VOLUME 30 · NUMBER 13 · MAY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Relationship Between Deficits in Overall Quality of Life and Non–Small-Cell Lung Cancer Survival

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Submitted December 29, 2010; accepted December 20, 2011; published online ahead of print at www.jco.org on March 26, 2012.

Supported by National Institutes of Health Research Grants No. CA77118, CA80127, and CA84354 (P.Y.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/12/3013-1498/$20.00

DOI: 10.1200/JCO.2010.33.4631

ABSTRACT

Purpose
Evidence has suggested a clinically meaningful relationship between self-reported quality of life (QOL) of a patient with cancer at the time of receiving a cancer diagnosis and overall survival (OS). This study evaluated the prognostic value of QOL assessments with regard to OS in a large cohort of patients with lung cancer.

Patients and Methods
A total of 2,442 patients with non–small-cell lung cancer were observed between 1997 and 2007 and completed a single-item measure of overall QOL within the first 6 months of receiving a lung cancer diagnosis; these were dichotomized using an a priori definition of a clinically deficient score (CDS; ≤ 50 $v > 50$). Kaplan-Meier estimates and Cox models were used to evaluate the prognostic importance of QOL on OS alone and in the presence of covariates. Logistic regression modeling was used to identify which clinical and patient characteristics were related to a clinically meaningful deficit in QOL.

Results
QOL deficits at time of lung cancer diagnosis were significantly associated with OS (hazard ratio [HR], 1.55; $P < .001$), as were performance status, older age, smoking history, male sex, treatment factors, and stage of disease. The median survival for patients with CDS QOL was 1.6 years versus 5.6 years for patients with non-CDS QOL. After controlling for all these covariates, the indication of a clinically deficient baseline QOL still contributed significantly to the prediction of patient survival (HR, 0.67; $P < .001$).

Conclusion
Overall QOL measured by a simple single item at the time of lung cancer diagnosis is a significant and independent prognostic factor for survival in patients with lung cancer.

J Clin Oncol 30:1498-1504. © 2012 by American Society of Clinical Oncology

INTRODUCTION

Quality of life (QOL) is a critical aspect of living with lung cancer.[1-5] Validated lung cancer–specific QOL measures such as the European Organisation for the Research and Treatment of Cancer and Functional Assessment for Chronic Illness Treatment tools have been applied in clinical studies.[6-12] A systematic review exists of QOL assessment in non–small-cell lung cancer (NSCLC).[13]

There is a strong association between QOL and survival in cancer populations.[14-18] Gotay et al[19] published a critical systematic review indicating that QOL at time of diagnosis was prognostic for survival. Quinten et al[20] carried out a meta-analysis involving more than 10,000 patients with cancer and found that baseline QOL was a prognostic indicator of survival. Efficace et al,[9,21] Montazeri et al,[22] Mauer et al,[23] and our research team[24,25] have replicated this finding in various cancer populations.

Information regarding factors associated with long-term cancer survival is expanding.[3,26-28] Most work has involved patients with breast cancer, indicating that the QOL of breast cancer survivors typically returns to normal over time. The situation is starkly different for lung cancer, because most patients with lung cancer will not live long after diagnosis. However, Mountain[29] reported 2-year survival as 37% to 86% and 5-year survival as 22% to 67% among patients with stage I or II disease; hence, a substantial proportion of patients with early-stage lung cancer will survive with considerable QOL issues.[30]

Few studies have described the QOL of lung cancer survivors beyond the acute treatment period. A prior study conducted by our group reported on the association between cigarette smoking and QOL

up to 3 years after lung cancer diagnosis, with only secondary attention given to other factors possibly associated with QOL.[31] Results of our companion study[32] indicated that long-term cancer survivors suffered substantial symptom burden that significantly impaired QOL.[33]

The primary aim of this study was to confirm the prognostic value of QOL at the time of lung cancer diagnosis in predicting survival among patients with lung cancer. A secondary aim was to identify a patient profile associated with poor QOL at the time of diagnosis of lung cancer. The overarching goal of this program of research is to explore which patients with lung cancer have poor QOL and then to design interventions that can be delivered in the cancer care setting to improve QOL, prevent QOL deficits, and perhaps ultimately improve survival.

PATIENTS AND METHODS

Sample

The Mayo Clinic Epidemiology and Genetics of Lung Cancer Research Program has enrolled and prospectively observed patients either diagnosed with and/or treated for lung cancer at the Mayo Clinic (Rochester, MN) since its inception in 1997. Between January 1, 1997, and December 31, 2009, more than 10,000 patients with lung cancer have been enrolled. Procedures for identifying and observing patients with lung cancer enrolled onto this program have been previously described.[34] Patients provided informed consent for the study, and it was approved by the relevant ethics committees. Patient follow-up was accomplished by a mailed questionnaire within 6 months after diagnosis and annually thereafter, as described in the parent protocol.[34]

QOL Assessment

QOL was assessed at all follow-up time points by means of one item from the Lung Cancer Symptom Scale.[35,36] The overall QOL item served as the primary end point in the current study. In the primary analysis, overall QOL was considered as a continuous variable, taking integer values from 0 to 100.[37-40] A score below 50 was indicative of a need for immediate exploration and intervention for the QOL deficit.[41-43] This cutoff has been validated by our research team[39,44] and independently by others.[45-47]

Analysis

The primary aim of the statistical analysis was to explore the prognostic power of a clinically meaningful deficit in QOL (score $\leq$ 50 on 0 to 100 point scale) in terms of predicting survival. Secondary aims included investigating the impact of concomitant covariates on the prognostic power of the QOL assessment. Ancillary aims included looking at the relationship among various baseline covariates and overall QOL.

Covariates considered in this study included a collection of baseline characteristics with purported association with QOL, as suggested by previous authors.[16,18,31] These variables can be broadly grouped into demographic (age, sex, race, comorbidities), social (employment status, marital status, years of education), smoking history (pack years, never, former, recent quitter, still smoking) disease-related (histology, stage, grade), and treatment-related (chemotherapy, radiation, surgery) characteristics. In previous studies, we examined the variability of time since diagnosis within the 6-month eligibility period for this study and found no impact on the findings reported herein.[32,34] Given the prevalence of cigarette smoking in patients with lung cancer, smoking classification was assessed in several ways. First was pack years, defined as the number of packs of cigarettes smoked over time. For example, a participant who smoked one pack of cigarettes per day for 20 years would have a 20-year pack history. Participants were also classified according to smoking status at the time they completed the QOL item: never smoker ($<$ 100 lifetime cigarettes), former smoker (quit $>$ 12 months), recent quitter (quit $>$ 30 days but $<$ 12 months), or current smoker (any tobacco usage in the past 30 days).

Collinearity among covariates was examined in previous studies[34] via the methods of Belsey et al,[48] including variance inflation factors and index numbers so that overlap among the independent variables did not affect the resultant findings. In two previous studies, we carried out extensive investigations for redundancy among the various covariates and only included in this study those that were identified as significant independent prognostic indicators on survival.[49,50]

The primary aim was accomplished using Kaplan-Meier survival estimates and associated multivariate Cox proportional hazards models to assess the prognostic power of QOL for survival in the presence of the aforementioned covariates. The secondary aim of identifying which patient and disease characteristics were associated with a report of a clinically meaningful deficit in QOL was explored using univariate Fisher's exact and *t*-tests followed by a stepwise logistic regression modeling process.

Power Considerations

The large sample (2,442 patients with lung cancer) available through the Mayo Clinic Epidemiology and Genetics of Lung Cancer Research Program provides considerable precision for all analytic procedures. Any percentage reported on the total sample is accurate to within 2% of the population percentage with 95% confidence. Any average QOL score is accurate to within 4% times the standard deviation, or less than one point on a 100-point scale.[51] A Fisher's exact test has 80% power to detect a difference of 6% between the incidence rates of men and women reporting a deficit in QOL. Finally, a Kaplan-Meier–based survival analysis log-rank test has 80% power to detect a median difference of 1 month in the median survival between those who report a clinically meaningful deficit in QOL versus those who do not. This power calculation assumes a 12-month median survival in the group not reporting a deficit in QOL. Because power was plentiful for this study, it was more important to examine the effect sizes observed instead of the *P* values.

RESULTS

Sample Characteristics

A total of 2,442 patients with lung cancer who completed the overall QOL item at least once within 6 months of receiving their lung cancer diagnosis were included in the analysis. Demographic variables are presented for the entire sample and classified by QOL score in Table 1. Over the 11-year study period, 120 (5%) of the 2,442 patients with lung cancer survived, and 2,320 (95%) died. A majority of patients were men, white, and married; had good performance status and early disease stage; were never or former smokers who had quit smoking more than 20 years ago; and had undergone surgical treatment.

QOL

Clinically significant deficits in QOL were reported by 510 patients (21%). Patients who reported a clinically significant deficit in QOL tended to be older than those who did not report a QOL deficit (59% *v* 53% $>$ 65 years of age). Patients with a QOL deficit were also more likely to be current smokers (36% *v* 28%) and men (65% *v* 50%) and to have worse performance status (51% *v* 93%). Patients with a QOL deficit were less likely to have had surgery (54% *v* 74%) and less likely to have early disease stage (44% *v* 61%) than those who did not report a QOL deficit. The average overall QOL scores were similar among different measurement approaches: first, when QOL was assessed the first time (70.8; standard deviation [SD], 24.04); second, when QOL scores were averaged across the early 3 years of assessment for each patient (70; SD, 23.01); third, when QOL scores were averaged across 5 years of assessment (73.3; SD, 20.49); and fourth, when averaged over all assessments (68.8; SD, 22.34). For the four measurement approaches, 24% (597 of 2,442 patients), 20% (471 of 2,335), 16% (108 of 691), and 23% (553 of 2,442) of the patients, respectively,

Table 1. Patient Demographics and Clinical Characteristics by First QOL Assessment (N = 2,442)

Characteristic	QOL > 50 (n = 1,932) No.	%	QOL ≤ 50 (n = 510) No.	%	Total (N = 2,442) No.	%	*P*
Age, years							.005
< 50	198	10	31	6	229	9	
50 to < 65	707	37	180	35	887	36	
65 to 80	914	47	276	54	1,190	49	
> 80	113	6	23	5	136	6	
Smoker category							< .001
Never	360	19	61	12	421	17	
Former	1,035	54	266	52	1,301	53	
Recent quitter/abstinent	316	16	104	20	420	17	
Current/persistent	221	11	79	16	300	13	
Treatment							< .001
Surgery	1,431	74	277	55	1,708	70	
Radiation or chemotherapy only	199	10	89	17	288	12	
Radiation plus chemotherapy	225	12	108	21	333	14	
Other	77	4	36	7	113	4	
Sex							< .001
Female	975	51	175	34	1,150	47	
Male	957	49	335	66	1,292	53	
Any minority							.16
Missing	0		1		1		
No	1,800	93	483	95	2,283	94	
Yes	132	7	26	5	158	6	
Race							.09
Missing	0		1		1		
White	1,802	92	487	95	2,289	92	
Hispanic	15	1	5	1	20	1	
Alaskan native	95	5	15	3	110	5	
Black	15	1	0	0	15	1	
Asian/Pacific Islander	5	1	2	1	7	1	
Marital status							.83
Missing	206		86		292		
Single	64	4	19	5	83	4	
Married	1,373	80	328	77	1,701	79	
Divorced	111	6	28	7	139	6	
Widowed	178	10	49	11	227	11	
Disease stage							< .001
I	973	50	181	36	1,154	48	
II	205	11	46	9	251	10	
III/limited	433	22	159	31	592	24	
IV/extensive	321	17	124	24	445	18	
ECOG performance status							< .001
Missing	40		12		52		
Fully active	840	44	27	6	867	36	
Light work	913	48	223	45	1,136	47	
Unable to work	122	6	159	31	281	12	
Limited self-care	15	1	74	14	89	4	
Disabled	2	1	15	3	17	1	
Smoking cessation, years							< .001
Quit ≥ 10 or never smoked	1,072	56	241	47	1,313	54	
Quit 3-9	251	13	66	13	317	13	
Quit 1-2	105	5	34	7	139	5	
Quit at or after diagnosis	414	21	125	25	539	22	
Never quit	90	5	44	8	134	6	
Pack years smoked							< .001
Missing	6		2		8		
0 to < 20	697	36	114	22	811	33	
20 to < 40	431	23	99	20	530	22	
40 to < 60	407	21	150	29	557	23	
> 60	391	20	145	29	536	22	
Mean time from diagnosis, years	1.36		1.39		1.37		.6960
SD	1.26		1.36		1.28		
Median	0.99		0.85		0.97		
Any other cancer							.4737
No	1,655	86	444	87	2,099	86	
Yes	277	14	66	13	343	14	
Any other lung disease							.8163
No	1,463	76	389	76	1,852	76	
Yes	469	24	121	24	590	24	
Any other disease							.0014
No	1,409	73	407	80	1,816	74	
Yes	523	27	103	20	626	26	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; QOL, quality of life; SD, standard deviation.

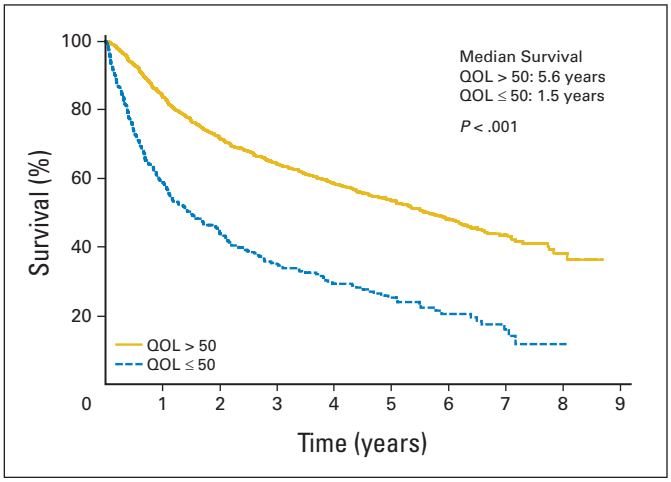

Fig 1. Kaplan-Meier survival curves for 2,442 patients with non–small-cell lung cancer by overall quality-of-life (QOL) categorization into clinically meaningful deficit versus no deficit.

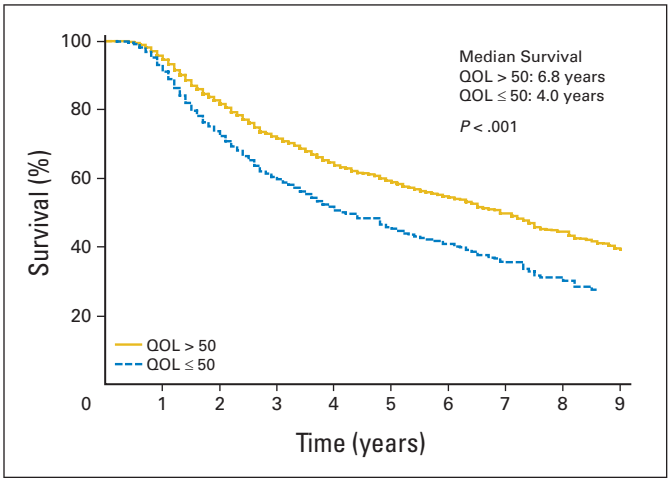

Fig 2. Kaplan-Meier survival curves by first quality-of-life (QOL) assessment adjusted for age, sex, treatment, and smoking status.

reported a clinically meaningful deficit in overall QOL (≤ 50). Subsequent analyses produced the same results for all measurement approaches. The score closest to the time of diagnosis has the most clinical utility for the cancer care practitioner, so results for the first QOL assessment are presented for the remainder of the report.

Survival Analysis

Kaplan-Meier estimate survival curves by QOL classification score are shown in Figure 1, indicating survival from the first QOL assessment between those who have a clinically deficient score (CDS) in QOL versus those who do not. Patients who reported CDS QOL had a median survival of 1.5 years, compared with 5.6 years for patients who reported a non-CDS QOL at baseline ($P < .001$).

Subsequent to the univariate survival analysis, exploration for significant concomitant influences was undertaken using a Cox regression model. Association with OS was indicated for age, treatment, sex, disease stage, Eastern Cooperative Oncology Group performance score, disease recurrence/progression, having any other cancer, and time since cancer diagnosis. Modified survival curves controlling for these variables are depicted in Figure 2, indicating a persistent difference in overall survival between patients who reported CDS QOL and those who reported non-CDS QOL. After controlling for all these factors, the indication of CDS QOL at first assessment continued to demonstrate a relationship with patient survival (Table 2; hazard ratio, 1.4; $P < .001$). Smoking category and status at follow-up, years since quitting smoking, and years of consuming one pack every day were not contributing factors for survival in this analysis. As previously stated, these analyses were repeated using QOL scores across the first 3 years after diagnosis and across all years, with similar results (data not shown).

QOL Correlates

Having established the importance of QOL at the time of lung cancer diagnosis as a prognostic indicator, we explored which factors affected baseline QOL (Table 3). A deficit in patient overall QOL was associated with a considerable number of variables in a univariate model including age, sex, disease stage, smoking status, treatment type, Eastern Cooperative Oncology Group performance score, smoking cessation, and pack years smoked. Clearly, many of these variables are related to one another. When these variables were input into a stepwise logistic regression procedure, age, sex, performance status, disease stage, disease recurrence, and presence of another cancer diagnosis were selected via the modeling process as significant influences on the likelihood for the presence of CDS QOL. This model had a pseudo-R^2 of 22%, indicating that overall QOL was much more than a simple amalgamation of performance status and some other demographic and clinical variables.

DISCUSSION

The importance of QOL to patients with cancer and their caregivers has been well documented. Patients with cancer care deeply about their mortality but also about their QOL during the time they have left. In this large sample of patients with lung cancer, QOL at the time of diagnosis was found to be related to mortality. Therefore, if these findings are confirmed by other investigators, perhaps QOL at the time of lung cancer diagnosis has a clinically meaningful impact both on QOL over time and on survival rates. Regardless, the strong association between deficits in overall QOL and survival observed in this large prospective sample of patients with lung cancer highlights the importance of assessing QOL of patients with lung cancer at the time of diagnosis as part of their ongoing cancer care. That this relationship remains significant even after controlling for known factors related to survival provides evidence that QOL is as important as smoking status or stage of disease in predicting survival from lung cancer.

Our findings are consistent with those of other studies that investigated the importance of QOL in patients with NSCLC, notably studies by the Radiation Therapy Oncology Group, indicating that QOL is a strong prognostic indicator in this patient population.[52,53] It is possible that interventions designed and tailored for patients with lung cancer may improve both their QOL and likelihood of survival. These findings add to the ever-growing research literature that points toward an important and crucial role for assessing QOL in clinical practice and hold the potential for identifying subsets of patients who are experiencing deficits in QOL and may therefore benefit from specific attention to these expressed QOL needs.[54-57]

Table 2. Saturated Multivariate Cox Regression Model Survival Analysis Using First QOL Assessment

Effect	HR	95% CI	*P*
QOL ($v > 50$)*			
≤ 50	1.55	1.30 to 1.85	< .001
Age, years ($v > 80$)*			
50 to < 65	0.36	0.27 to 0.48	< .001
65 to 80	0.56	0.43 to 0.73	< .001
≤ 50	0.35	0.24 to 0.51	< .001
Smoker category (*v* current smoker)*			
Never	1.31	0.83 to 2.08	.24
Former	1.22	0.83 to 1.8	.32
Recently quit	1.51	1.14 to 1.99	.004
Treatment (*v* other)*			
Radiation or chemotherapy only	0.87	0.58 to 1.30	.5
Radiation plus chemotherapy	0.61	0.40 to 0.91	.02
Surgery	0.23	0.15 to 0.34	< .001
Sex (*v* male)*			
Female	0.83	0.72 to 0.975	.015
Stage (*v* IV)*			
I	0.39	0.31 to 0.48	< .001
II	0.59	0.45 to 0.78	< .001
III/limited	0.67	0.55 to 0.81	< .001
Recurrence and/or progression (*v* yes)*			
No	0.51	0.44 to 0.6	< .001
ECOG performance status (*v* 2, 3, 4)*			
0, 1	0.53	0.44 to 0.64	< .001
Smoking cessation, years (*v* never quit)*			
Quit 1-2	0.73	0.45 to 1.19	.21
Quit 3-9	0.64	0.4 to 1.01	.06
Quit ≥ 10 or never smoked	0.6	0.38 to 0.96	.03
Quit at or after diagnosis	0.45	0.32 to 0.62	< .001
Pack years smoked ($v > 60$)*			
0 to < 20	0.73	0.57 to 0.95	.02
20 to < 40	0.89	0.72 to 1.09	.24
40 to < 60	1.14	0.94 to 1.38	.18
Any other cancer (*v* yes)*			
No	1.32	1.09 to 1.58	.004
Time from diagnosis, per year	0.66	0.62 to 0.71	< .001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; QOL, quality of life.
*Reference group.

Table 3. Univariate and Stepwise Logistic Regression Model Results: Variables Associated With QOL at First Assessment

Variable	Univariate *P**	Logistic Regression	
		Estimate	*P*
Intercept		−6.19	< .001
Age	.02	0.22	.02
Sex	< .001	0.35	.006
Stage	< .001	0.13	.03
Smoking status	< .001	−0.2	.33
Treatment	< .001	0.12	.50
ECOG performance status	< .001	0.17	.04
Recurrence and/or progression	.25	2.33	< .001
Smoking cessation	< .001	0.16	.26
Pack years smoked	< .001	0.15	.06
Any other cancer	.54	0.16	.011
Time from diagnosis	.67	0.01	.81

Abbreviations: ECOG, Eastern Cooperative Oncology Group; QOL, quality of life.
*Fisher's exact test for categorical variables; two-sample *t* test for continuous variables.

Although the study had a high enrollment and adherence rate, the interplay of many forces makes interpreting longitudinal QOL results challenging. The data presented here came from a set of patients with lung cancer able and willing to respond to the mailed questionnaires and do not accurately represent our overall cohort of patients with lung cancer, potentially introducing bias. A recently reported study conducted by our group restricted to long-term lung cancer survivors with QOL assessments within 3 and beyond 5 years after diagnosis did demonstrate worsening QOL over time (Yang et al, manuscript submitted for publication). The cohort in the current study did not include long-term survivors exclusively; rather, it was a group of survivors observed longitudinally beginning at diagnosis and continuing to death.

The relationship between QOL and survival also has a possible psychosocial connection that warrants investigation. Adherence to cancer care is important for positive health outcomes. Perhaps, given their poor functioning, individuals with poor QOL demonstrate poor adherence to their medical treatment.[58,59] If a patient with lung cancer is not feeling well, optimistic, or motivated, it would seem possible that he or she may be less likely to keep medical appointments, attend treatment sessions, or adhere to medication plans. Future investigators should include measures of adherence to cancer treatment when examining QOL deficits in patients with lung cancer.

The use of a single-item assessment for identifying deficits in QOL is naturally appealing for its simplicity, although it naturally is unable to describe the precise nature of the deficit observed. Herein lie the complementary roles that single- and multiple-item QOL assessments can play in cancer research and clinical practice, as described by Sloan et al.[37,38] The single-item QOL assessment has the advantage of covering any and all domains that the patient defines as important to his or her QOL, which a predefined multiple-item scale might not include. However, once these are identified, the role of the multiple-item scale in describing the precise nature of the deficit and identifying potential follow-up interventions is obvious.

We have begun to use brief QOL assessments routinely at baseline in North Central Cancer Treatment Group clinical trials and during clinical oncology visits at the Mayo Clinic to begin incorporating this information into patient care decisions. Preliminary findings indicate that as many as 20% of oncology practice patients report a clinically significant deficit in QOL, with scores ≤ 2 on a scale of 0 to 10. Furthermore, between 20% and 50% of our patients with cancer report clinically deficient QOL in domains that can be ameliorated with relatively simple and established interventions, such as antidepressants for fatigue, pharmacologic solutions for erectile dysfunction, and counseling for social and financial aspects of QOL.

In summary, this prospective study of a large cohort of patients with lung cancer adds to the growing evidence that patient-reported QOL outcomes at the time of cancer diagnosis can identify vulnerable subpopulations. Over and above performance status and key clinical and demographic variables, a QOL patient-reported outcome assessment can identify deficits that are independently associated with abbreviated survival. The next step in this line of research is to develop

and test interventions to apply when QOL deficits occur to improve patient QOL and survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jeff A. Sloan, Matthew M. Clark, Ping Yang
Collection and assembly of data: Jeff A. Sloan, Jason Wampfler, Ping Yang
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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