressive based on the coding by the International Classification of Diseases for Oncology-3 (ICD-0-3) codes[12].

In an effort to closely evaluate differences in QOL between incurable indolent lymphoma and potentially cured aggressive NHL, we focused our analytic sample. To do this, we excluded all subjects with potentially curable stage 1–2 indolent NHL at time of diagnosis, unless it subsequently relapsed. Individuals with indolent lymphoma who were actively undergoing chemotherapy were also excluded to remove the confounding effects of chemotherapy on QOL. We focused on the potentially cured aggressive lymphoma individuals by excluding survivors currently receiving chemotherapy.

Outcome Measures

The Functional Assessment of Cancer Therapy - Lymphoma was used to assess cancer-specific wellbeing[13]. It consists of a cancer-specific FACT-G measure of QOL (incorporating subscales related to physical, social/family, emotional, and functional well-being) and also a 15-item lymphoma-specific symptom subscale. Although this measure was

originally developed for patients actively receiving treatment, it is increasingly being administered to post-treatment survivors. Reliability statistics for all subscales range from α =.77–.93. In addition, the Impact of Cancer (IOC) was used to assess survivors' perceptions of the positive and negative impacts of cancer in several aspects of their well-being through the use of four positive and four negative subscale domains and two summary scores (Positive and Negative Impact)[14]. Reliability estimates range from α =.62–91 in this sample. Higher scores on the FACT-G[15], FACT-LYM (composed of the FACT-G plus the lymphoma subscale) and IOC indicate better QOL, except for the IOC Negative Impact subscales and total score, for which higher scores represent greater negative impacts of cancer. Also, the Appraisal and Life Threat and Treatment Intensity Questionnaire (ALTTIQ) contributed six items (range 6–30, α =.80) to assess the extent to which cancer and related treatment are perceived as life-threatening and intense[16].

Statistical Procedures

Descriptive statistics were used to describe the QOL outcomes for this sample overall and by NHL histology type (aggressive and indolent). Chi square and ANOVA were used to compare distributions and mean scores on the outcome variables across the two survivor groups. A two-way interaction of survivor status and tumor type was tested to assess whether QOL differences between lymphoma types were dependent on the length of time since diagnosis. Short- and long-term survivor status was determined by the number of years post-diagnosis (<6 years and >6 years post-diagnosis, respectively). Statistical analyses were conducted with SPSS v14.

RESULTS

After excluding all potentially curable indolent lymphoma subjects, all those receiving chemotherapy, and subjects with aggressive NHL who were not in a remission, 553 subjects were included in our analysis (Table 1). Significantly more individuals with indolent NHL had advanced stage disease at diagnosis (69% stage III/IV indolent; 45% stage III/IV aggressive; p<.001). Additionally, more people with aggressive NHL had received chemotherapy (94% vs. 79%, p<0.001) and stem cell transplant (21% vs. 13%, p=0.01).

The aggressive lymphoma survivors reported more distress on the overall score for the ALTTIQ (p=.01) with significantly higher score on treatment intensity (p<.001) and past life threat (p=.03) but a decreased score on current life threat (p=.01), although the difference on the total score differed by only 1.3 points (on a 35 point scale). In terms of the FACT scores, survivors with aggressive lymphoma had higher emotional well-being scores (p= .04) than did those with indolent lymphoma (0.7 points on 24 point scale). Otherwise, the overall QOL on the FACT score between aggressive and indolent lymphoma survivors was similar (Table 1), and there also were no significant differences on the positive or negative impact of cancer scores.

Differences in QOL between the indolent and aggressive lymphoma groups were greater in the short-term survivors (Table 2). Time had a significant relationship to the overall appraisal of life threat score (p=.04) and the positive impact of cancer (p=.03). The FACT score also significantly related to time since diagnosis (p=.02) with a greater difference in scores for

the short term indolent survivors (FACT-G total score 81.20) compared to the aggressive survivors (FACT-G total score 88.00). For the long term survivors, the scores were 88.04 and 87.41, respectively.

DISCUSSION

This manuscript compares QOL in indolent and aggressive NHL survivors, as well as differences for short-term versus long-term survivors, to examine whether time related to the QOL of these two groups differently. We hypothesized that the incurable nature of indolent NHL would relate to worse QOL in long-term survivors, while the potentially cured long-term survivors of aggressive lymphoma would have better QOL. Our data demonstrate that overall, QOL was similar between the indolent and aggressive NHL survivors, other than slightly higher appraisal of life threat scores in the aggressive lymphoma survivors. As expected, time since diagnosis did significantly relate to difference in some QOL scores between the indolent and aggressive NHL. However, unexpectedly, rather than a greater difference with increased time since diagnosis, we found the QOL scores between the two lymphoma groups were smaller in the long-term follow up group.

The longer-term follow up indolent lymphoma group had higher QOL scores than their short-term counterparts, which was the opposite of what we hypothesized; for the overall FACT-G, the difference was almost 7 points on a 0–108 scale. It may be that the longer people live with their diagnosis of indolent lymphoma, the more adjusted to it they become. Those with indolent lymphoma can live for many years without needing treatment as long as they remain asymptomatic; consequently, it is likely that individuals who are long-term survivors not only have received less aggressive treatment but may have gone many years without requiring any treatment. Furthermore, long-term follow up and reports of event free survival in several clinical trials demonstrated that the rate of relapse in indolent lymphomas is much higher in the first few years after treatment and decreases substantially after 3–4 years of continued remission (although relapses never completely stop)[17,18]. Therefore, a large number of the long-term survivors may have been in long-term remissions, thereby alleviating some of their concerns about their indolent lymphoma and allowing them to live more comfortably with uncertainty. For example, long-term survivors of indolent lymphoma have probably adapted and developed their coping skills and gained more familiarity with the health care setting. However, the higher Appraisal of Life Threat and Treatment Intensity scores seen in the longer term indolent lymphoma survivors compared to the short term survivors (a 1.4 point difference on a scale of 0–35) suggests that even as subject's QOL improves over time, they continue to be worried about their lymphoma such as risk of relapse or need for future chemotherapy.

In contrast, the FACT score for the aggressive NHL subjects is relatively similar between the short- and the longer-term follow up groups (a difference of 0.6 points; $p>.05$), which is not surprising since the subjects in the short-term survivor group were all 2–6 years out from diagnosis. Individuals with aggressive NHL who are 5 years out from treatment are generally considered cured, but since most relapses occur within the first two years, even this short-term survivor group might have started to worry less about relapse[19]. Furthermore, by 2 years after diagnosis, most of the side effects from chemotherapy would have resolved

or at least stabilized, resulting in fewer differences between the short- and longer-term aggressive lymphoma survivors.

Our initial analysis of incurable indolent lymphoma and cured aggressive lymphoma survivors included indolent lymphoma subjects who were actively receiving chemotherapy. That analysis demonstrated a better QOL in the subjects with aggressive NHL (data not shown), but when we excluded the indolent lymphoma survivors receiving chemotherapy, most of these differences disappeared, suggesting that some of these differences in QOL might have been related to ongoing chemotherapy. By limiting our subject population, we not only removed the impact of ongoing chemotherapy, but also some of those with recently relapsed disease; it is likely that both of these changes resulted in better QOL scores for this subpopulation of the indolent lymphoma group. It has been previously reported that patients with relapsed follicular lymphoma, the most common form of indolent lymphoma, have inferior health related QOL compared to patients with newly diagnosed follicular lymphoma or lymphoma that is in a remission[20]. Although our decision to examine this subgroup of indolent lymphoma individuals makes these results relevant to a smaller group of people, it allowed us to remove confounding factors (chemotherapy and active relapse) and thus more specifically assess whether simply having an incurable lymphoma relates to poorer QOL compared to having a lymphoma that is likely cured.

Our results add to the current body of literature by evaluating the QOL in long term survivors who were on average more than 10 years since diagnosis, using data from over 500 people[1,3,4]. Blaes and colleagues reported results of two QOL questionnaires (Medical Outcomes Study 36-Item Short-form Healthy Survey and the Functional Assessment in Cancer Therapy-Fatigue scores) administered to 58 patients with aggressive NHL and 51 patients with indolent NHL who were at least 1 year out from diagnosis and 3 months from most recent chemotherapy[4]. They found no statistical difference in overall physical and mental component QOL scores between survivors of indolent NHL compared to aggressive NHL, although there was better physical function in the indolent group. Data from the Netherlands looked specifically at fatigue in lymphoma survivors who were a mean of 4.2 years since diagnosis, and did not find indolent versus aggressive lymphoma to be associated with higher fatigue score[3]. While our data support prior findings that there is no significant difference in QOL between individuals with indolent versus aggressive lymphoma, it expands on the previously available data by looking at a group much further out from the time of diagnosis. Furthermore, our subgroup analysis made an effort to remove confounding factors such as ongoing chemotherapy in order to look at the QOL of those with indolent lymphoma without potential cure versus those with aggressive lymphoma who, in all likelihood, were cured. This strategy allowed us to start to examine the question, “Do people with a long-term incurable disease have a worse QOL than those whose disease is cured?” Our findings provide increased information about the long-term relationship of different lymphoma types on survivor QOL, and demonstrate that people with indolent, incurable NHL can have QOL similar to their aggressive lymphoma counterparts.

One of the major limitations of this study is its cross sectional design. Therefore, although we looked at short- and longer-term survivor groups, we could not assess how the QOL changed for individuals with the passage of time. In addition, although we hypothesized that

time since last treatment impacted the QOL responses, we do not have data on when last treatment was received and we cannot demonstrate a causal relationship. Lastly, we did not administer the questionnaires to healthy people, so we cannot compare the QOL of lymphoma to the normal population.

These results are important as they may impact our long-term management of people with indolent lymphoma. Patients with indolent lymphoma live for many years, so focusing on their QOL is important. It is encouraging that the QOL of patients with indolent lymphoma, even when facing the incurable nature of their disease, is overall similar to that seen in subjects with aggressive NHL who have been cured.

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Table 1

Characteristics of the Study Sample (N=553)

	All Survivors		Indolent NHL		Aggressive NHL		*P*
	N=553	%	N=194	%	N=359	%	
DEMOGRAPHIC CHARACTERISTICS							
Gender							
Female	274	50	100	51	174	49	.49
Male	279	50	94	49	185	51	
Race							
White	487	88	173	89	314	87	.55
Black	44	8	13	7	31	9	
Other	22	4	8	4	14	4	
Income							
<$30,000	127	23	39	20	88	24	.57
$30,000 – $59,999	150	27	58	30	92	26	
$60,000 – $89,999	96	17	32	16	64	18	
≥$90,000	124	23	44	23	80	22	
Missing	56	10	21	11	35	10	
Education							
Less than college degree	314	57	115	59	199	55	.33
College graduate	229	41	75	39	154	43	
Missing	10	2	4	2	6	2	
Marital status							
Married	421	76	153	79	268	75	.27
Not married	130	23	41	21	89	24	
Missing	2	1	0	0	2	1	
Employment status							
Employed	229	41	76	39	153	43	.11
Retired	285	52	108	56	177	49	
Unemployed	30	5	6	3	24	7	
Missing	9	2	4	2	5	1	

	All Survivors		Indolent NHL		Aggressive NHL		*P*
	N=553	**%**	**N=194**	**%**	**N=359**	**%**	
Age (mean±SD)	61.9±13.5		62.9±12.1		61.3±14.1		.17
CLINICAL CHARACTERISTICS							
Years since diagnosis (mean±SD)	10.6±6.9		11.2±7.3		10.2±6.7		.11
Stage of disease							
I	127	23	38	20	89	25	**<.001**
II	105	19	21	11	84	23	
III	113	21	49	25	64	18	
IV	184	33	86	44	98	27	
Missing	24	4	0	0	24	7	
Ever received chemotherapy							
No	63	11	40	21	23	6	**<.001**
Yes	490	89	154	79	336	94	
Ever received a transplant [1]							
No	452	82	169	87	283	79	**.01**
Yes	101	18	25	13	76	21	
Appraisal of Life Threat and							
ALITTIQ Total Score [2]	20.0±5.6		19.2±6.2		20.5±5.2		**.01**
Treatment Intensity	10.1±3.1		9.3±3.3		10.6±3.0		**<.001**
Current Life Threat	2.9±1.5		3.2±1.5		2.8±1.5		**.01**
Past Life Threat	7.0±2.3		6.7±2.6		7.1±2.2		**.03**
Impact of Cancer							
Negative Impact Summary score [3]	2.2±0.7		2.3±0.8		2.2±0.7		.23
Appearance concerns	1.6±0.8		1.7±0.9		1.6±0.8		.19
Body change concerns	2.4±1.2		2.4±1.2		2.4±1.2		.81
Life interferences	1.9±0.7		2.0±0.7		1.9±0.6		.50
Worry	2.6±1.0		2.6±1.1		2.5±1.0		.15
Positive Impact Summary score [4]	3.5±0.7		3.5±0.8		3.6±0.7		.17
Altruism/Empathy	3.9±0.9		3.9±0.9		3.9±0.9		.49
Health awareness	3.7±0.8		3.7±0.8		3.7±0.9		.52
Meaning of cancer	2.8±1.1		2.7±1.1		2.8±1.1		.24

	All Survivors		Indolent NHL		Aggressive NHL		*P*
	N=553	%	N=194	%	N=359	%	
Positive self-evaluation	4.0±0.9		3.9±0.9		4.0±0.9		.12
Functional Assessment of Cancer							
Physical well-being[5]	23.2±5.2		23.5±5.2		23.2±5.2		.58
Social/Family well-being[6]	22.7±5.0		22.8±4.6		22.6±5.2		.78
Emotional well-being[7]	20.0±3.9		19.5±4.1		20.2±3.8		**.04**
Functional well-being[8]	21.1±5.9		20.7±6.2		21.4±5.7		.22
FACT-G Total Score[9]	87.1±15.9		86.3±16.6		87.6±15.5		.37
Lymphoma subscale[10]	49.0±9.1		48.0±9.6		49.5±8.8		.07
FACT-LYM Total Score[11]	136.2±23.7		134.2±25.2		137.2±22.8		.16

[1] Bone marrow or stem cell transplant

[2] Appraisal of Life Threat and Treatment Intensity Questionnaire; possible range, 0 – 35; higher scores indicate more negative appraisals (lower quality of life)

[3] Impact of Cancer score; possible range, 1–5; higher scores indicate more negative impact (lower quality of life)

[4] Impact of Cancer score; possible range, 1–5; higher scores indicate more positive impact (higher quality of life)

[5] FACT PWB; possible range, 0–28

[6] FACT SFWB; possible range, 0–28

[7] FACT EWB; possible range, 0–24

[8] FACT FWB; possible range, 0–28

[9] FACT-General Total Score; possible range, 0–108

[10] FACT-Lymphoma module; possible range, 0–60

[11] FACT-Lymphoma Total Score; possible range, 0–168

Table 2

Means and Interaction Effects for Short-term and Long-Term Survivors, Indolent and Aggressive NHL (N=553)

	Short-term Survivors			Long-term Survivors			
	Indolent N=50	**Aggressive N=115**	***P***	**Indolent N=144**	**Aggressive N=244**	***P***	***P*[1]**
Appraisal of Life Threat and Treatment Intensity							
ALTTIQ Total Score[2]	18.10	21.04	**.01**	19.59	20.23	.28	**.04**
Treatment Intensity	8.81	10.60	**.004**	9.44	10.53	**.001**	.26
Current Life Threat	3.08	3.04	.86	3.19	2.68	**.002**	.12
Past Life Threat	6.32	7.28	**.02**	6.78	7.02	.33	.12
Impact of Cancer							
Negative Impact Summary score[3]	2.33	2.24	.45	2.20	2.11	.28	.93
Appearance concerns	1.72	1.59	.32	1.70	1.62	.36	.77
Body change concerns	2.63	2.62	.97	2.35	2.29	.64	.83
Life interferences	1.98	1.93	.66	1.96	1.92	.59	.91
Worry	2.79	2.65	.46	2.59	2.45	.17	.99
Positive Impact Summary score[4]	3.39	3.71	**.01**	3.51	3.50	.93	**.03**
Altruism/Empathy	3.79	4.06	.07	3.88	3.85	.73	.10
Health awareness	3.60	3.88	**.04**	3.71	3.66	.61	.06
Meaning of cancer	2.67	2.94	.15	2.68	2.72	.70	.32
Positive self-evaluation	3.70	4.14	**.003**	3.97	3.97	.96	**.01**
Functional Assessment of Cancer Therapy							
Physical well-being[5]	22.47	22.93	.63	23.80	23.34	.38	.38
Social/Family well-being[6]	22.41	23.30	.28	22.87	22.32	.30	.15
Emotional well-being[7]	18.00	19.93	**.02**	20.03	20.36	.42	**.04**
Functional well-being[8]	18.52	21.84	**.003**	21.46	21.15	.61	**.002**
FACT-G Total Score[9]	81.20	88.00	**.03**	88.04	87.41	.70	**.02**
Lymphoma subscale[10]	46.00	48.89	.10	48.67	49.74	.26	.32
FACT-LYM Total Score[11]	127.10	136.98	**.04**	136.67	137.36	.78	.06

[1] P value is for two-way interaction of long-term survivor (<6 years vs. ≥6 years post-diagnosis) X tumor type (indolent vs. aggressive)

[2] Appraisal of Life Threat and Treatment Intensity Questionnaire; possible range, 0 – 35; higher scores indicate more negative appraisals (lower quality of life)

[3] Impact of Cancer score; possible range, 1–5; higher scores indicate more negative impact (lower quality of life)

[4] Impact of Cancer score; possible range, 1–5; higher scores indicate more positive impact (higher quality of life)

[5] FACT PWB; possible range, 0–28

[6] FACT SFWB; possible range, 0–28

[7] FACT EWB; possible range, 0–24

[8] FACT FWB; possible range, 0–28

[9] FACT-General Total Score; possible range, 0–108

[10] FACT-Lymphoma module; possible range, 0–60

[11] FACT-Lymphoma Total Score; possible range, 0–168