Prognostic Significance of Decline in Patient-Reported Quality of Life during Early Lung Cancer Survivorship: Pooled Secondary Analysis of RTOG 0212 and 0214

Short/Running Title: Prognostic Significance of QOL Decline in Lung Cancer

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Conflict of Interest Statement: None

Funding Statement
This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP) from the National Cancer Institute (NCI).

Data Availability Statement
All data will be made available per the NCTN Data Archive rules. The link for the archive is: https://nctn-data-archive.nci.nih.gov/.

Presentation Information: (if available)

Keywords: Lung cancer, quality of life, RTOG 0212, RTOG 0214, prophylactic

Acknowledgements: (if available)

www.ClinicalTrials.gov
NRG Oncology RTOG 0212 NCT00057746
NRG Oncology RTOG 0214 NCT00048997

Abstract

Purpose: To assess the impact of longitudinal decline in patient-reported quality of life (QOL) on subsequent disease relapse and overall survival following curative treatment for limited-disease small cell lung cancer (LD-SCLC) and locally advanced non-small-cell lung cancer (LA-NSCLC).

Patients and Methods: Patients with LD-SCLC and LA-NSCLC were enrolled on RTOG trials 0212 and 0214, respectively. QOL was assessed as a secondary endpoint using EORTC QLQ-C30 and BN20 questionnaires at baseline (following locoregional therapy but before PCI or observation) and at 6 and 12 months follow-up. Data were pooled for this analysis. Patients who developed any relapse prior to follow-up evaluation were excluded. Decline in quality of life at 6 and 12 months follow-up, compared to baseline, was defined using the reliable change index method and correlated with overall survival and subsequent brain and any distant relapse.

Results: 552 (91%) of the 604 eligible patients who accrued to RTOG 0212 and RTOG 0214 had baseline QOL assessments and were included in this pooled analysis. Decline in global health status/QOL at 6 months was associated with higher subsequent distant relapse rates (p=0.02) and inferior overall survival (p<0.0001). In addition, decline in global health status/QOL (p=0.009) and cognitive functioning (p=0.04) at 12 months was associated with inferior overall survival.

Conclusion: Longitudinal decline in global health status/QOL in relapse-free 6-month survivors of lung cancer is a potential early surrogate marker for subsequent distant relapse and poor prognosis. Consideration should be given to incorporating QOL monitoring into standard clinical approaches for disease surveillance.

Introduction

Multiple studies have identified pre-treatment quality of life as an independent predictor of long-term survival in lung cancer [1-5]. However, pre-treatment quality of life represents a single snapshot in the longitudinal process of treatment, follow-up and survivorship in lung cancer patients. During this process, dynamic changes in patient-reported quality of life may have prognostic implications[1]. However, assessing longitudinal changes in quality of life on prospective lung cancer trials is commonly impeded by poor survival and long-term non-compliance. Therefore, to assess the significance of longitudinal change in quality of life, we pooled data from two recently published lung cancer trials from the Radiation Therapy Oncology Group (RTOG).

RTOG 0212 was a randomized trial of high- or standard-dose prophylactic cranial irradiation (PCI) in limited disease small cell lung cancer (LD-SCLC) following complete response to chemotherapy and thoracic radiotherapy [6]. RTOG 0214 was a randomized trial of PCI or observation in patients with locally advanced non-small cell lung cancer (LA-NSCLC) with stable disease or complete/partial response after potentially curative therapy[7]. In both trials, patient-reported quality of life was assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)[8] and its brain module (EORTC BN20)[9]. In addition, in both trials baseline QOL was evaluated following curative loco-regional treatment, with follow-up serial assessments occurring at the same time points (i.e., 6 and 12 months after randomization). Within each study, quality of life analyses were limited by sample size and non-compliance[10,11]. Given the uniformity of QOL instruments and serial assessment time points, we sought to pool these quality of life data into a larger analysis of the prognostic significance of longitudinal QOL change.

Patients and Methods

The details regarding patient eligibility and treatment on RTOG 0212 and RTOG 0214 have been previously described [6,7]. Briefly, eligibility for RTOG 0212 was limited to patients with LD-SCLC with complete response to chemotherapy and thoracic radiotherapy; negative findings on MRI or CT scans of the brain at most 1 month before study entry; Zubrod performance status≤1; and, RTOG neurologic function class of 1 or 2. Eligibility on RTOG 0214 was limited to patients with stage IIIA/B NSCLC with stable disease or complete/partial response after definitive locoregional therapy; no evidence of progressive intra-thoracic disease, brain metastases or extra-cranial metastases on post-treatment restaging scans (CT scan of the chest and abdomen and MRI or CT of the brain) obtained within 6 weeks of study entry; and, resolution to grade≤2 of any acute or subacute grade≥3 toxicities from prior therapy. All patients signed an institutional review board-approved, study-specific consent form.

RTOG 0212 stratified patients by age (≤60 vs. >60) and interval from the start of induction therapy to randomization (≤90 days vs. 91-180 days vs. 181-240 days) and randomized them to standard-dose PCI (25 Gy in 10 daily fractions) or high-dose PCI (36 Gy in 18 daily or 24 twice daily fractions). RTOG 0214 stratified patients by stage (IIIA vs. IIIB), histology (squamous cell vs. non-squamous cell), and prior therapy (surgery vs. no surgery) and randomized them to PCI (30 Gy in 15 daily fractions) or observation.

Quality of Life Assessments

In both studies, patient-reported outcomes were captured prospectively using the EORTC Core Quality of Life Questionnaire (QLQ-C30) and the EORTC Brain Cancer Module (BN20). EORTC QLQ-C30 is a 30-item self-report questionnaire containing the following domains (scales): physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), global quality of life (2 items), fatigue (3 items), pain (2 items), nausea and vomiting (2 items), and single items for dyspnea, insomnia, anorexia, constipation, diarrhea and financial impact [8]. EORTC BN20 is a 20-item supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain cancer and containing 4 multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizure, drowsiness, hair loss, itching, weakness of both legs, and difficulties with bladder control)[9]. Scores for the QLQ-C30 and BN20 were converted to lie in a range between 0-100, according to the guidelines of EORTC[12]. For the functioning scales and global QOL scale, higher scores indicate better functioning, whereas for the symptoms higher scores indicate greater symptom severity. Both instruments have been previously shown to be reliable and valid instruments in the setting of recurrent high-grade gliomas[9,13]. In addition, QLQ-C30 has demonstrated adequate reliability in patients with lung and other cancer diagnoses[8,14-16].

In both studies, baseline QOL assessments were completed within 1 week prior to study entry, that is, following curative locoregional therapy but before the initiation of PCI or observation. Serial follow-up evaluations of QOL were performed at 6 and 12 months after study entry. Since patient follow-up did not always occur at exactly 6 and 12 months follow-up, data obtained within 4 weeks before or after these time points were included.

Statistical Methods

Data from RTOG 0212 and RTOG 0214 were pooled for this analysis. Given the potential impact of relapse on quality of life, patients who developed any relapse (intra-thoracic, brain or extra-cranial distant) prior to or at the time of the follow-up evaluation were excluded. Comparisons of categorical patient characteristics were done using chi-square test statistics, and comparisons of continuous patient characteristics were done using the F statistic from analysis of variance. Baseline comparisons of continuous EORTC QLQ-C30 and BN20 values were done using the Kruskal-Wallis two-sided rank test to compare means. Due to multiple testing for correlations between patient characteristics and EORTC QLQ-C30 and BN20 scores, only p-values <0.001 were considered statistically significant for those correlations. Follow-up EORTC QLQ-C30 and BN20 differences were categorized as decline or no decline from baseline using the reliable change index (RCI) method[17] and comparisons were made using chi-square test statistics.

An overall survival event was death due to any cause. Overall survival time was estimated from the date of randomization to the date of death or last follow-up if the patient was still alive. Overall survival rates were estimated using the Kaplan-Meier method, and comparisons tested using the log-rank statistic. The development of at least one brain metastasis was considered a failure for the brain relapse endpoint; the development of at least one distant metastasis, including in the brain, was considered a failure for the distant relapse endpoint. For both relapse endpoints, death without a relevant metastasis was considered a competing risk, and patients still alive without developing relapse were censored at the date of last follow-up. Time to brain or distant relapse was estimated from the date of randomization to the date relapse was first diagnosed or the date of death or last-follow-up if the patient did not develop relapse. Brain and distant relapse failure rates were estimated using the cumulative incidence method and tested using Gray's test.

To determine whether a given QOL measure was independently associated with outcomes, Cox proportional hazards models were used for overall survival, and Fine and Gray's proportional hazards models were used for brain and distant relapse. A p-value<0.05 was considered statistically significant. The following patient characteristics were considered individually for inclusion in multivariate models of QOL and outcomes: age (continuous or categorical ≤60 (reference level (RL)) vs. >60), gender (female (RL) vs. male), education level (< high school (RL) vs. high school vs. >high school), marital status (married/living as married (RL) vs. single/divorced/widowed), histology (SCLC [RL] vs. NSCLC), PCI use (PCI (RL) vs. no PCI), PCI dose group (standard dose (2.5 Gy x 10 on RTOG 0212 or 3.0 x 10 Gy on RTOG 0214) (RL) vs. high dose (2.0 Gy x 18 or 1.5 Gy x 24 on RTOG 0212) vs. no PCI), and baseline Zubrod performance status (0 (RL) vs. 1). Analyses of Zubrod PS excluded patients with Zubrod PS ≥2 due to small numbers and since RTOG 0214 excluded such patients. Baseline EORTC score and any characteristic associated in univariate modeling with a given outcome at a significance level of $p<0.05$, were included in multivariate modeling. Fisher's exact test was used to test for potential correlations between probabilities of decline in different EORTC functional or symptom scales.

Statistical Analysis Software® (SAS Institute, Cary, NC) version 9.2 was used for all statistical analyses except for Fine and Gray's modeling which was analyzed using R software.

Results

A total of 604 eligible patients were accrued to RTOG 0212 (n=264) and RTOG 0214 (n=340) (CONSORT). Compliance with EORTC QLQ-C30 and BN20 assessments was similar between RTOG 0212 and RTOG 0214 at baseline ($p = 0.61$) but higher in RTOG 0214 at 6 months (p=0.01) and 12 months (p=0.001). ≥98% patients completing QOL questionnaires responded to all questions. Baseline characteristics in patients enrolled on RTOG 0212 and those enrolled on RTOG 0214 were similar, except for more advanced education reported by patients enrolled on RTOG 0212 (p=0.01; Table 1).

Comparisons of baseline EORTC QLQ-C30 scores demonstrate better QOL and symptoms across multiple measures for patients with Zubrod PS 0 compared to Zubrod PS 1 (online only). In addition, patients older than 60 reported better emotional functioning (p=0.0001) and less severe pain (p<0.0001), insomnia (p=0.0003) and financial difficulties (p<0.0001), compared to patients 60 years of age or younger. Other significant associations were 1) more severe dyspnea reported amongst patients with NSCLC compared to SCLC (p=0.0004), 2) worse emotional functioning amongst women compared to men (p=0.0001), and 3) less financial difficulty amongst patients with more than a high school education (p=0.0007). Similar comparisons of baseline BN20 scores revealed more severe headaches (p<0.0001), hair loss (p<0.0001) and bladder control (p<0.0001) reported by women; less future uncertainty reported by patients with Zubrod PS 0 (p=0.0008); and, greater future uncertainty (p<0.0001) and more severe headaches (p<0.0001) reported by patients ≤60 years of age.

PCI use was associated with higher rates of decline in patient-reported cognitive functioning at 6 months (p<0.0001; Table 2) and 12 months (p<0.0001; Table 3). PCI dose also predicted for patient-reported cognitive functioning at 6 months (p<0.0001) and 12 months (p=0.0002), but this was attributed to differences between PCI and no PCI cohorts rather than differences between standard- vs. high-dose PCI. In addition, higher rates of decline in reported motor dysfunction at 12 months follow-up was associated with PCI use (p=0.002).

Univariate modeling identified statistically significant associations between an increased risk of subsequent distant relapse and decline in patient-reported global health status/QOL at 6 months (p=0.02) (Figure 1; Table 4). Univariate analysis for risk of subsequent brain relapse showed no significant associations with decline in any EORTC or BN20 measure (data not shown). Univariate modeling of other patient characteristics demonstrated significant associations between increased risk of subsequent distant relapse and younger age (both as a continuous (p=0.006) and categorical (p=0.006, ≤60 vs. >60) variable) and SCLC histology (p=0.002). All other patient characteristics were not significantly associated with risk of subsequent distant relapse (data not shown). Adjusting for age (as a categorical variable), histology and baseline EORTC score on multivariate analysis, decline in patient-reported global health status/QOL at 6 months was significantly associated with an increased risk of subsequent distant relapse (Hazard Ratio (HR), 1.60; 95% Confidence Interval (CI), 1.07-2.38, p=0.02;

Table 4). Similar findings were observed when adjusting for age as a continuous variable (data not shown).

Inferior overall survival was associated with decline in patient-reported global health status/QOL amongst 6-month relapse-free survivors (median survival time (MST) improvement/no decline, 37.8 months (95% CI, 38.2-58.2 months), vs. decline, 23.7 months (95% CI, 17.9-31.0 months); $p<0.0001$) (Figure 2). Amongst 12-month relapse-free survivors, inferior overall survival was also correlated with decline in patient-reported global health status/QOL (MST 49.0 months (95% CI, 37.8 months-not reached) vs. 32.1 months (95% CI, 25.4-53.4 months); $p=0.02$) and cognitive functioning (MST 49.0 months (95% CI, 38.6 months-not reached) vs. 34.1 months (95% CI, 27.0-53.4 months); $p=0.04$). Other covariates associated with inferior overall survival on univariate modeling were lower baseline global health status/QOL score assessed continuously ($p=0.047$), single/divorced/widowed status ($p=0.02$) and post-secondary education level less than high school ($p=0.0001$). Adjusting for these factors on multivariate analysis, decline in patient-reported global health status/QOL at 6 months (HR, 2.10; 95% CI, 1.46-3.03, $p<0.0001$) and 12 months (HR, 2.07; 95% CI, 1.20-3.58, $p=0.009$) and decline in patient-reported cognitive functioning at 12 months (HR, 1.73; 95% CI, 1.03-2.92, $p=0.04$) predicted for inferior overall survival (Table 4). Test for correlation demonstrated no association between decline in patient-reported global health status/QOL and decline in patient-reported cognitive functioning at 12 months ($p=0.74$).

Discussion

This analysis of patient-reported QOL data pooled from RTOG 0212 and RTOG 0214 demonstrates prognostic significance with longitudinal decline in global health status/QOL during early survivorship following definitive loco-regional treatment of LD-SCLC and LA-NSCLC. Multiple reports have documented the independent prognostic effect of baseline QOL in lung cancer[1-5]. Other reports have demonstrated prognostic significance of QOL decline during chemotherapy for metastatic NSCLC[1] and a trend to prognostic significance of QOL decline 1 month following completion of definitive radiotherapy for LA-NSCLC[18]. However, our study is the first to observe a 14-month shortening of median survival with QOL decline amongst 6-month relapse-free survivors and a 17-month shortening of median survival with QOL decline amongst 12-month relapse-free survivors of lung cancer. Thus, our study provides evidence supporting the importance of monitoring patient-reported QOL not just before, during or shortly after treatment, but also during the early survivorship phase of lung cancer management.

Monitoring QOL during early lung cancer survivorship may also aid in detecting subsequent disease relapse. In this study declining QOL at 6 months following curative treatment was associated with a 60% relative increased risk of subsequent distant relapse. Importantly, this finding occurred in patients who had not yet manifested clinical or radiographic evidence of relapse. One plausible explanation for this finding is the potential for QOL decline to serve as a noninvasive surrogate marker of distant micro-metastatic relapse. Thus, this study suggests that QOL monitoring may serve as a cost-effective approach to enhancing disease surveillance beyond standard clinical and radiographic examinations.

The benefits of QOL monitoring outlined in this study highlight a potential role for QOL monitoring in daily clinical practice. Prior clinical trials have also demonstrated other benefits to QOL monitoring, including heightened physician awareness of QOL issues and enhanced patient-physician discussion[19]. However, as discussed by Snyder and Aaronson[20], there are several logistical barriers to incorporating QOL monitoring into clinical practice. First, the administrative burdens of conventional pen-and-paper tests prevent widespread adoption of QOL monitoring and limit institutional compliance. Recent technological advances have introduced user-friendly web-based platforms for QOL data collection. One such web-based platform was recently pilot-tested in RTOG 0828 and has shown dramatic improvements in 6-month QOL compliance rates and the time required for completing the QOL assessment[21]. A second logistical barrier involves the real-time interpretation of data at the time of patient-physician interaction. Based on our findings of prognostic significance with QOL decline, defined using the reliable change index, population-based normative data could be used to facilitate the real-time calculation of the reliable change index and determination of meaningful QOL decline. Lastly, incorporation of QOL monitoring into daily clinical practice requires clinicians' buy-in on the potential benefits of QOL monitoring. To address this issue, future studies of the clinical relevance of dynamic QOL changes in other cancer sites would be warranted.

Inferior prognosis was also associated with decline in patient-reported cognitive function amongst 12-month relapse-free survivors, but this domain did not predict for risk of subsequent distant or brain relapse. Importantly, decline in global health status/QOL and decline in patient-reported cognitive functioning at 12 months were not closely correlated. Thus, these data suggest that monitoring of patient-reported cognitive functioning may serve as an additional metric to further enhance the overall sensitivity of QOL monitoring as a surrogate marker of prognosis.

This study does have important limitations. First, potential biases introduced by QOL noncompliance should be considered in the interpretation of these results. Though favorable in comparison to other QOL studies in lung cancer[22,23], QOL compliance was 61% and 45% amongst 6- and 12-month survivors, respectively. Second, to allow for analysis of longitudinal QOL data with sufficient sample size, data from two separate RTOG trials studying PCI (RTOG 0212 and 0214) were pooled. Though both trials used uniform QOL instruments and follow-up assessment time points, these RTOG trials did involve different disease entities (LD-SCLC and LA-NSCLC, respectively) and different randomizations (high- vs. low-dose PCI and PCI vs. observation, respectively). To account for the differences, we included only relapse-free patients. To adjust for PCI dose, we pooled patients receiving PCI (30 Gy in 10 fractions) on RTOG 0214 into the standard-dose PCI cohort (25 Gy in 10 fractions) and observed no effect of PCI dose on relapse or overall survival. Lastly, the potential for practice effects from repeated QOL assessments can limit interpretation of data. However, our use of the reliable change index to define meaningful decline in QOL, in part, adjusted for this.

Conclusion

In this pooled secondary analysis of RTOG 0212 and 0214, we observe that longitudinal decline of global health status/QOL in relapse-free survivors of lung cancer is a potential surrogate marker for subsequent distant relapse and inferior overall survival. These data emphasize the importance of monitoring patient-reported QOL throughout the longitudinal process of diagnosis, treatment, and early survivorship in lung cancer patients and provide rationale for incorporating QOL monitoring into not just clinical trials, but also clinical practice.

1. Eton DT, Fairclough DL, Cella D, et al: Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: results from Eastern Cooperative Oncology Group Study 5592. J Clin Oncol 21:1536-43, 2003

2. Movsas B, Moughan J, Sarna L, et al: Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. J Clin Oncol 27:5816-22, 2009

3. Brown J, Thorpe H, Napp V, et al: Assessment of quality of life in the supportive care setting of the big lung trial in non-small-cell lung cancer. J Clin Oncol 23:7417-27, 2005

4. Maione P, Perrone F, Gallo C, et al: Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 23:6865-72, 2005

5. Montazeri A, Milroy R, Hole D, et al: Quality of life in lung cancer patients: as an important prognostic factor. Lung Cancer 31:233-40, 2001

6. Wolfson AH, Bae K, Komaki R, et al: Primary Analysis of a Phase II Randomized Trial Radiation Therapy Oncology Group (RTOG) 0212: Impact of Different Total Doses and Schedules of Prophylactic Cranial Irradiation on Chronic Neurotoxicity and Quality of Life for Patients with Limited-Disease Small-Cell Lung Cancer. Int J Radiat Oncol Biol Phys

7. Gore EM, Bae K, Wong SJ, et al: Phase III Comparison of Prophylactic Cranial Irradiation Versus Observation in Patients With Locally Advanced Non-Small-Cell Lung

Cancer: Primary Analysis of Radiation Therapy Oncology Group Study RTOG 0214. J Clin Oncol

8. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-76, 1993

9. Osoba D, Aaronson NK, Muller M, et al: The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. Qual Life Res 5:139-50, 1996

10. Jacot W, Colinet B, Bertrand D, et al: Quality of life and comorbidity score as prognostic determinants in non-small-cell lung cancer patients. Ann Oncol 19:1458-64, 2008

11. Sun A, Bae K, Gore EM, et al: Phase III Trial of Prophylactic Cranial Irradiation Compared With Observation in Patients With Locally Advanced Non-Small-Cell Lung Cancer: Neurocognitive and Quality-of-Life Analysis. J Clin Oncol

12. Fayers P, Aaronson NK, Bjordal K, et al: EORTC QLQ-C30 Scoring Manual. Brussels, Belgium, EORTC Publications, 2001

13. Osoba D, Aaronson NK, Muller M, et al: Effect of neurological dysfunction on health-related quality of life in patients with high-grade glioma. J Neurooncol 34:263-78, 1997

14. Osoba D, Aaronson N, Zee B, et al: Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. Qual Life Res 6:103-8, 1997

15. Bergman B, Sullivan M, Sorenson S: Quality of life during chemotherapy for small cell lung cancer. II. A longitudinal study of the EORTC Core Quality of Life Questionnaire and comparison with the Sickness Impact Profile. Acta Oncol 31:19-28, 1992

16. Osoba D, Zee B, Pater J, et al: Psychometric properties and responsiveness of the EORTC quality of Life Questionnaire (QLQ-C30) in patients with breast, ovarian and lung cancer. Qual Life Res 3:353-64, 1994

17. Jacobson NS, Truax P: Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol 59:12-9, 1991

18. Auchter RM, Scholtens D, Adak S, et al: Quality of life assessment in advanced non-small-cell lung cancer patients undergoing an accelerated radiotherapy regimen: report of ECOG study 4593. Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 50:1199-206, 2001

19. Detmar SB, Muller MJ, Schornagel JH, et al: Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. JAMA : the journal of the American Medical Association 288:3027-34, 2002

20. Snyder CF, Aaronson NK: Use of patient-reported outcomes in clinical practice. Lancet 374:369-70, 2009

21. Movsas B, Hunt D, Watkins-Bruner D, et al: Electronic web-based technology significantly improves quality of life data collection: Analysis of RTOG 0828. Int J Radiat Oncol Biol Phys 81:S111, 2011

22. Gregor A, Cull A, Stephens RJ, et al: Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). Eur J Cancer 33:1752-8, 1997

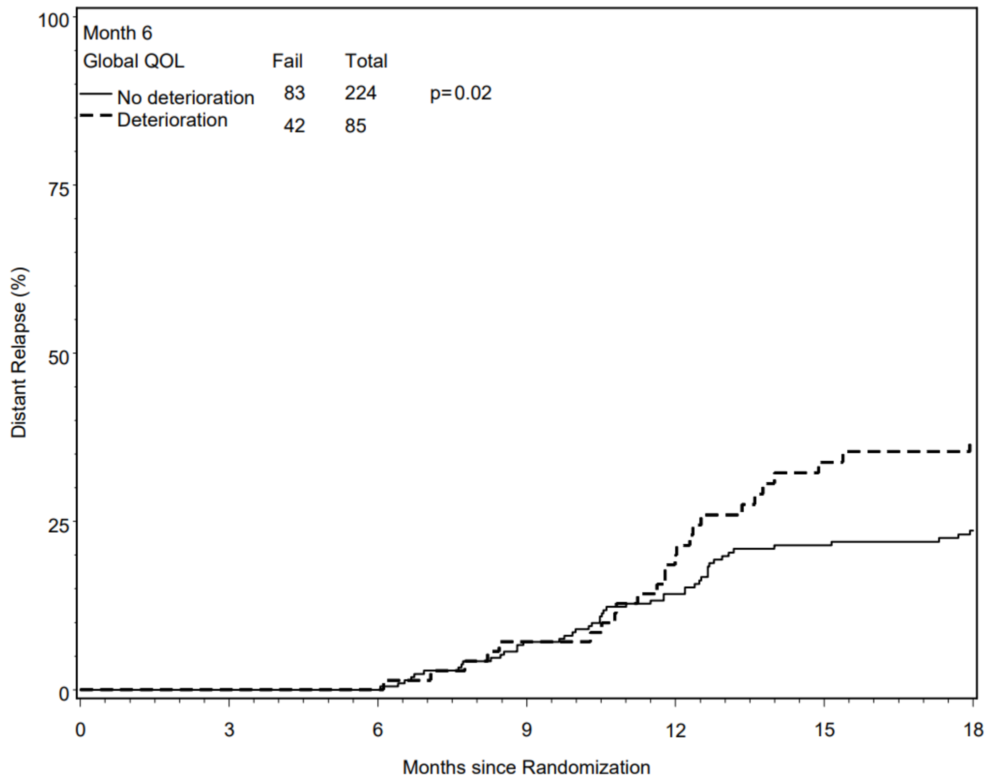
23. Slotman BJ, Mauer ME, Bottomley A, et al: Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 27:78-84, 2009

Figure Legends

Figure 1—Association between decline in patient-reported global health status/QOL in 6-month relapse-free survivors and subsequent increased risk of distant relapse.

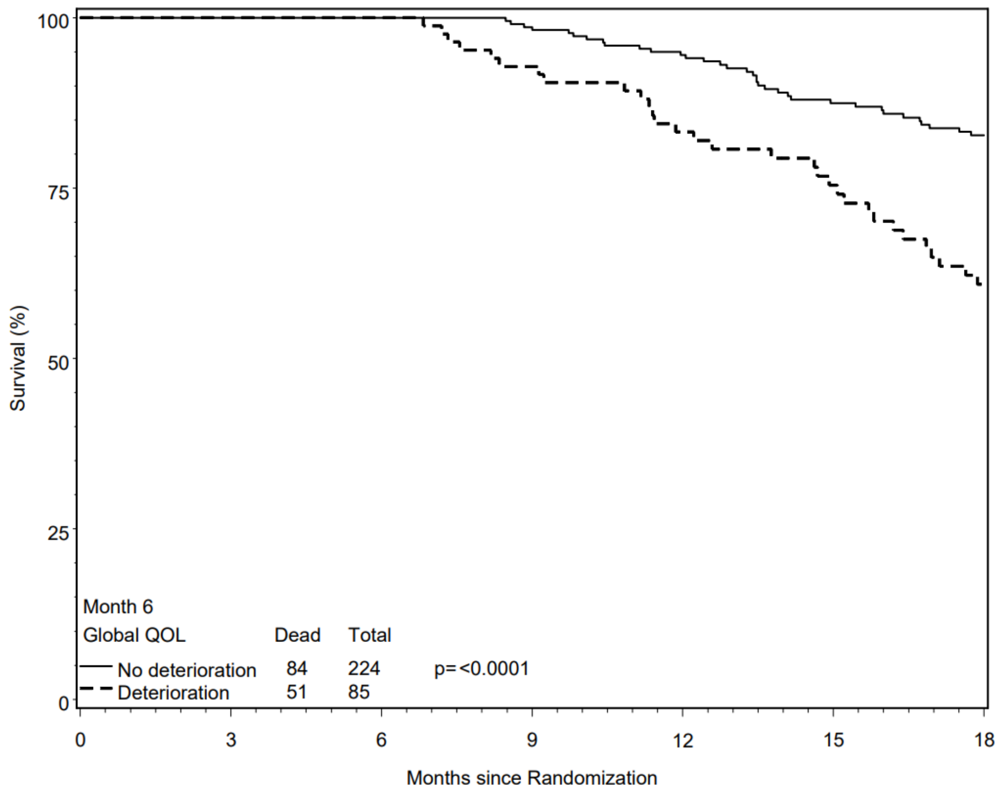
Figure 2—Association between decline in patient-reported global health status/QOL in 6-month relapse-free survivors and inferior overall survival.

Figure 1



Patients at Risk							
No deterioration	224	224	221	196	171	138	128
Deterioration	85	85	79	64	53	39	32

Figure 2



Patients at Risk							
No deterioration	224	224	223	218	201	168	154
Deterioration	85	85	85	78	68	57	46

Table 1—Patient Characteristics.

	RTOG 0212 (n=243)	**RTOG 0214 (n=309)**	***p* value**
Age[£]			*0.054*
Median	62	63	
Range	39-86	39-84	
Gender			*0.17*
Male	137 (56%)	192 (62%)	
Female	106 (44%)	117 (38%)	
PCI Dose*			*N/A**
Standard Dose (25-30 Gy)	120 (49%)	147 (48%)	
High-Dose (36Gy)	123 (51%)	0 (0%)	
No PCI	0 (0%)	162 (52%)	
Race			*0.31*
White	214 (88%)	263 (85%)	
Non-White	29 (12%)	46 (15%)	
Education Level			0.01
< High School	50 (21%)	95 (31%)	
High School	93 (38%)	89 (29%)	
> High School	83 (34%)	104 (34%)	
Unknown	17 (7%)	21 (7%)	
Partner Status			*0.56*
Partnered	154 (63%)	208 (67%)	
Not Partnered	80 (33%)	97 (31%)	
Unknown	9 (4%)	4 (1%)	
Zubrod Performance Status[¥]			*0.69*
0	56 (53%)	164 (56%)	
1	49 (47%)	131 (44%)	
QOL Compliance at 6 months			*0.01*
Completed	131 (54%)	182 (59%)	
Not Completed	70 (29%)	58 (19%)	
Relapsed Prior to 6 Months	24 (10%)	51 (17%)	
Died Prior to 6 Months	18 (7%)	18 (6%)	

QOL Compliance at 12 months			*0.001*
Completed	69 (28%)	122 (39%)	
Not Completed	65 (27%)	54 (17%)	
Relapsed Prior to 6 Months	44 (18%)	68 (22%)	
Died Prior to 12 Months	65 (27%)	65 (21%)	

[¥]Baseline Zubrod performance (PS) was collected on 105 (43.2%) of the patients enrolled on RTOG 0212 and 295 (95.5%) of the patients enrolled on RTOG 0214.

Abbreviations: PCI, prophylactic cranial irradiation.

Table 2—Percentage of patients with decline in patient-reported quality of life (QOL) scores at 6 months, compared to baseline, according to patient characteristics. P-values <0.001 were considered statistically significant.

	PCI Dose Group				PCI Use			Gender			Partnered			Age		
	Std	High	No PCI	p	PCI	No PCI	p	Male	Female	p	Yes	No	p	≤60	<60	p
Global Health QOL	26%	28%	29%	0.90	27%	29%	0.76	29%	26%	0.57	24%	32%	0.16	25%	29%	0.35
Functional Scales																
Physical	26%	32%	14%	0.03	28%	14%	0.006	22%	26%	0.38	20%	29%	0.12	22%	25%	0.58
Role	27%	30%	28%	0.87	28%	28%	0.96	27%	29%	0.63	21%	40%	0.0008	24%	31%	0.18
Emotional	20%	16%	14%	0.53	19%	14%	0.36	18%	17%	0.93	17%	18%	0.77	18%	17%	0.82
Cognitive	43%	48%	19%	<0.0001	45%	19%	<0.0001	38%	37%	0.88	34%	42%	0.19	37%	37%	0.92
Social	22%	28%	18%	0.34	24%	18%	0.24	22%	22%	0.98	19%	26%	0.24	21%	22%	0.83
Symptom Scales																
Fatigue	39%	39%	29%	0.24	39%	29%	0.08	41%	30%	0.04	33%	42%	0.12	29%	41%	0.03
Nausea/ Vomiting	14%	22%	10%	0.12	17%	10%	0.10	14%	16%	0.54	14%	15%	0.68	19%	12%	0.12
Pain	31%	32%	22%	0.28	31%	22%	0.09	31%	26%	0.31	28%	30%	0.78	29%	29%	0.98
Dyspnea	17%	20%	30%	0.05	18%	30%	0.03	22%	20%	0.72	19%	26%	0.22	19%	23%	0.43
Insomnia	23%	24%	18%	0.60	23%	18%	0.29	23%	20%	0.47	24%	16%	0.13	22%	21%	0.83
Appetite Loss	33%	42%	16%	0.0008	36%	16%	<0.0001	29%	32%	0.54	28%	34%	0.28	23%	34%	0.03
Constipation	23%	28%	12%	0.04	25%	12%	0.006	19%	24%	0.25	20%	22%	0.80	17%	24%	0.17

Diarrhea	11%	13%	6%	0.26	11%	6%	0.08	9%	11%	0.55	10%	9%	0.77	14%	7%	0.05
Financial Difficulties	16%	16%	11%	0.54	16%	11%	0.23	13%	17%	0.27	13%	18%	0.28	16%	14%	0.67
<u>Domains</u>																
Future Uncertainty	26%	17%	12%	0.03	23%	12%	0.01	19%	22%	0.61	19%	21%	0.76	23%	18%	0.31
Visual Disorder	30%	25%	18%	0.10	29%	18%	0.04	29%	21%	0.14	24%	29%	0.44	29%	24%	0.32
Motor Dysfunction	38%	51%	25%	0.003	42%	25%	0.003	38%	35%	0.66	34%	42%	0.17	32%	40%	0.14
Communication Deficit	27%	32%	16%	0.05	29%	16%	0.009	26%	23%	0.48	24%	24%	0.99	25%	25%	0.91
<u>Single Items</u>																
Headaches	27%	28%	19%	0.31	27%	19%	0.11	23%	28%	0.35	26%	22%	0.37	30%	22%	0.13
Seizures	2%	1%	2%	0.94	2%	2%	0.82	3%	0%	0.01	2%	1%	0.51	2%	2%	0.76
Drowsiness	26%	23%	23%	0.82	25%	23%	0.66	21%	29%	0.15	25%	23%	0.66	17%	30%	0.006
Hair Loss	14%	18%	10%	0.41	15%	10%	0.23	10%	19%	0.03	13%	16%	0.40	18%	11%	0.08
Itchy Skin	19%	27%	14%	0.12	22%	14%	0.08	18%	22%	0.38	18%	20%	0.68	24%	17%	0.15
Weakness of Legs	21%	28%	17%	0.25	23%	17%	0.24	24%	18%	0.19	21%	20%	0.88	20%	22%	0.64
Bladder Control	9%	12%	9%	0.77	10%	9%	0.88	10%	8%	0.44	8%	11%	0.43	7%	11%	0.31

	Education Level				**Baseline Zubrod Performance Score**		
	<HS	HS	>HS	p	0	1	p

<u>Global Health QOL</u>	24%	30%	26%	0.68	27%	30%	0.63
<u>Functional Scales</u>							
Physical	24%	20%	23%	0.88	24%	16%	0.13
Role	28%	24%	25%	0.80	26%	32%	0.35
Emotional	21%	18%	14%	0.43	16%	22%	0.26
Cognitive	39%	45%	28%	0.03	29%	35%	0.37
Social	20%	22%	22%	0.93	18%	28%	0.09
<u>Symptom Scales</u>							
Fatigue	28%	39%	39%	0.15	34%	42%	0.22
Nausea/ Vomiting	12%	17%	13%	0.58	9%	17%	0.09
Pain	28%	34%	25%	0.33	26%	30%	0.55
Dyspnea	21%	17%	23%	0.59	24%	22%	0.84
Insomnia	20%	19%	24%	0.73	21%	20%	0.85
Appetite Loss	31%	36%	22%	0.08	31%	28%	0.60
Constipation	21%	18%	24%	0.60	18%	18%	0.89
Diarrhea	11%	11%	10%	0.94	4%	10%	0.07
Financial Difficulties	17%	13%	15%	0.72	17%	8%	0.06
<u>Domains</u>							
Future Uncertainty	19%	22%	18%	0.77	21%	18%	0.54

Visual Disorder	31%	25%	24%	0.55	21%	27%	0.38
Motor Dysfunction	35%	41%	33%	0.44	30%	42%	0.07
Communication Deficit	26%	29%	21%	0.46	24%	26%	0.77
<u>Single Items</u>							
Headaches	31%	22%	21%	0.23	25%	26%	0.95
Seizures	1%	2%	2%	0.86	1%	3%	0.23
Drowsiness	22%	23%	27%	0.70	23%	27%	0.49
Hair Loss	12%	17%	13%	0.49	14%	13%	0.94
Itchy Skin	17%	20%	19%	0.89	19%	21%	0.71
Weakness of Legs	22%	17%	21%	0.70	16%	23%	0.17
Bladder Control	12%	9%	8%	0.66	13%	5%	0.04

Abbreviations: PCI, prophylactic cranial irradiation; std dose, standard-dose; SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer; HS, high school.

Table 3—Percent of patients with deterioration in patient-reported quality of life (QOL) and neurocognitive scores at 12 months, compared to baseline, according to patient characteristics. P-values <0.001 were considered statistically significant.

	PCI Dose Group				**PCI Use**			**Gender**			**Partnered**			**Age**		
	Std	High	No PCI	p	≤60	<60	p	Male	Female	p	Yes	No	p	≤60	<60	p
Global Health QOL	18%	29%	36%	0.05	21%	36%	0.03	28%	23%	0.43	25%	27%	0.79	25%	27%	0.76
Functional Scales																
Physical	25%	37%	22%	0.25	28%	22%	0.37	26%	26%	0.95	24%	30%	0.37	22%	28%	0.32
Role	24%	34%	21%	0.32	27%	21%	0.37	26%	22%	0.51	24%	27%	0.66	31%	21%	0.15
Emotional	23%	34%	24%	0.39	26%	24%	0.74	22%	30%	0.24	23%	30%	0.28	26%	25%	0.78
Cognitive	45%	60%	21%	0.0002	50%	21%	<0.0001	39%	40%	0.99	39%	40%	0.93	40%	39%	0.96
Social	24%	31%	16%	0.21	26%	16%	0.11	23%	22%	0.91	20%	25%	0.37	29%	19%	0.11
Symptom Scales																
Fatigue	35%	46%	30%	0.28	38%	30%	0.26	42%	26%	0.02	33%	38%	0.50	29%	38%	0.21
Nausea/ Vomiting	12%	14%	18%	0.62	13%	18%	0.37	12%	19%	0.21	13%	19%	0.32	16%	14%	0.67
Pain	33%	23%	30%	0.57	30%	30%	0.99	31%	28%	0.71	28%	33%	0.54	25%	33%	0.26
Dyspnea	20%	17%	25%	0.59	19%	25%	0.35	27%	14%	0.02	24%	17%	0.29	21%	22%	0.82
Insomnia	31%	34%	19%	0.17	32%	19%	0.05	31%	23%	0.18	26%	29%	0.74	26%	28%	0.81
Appetite Loss	15%	29%	18%	0.19	19%	18%	0.89	18%	19%	0.82	18%	22%	0.45	19%	18%	0.86
Constipation	19%	35%	15%	0.06	24%	15%	0.14	16%	28%	0.05	19%	24%	0.41	18%	23%	0.42

Diarrhea	10%	11%	6%	0.58	11%	6%	0.26	9%	9%	0.92	11%	6%	0.32	13%	7%	0.16
Financial Difficulties	14%	17%	11%	0.64	15%	11%	0.40	16%	10%	0.26	11%	16%	0.40	13%	13%	0.98
<u>Domains</u>																
Future Uncertainty	24%	29%	19%	0.53	25%	19%	0.35	21%	26%	0.44	16%	36%	0.004	21%	25%	0.52
Visual Disorder	30%	32%	18%	0.15	31%	18%	0.04	28%	25%	0.66	21%	34%	0.06	28%	25%	0.71
Motor Dysfunction	44%	44%	22%	0.01	44%	22%	0.002	37%	36%	0.90	33%	44%	0.14	35%	37%	0.83
Communication Deficit	36%	50%	27%	0.07	40%	27%	0.06	34%	37%	0.66	32%	41%	0.25	41%	32%	0.21
<u>Single Items</u>																
Headaches	28%	26%	10%	0.02	28%	10%	0.002	18%	26%	0.22	17%	30%	0.06	24%	20%	0.63
Seizures	0%	3%	1%	0.33	1%	1%	0.69	2%	0%	0.15	1%	2%	0.67	1%	1%	0.70
Drowsiness	21%	35%	19%	0.17	25%	19%	0.35	25%	21%	0.54	21%	27%	0.43	16%	27%	0.07
Hair Loss	16%	18%	10%	0.53	16%	10%	0.25	13%	16%	0.54	11%	19%	0.20	19%	11%	0.17
Itchy Skin	24%	29%	16%	0.29	25%	16%	0.13	23%	21%	0.72	19%	30%	0.11	24%	21%	0.69
Weakness of Legs	23%	38%	24%	0.21	28%	24%	0.58	28%	24%	0.51	23%	30%	0.33	24%	28%	0.58
Bladder Control	16%	33%	9%	0.008	20%	9%	0.02	16%	17%	0.78	12%	24%	0.06	10%	20%	0.06

	Education Level				**Baseline Zubrod Performance Score**		
	<HS	HS	>HS	p	0	1	p

Global Health QOL	33%	24%	17%	0.11	29%	29%	0.96
Functional Scales							
Physical	28%	27%	23%	0.77	28%	21%	0.33
Role	23%	24%	21%	0.92	24%	24%	0.97
Emotional	32%	24%	20%	0.33	25%	29%	0.56
Cognitive	38%	45%	41%	0.78	34%	34%	0.98
Social	25%	22%	19%	0.70	21%	21%	0.98
Symptom Scales							
Fatigue	37%	35%	34%	0.96	35%	31%	0.59
Nausea/ Vomiting	20%	16%	7%	0.09	16%	10%	0.23
Pain	37%	29%	27%	0.47	35%	29%	0.45
Dyspnea	28%	8%	21%	0.03	26%	23%	0.67
Insomnia	40%	21%	19%	0.01	26%	29%	0.67
Appetite Loss	21%	23%	14%	0.45	20%	15%	0.43
Constipation	22%	18%	22%	0.87	23%	13%	0.12
Diarrhea	7%	10%	9%	0.81	6%	13%	0.16
Financial Difficulties	16%	10%	14%	0.70	17%	6%	0.05
Domains							
Future Uncertainty	30%	22%	19%	0.32	20%	24%	0.52

Visual Disorder	28%	24%	23%	0.79	27%	23%	0.56
Motor Dysfunction	37%	37%	33%	0.90	36%	32%	0.63
Communication Deficit	38%	33%	35%	0.82	29%	42%	0.11
<u>Single Items</u>							
Headaches	20%	29%	19%	0.41	21%	21%	0.99
Seizures	0%	2%	1%	0.57	1%	2%	0.82
Drowsiness	18%	24%	29%	0.37	23%	23%	0.92
Hair Loss	17%	10%	14%	0.62	14%	13%	0.85
Itchy Skin	20%	27%	22%	0.71	21%	25%	0.60
Weakness of Legs	17%	31%	30%	0.14	26%	25%	0.86
Bladder Control	15%	19%	14%	0.81	15%	15%	0.95

Abbreviations: PCI, prophylactic cranial irradiation; std dose, standard-dose; SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer; HS, high school.

CONSORT Diagram