Quality of Life Analysis of a Radiation Dose-Escalation Study of Patients With Non-Small-Cell Lung Cancer: A Secondary Analysis of the Radiation Therapy Oncology Group 0617 Randomized Clinical Trial

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Quality of Life Analysis of a Radiation Dose–Escalation Study of Patients With Non–Small-Cell Lung Cancer: A Secondary Analysis of the Radiation Therapy Oncology Group 0617 Randomized Clinical Trial

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**IMPORTANCE** A recent randomized radiation dose–escalation trial in unresectable stage III non–small-cell lung cancer (NSCLC) (Radiation Therapy Oncology Group [RTOG] 0617) showed a lower survival rate in the high-dose radiation therapy (RT) arm (74 Gy) than in the low-dose arm (60 Gy) with concurrent chemotherapy.

**OBJECTIVE** The primary QOL hypothesis predicted a clinically meaningful decline in quality of life (QOL) via the Functional Assessment of Cancer Therapy (FACT)–Lung Cancer Subscale (LCS) in the high-dose RT arm at 3 months.

**DESIGN, SETTING, AND PATIENTS** The RTOG 0617 trial was a randomized phase 3 study (conducted from November 2007 to November 2011) in stage III NSCLC using a 2 × 2 factorial design and stratified by histology, positron emission tomography staging, performance status, and irradiation technique (3-dimensional conformal RT [3D-CRT] vs intensity-modulated RT [IMRT]). A total of 185 institutions in the United States and Canada took part. Of 424 eligible patients with stage III NSCLC randomized, 360 (85%) consented to QOL evaluation, of whom 313 (88%) completed baseline QOL assessments.

**INTERVENTION** Treatment with 74-Gy vs 60-Gy RT with concurrent and consolidation carboplatin/paclitaxel with or without cetuximab.

**MAIN OUTCOMES AND MEASURES** The QOL data were collected prospectively via FACT Trial Outcome Index (FACT-TOI), calculated as the sum of the following measures: Physical Well Being (PWB), Functional Well Being (FWB), and the LCS. Data are presented at baseline and 3 and 12 months via minimal clinically meaningful changes of 2 points or more for PWB, FWB, and LCS or 5 points or more for TOI.

**RESULTS** Of the 313 patients who completed baseline QOL assessments, 219 patients (70%) completed the 3-month QOL assessments, and 137 of the living patients (57%) completed the 12-month assessment. Patient demographics and baseline QOL scores were comparable between the 74-Gy and 60-Gy arms. Significantly more patients in the 74-Gy arm than in the 60-Gy arm had clinically meaningful decline in FACT-LCS at 3 months (45% vs 30%; \(P = .02\)).

At 12 months, fewer patients who received IMRT (vs 3D-CRT) had clinically meaningful decline in FACT-LCS (21% vs 46%; \(P = .003\)).

Baseline FACT-TOI was associated with overall survival in multivariate analysis.

**CONCLUSIONS AND RELEVANCE** Despite few differences in clinician-reported toxic effects between treatment arms, QOL analysis demonstrated a clinically meaningful decline in QOL in the 74-Gy arm at 3 months, confirming the primary QOL hypothesis. Baseline QOL was an independent prognostic factor for survival.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00533949


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**Corresponding Author:** Benjamin Movsas, MD, Department of Radiation Oncology, Henry Ford Hospital, 2799 W Grand Blvd, M2 Unit, Detroit, MI 48202 (BMovsas1@hfhs.org).
T he Radiation Therapy Oncology Group (RTOG) 0617 study was an intergroup phase 3 trial that randomized patients with unresectable stage III non–small-cell lung cancer (NSCLC) to 1 of 4 treatment arms in a 2 × 2 factorial design: 60-Gy radiation therapy (RT) (standard dose) vs 74-Gy RT (high dose) with concurrent and consolidation chemotherapy with or without cetuximab. This study asked whether or not RT dose escalation (and/or cetuximab) improved overall survival. The sobering answer was no: the survival rate was lower in the high-dose RT arm, and the addition of cetuximab made no difference.1

The survival result of this randomized clinical trial (RCT) was not as hypothesized from the favorable phase 2 clinical trial data supporting the high-dose RT approach.2–4 While there were more grade 5 treatment-related toxic effects in the high-dose RT arm (8 vs 3 patients), this difference was not significant. Based on the clinician-reported toxic effect scores, the only significant difference between the 2 arms was severe, albeit transient, esophagitis, which was higher in the 74-Gy arm (21% vs 7%; P < .001).

Patient-reported outcomes are an important secondary endpoint of this study. Quality of life (QOL) data were collected prospectively via a validated lung cancer instrument, the Functional Assessment of Cancer Therapy (FACT)-Trial Outcome Index (TOI),5,6 which has been associated with clinically meaningful changes in patients with lung cancer.7 The primary QOL hypothesis predicted a clinically meaningful decline (CMD) in the FACT Lung Cancer Subscale (LCS) in the high-dose RT arm at 3 months. The prognostic value of QOL in predicting survival was also studied, as was the potential impact of irradiation technique on QOL.

Methods

Study Design and Patients

The methodology for the RCT is described in detail in the clinical outcomes article.1 Briefly, the study used a 2 × 2 factorial design with RT dose as one factor and cetuximab as the other, stratified by RT technique, Zubrod performance status, use of positron emission tomography during staging, and histology, with a primary end point of overall survival. The study is registered with clinicaltrials.gov (NCT00533949). The institutional review board of each participating institution reviewed and approved the study protocol. All patients read and signed an informed consent document. Concurrent chemoradiation included weekly paclitaxel (45 mg/m²) and carboplatin (AUC, 2) followed by 2 cycles of consolidation chemotherapy. In addition to the RT dose randomization (60 Gy vs 74 Gy), patients randomized to cetuximab received a 400-mg/m² loading dose on day 1 followed by weekly doses of 250 mg/m². For the analysis, race was self-reported by the patients (using options defined by the investigators).

Health-Related QOL Measures

Quality of life was measured via the use of FACT-TOI, a validated component of the FACT-Lung (FACT-L) QOL instrument, which can be completed in less than 10 minutes and has been extensively used in patients with lung cancer.5,6 The FACT-TOI includes the Physical Well Being (PWB), the Functional Well Being (FWB), and the Lung Cancer Subscale (LCS) measurements. Importantly, the FACT-TOI has been associated with clinically meaningful changes in patients with lung cancer.7 The LCS consists of 9 items involving common lung cancer symptoms, such as shortness of breath, weight loss, coughing, and loss of appetite. All items are rated on a 5-point Likert scale, from 0 (not at all) to 4 (very much). Cella et al7 have reported minimal clinically meaningful changes of 2 points or more for PWB, FWB, and LCS or 5 points or more for TOI, criteria used in the present analysis.

The primary QOL hypothesis predicted a CMD in LCS in the high-dose RT arm at 3 months. While radiation dose escalation was hypothesized to yield greater tumor cell kill, it may also increase the toxic effects to normal tissue, thereby leading to a decrease in QOL. The measurements for the present QOL analysis were taken at baseline (pretreatment), during the last week of chemoradiation, and at 3 and 12 months from the start of treatment. The patients were given the QOL instrument to be completed in the clinic at the specified time points. If the patient did not come into the clinic, the questionnaire was mailed to the patient.

Statistical Considerations

All registered patients were offered the opportunity to prospectively participate in the QOL study. The differences in QOL scores (ie, FACT-TOI and its subscales) between baseline and each follow-up evaluation were computed for each individual patient and then classified as a clinically meaningful change or not, based on the criteria defined by Cella et al.7 Completion of the QOL assessments and reasons for noncompliance were reported. The effects of missing QOL measurements were systematically assessed by determining whether patients with and without QOL data at each time point had similar distributions in the treatment arms, pretreatment characteristics, and overall survival; we also used interaction tests to determine if the associations between treatment arms and pretreatment characteristics or treatment arms and overall survival differed between patients with and without QOL data.

Descriptive statistics were presented for both categorical and continuous variables. Differences between study groups in pretreatment characteristics and QOL scores were assessed by using the χ² test or the Fisher exact test for categorical variables and t tests or Wilcoxon rank sum tests. Effect sizes

At a Glance

- The primary hypothesis predicted a clinically meaningful decline in quality of life (QOL) in the high-dose radiation therapy (RT) arm at 3 months of a randomized RT dose-escalation study of stage III non–small-cell lung cancer.
- More patients in the high-dose (74-Gy) than in the standard-dose (60-Gy) RT arm had clinically meaningful decline in QOL at 3 months (45% vs 30%; P = .02).
- Despite few differences in clinician-reported toxic effects between arms, QOL analysis showed a clinically meaningful decline in QOL in the high-dose RT arm at 3 months.
of QOL score changes between study groups were calculated based on the Cohen $d$ statistic. Differences between study groups in CMD were assessed univariately using Cochran-Mantel-Haenszel statistics (stratified by cetuximab usage) and multivariately using logistic regression adjusting for important pretreatment characteristics and dosimetric parameters.

The Kaplan-Meier method was used to estimate rates of overall survival (duration from randomization to death or to last follow-up), and the log-rank test was used to compare these estimates between groups. Cox proportional hazards models were used to quantify the prognostic value of baseline QOL on overall survival after adjusting for RT level, cetuximab usage, and potential prognostic factors. To address potential guarantee-time bias, a conditional landmark analysis in conjunction with Cox proportional hazard models was used to evaluate the prognostic value of CMD on conditional survival after adjusting for potential confounding variables. In this landmark analysis, patients whose last follow-up was prior to the landmark time (eg, 3 months) were excluded from the analysis, and the change at the prespecified landmark time (eg, 3 months) was used as a predictor for survival conditional on surviving the landmark time. A 2-sided significance level of .05 was used throughout. Of note, the extent of QOL decline was analyzed based on predefined and independently validated clinically meaningful changes, already representing moderate effects. All analyses were performed with SAS software, version 9.2 (SAS Institute Inc).

## Results

Between November 2007 and June 2011, the end of the RT-level randomization, the trial accrued 464 patients, of whom 424 were ultimately eligible for analysis. Figure 1 is a QOL Consolidated Standards of Reporting Trials (CONSORT) diagram detailing the level of QOL participation at each time point. Briefly, 360 participants (85%) consented to QOL evaluation, of whom 313 (87%) completed the baseline QOL form (FACT-TOI). Other than patient attrition (as expected), the main reason for missing data was institutional error (QOL form not given or collected on time).

Table 1 summarizes the pretreatment characteristics for patients consenting to QOL evaluation by RT dose arm and RT technique. For both RT dose arms and techniques, approximately 60% of patients were male and 40% female. There were no significant differences between RT dose arms in demographics (including race), and there was equal use of cetuximab. Similarly, among patients who completed QOL assessments at subsequent time points, there were no significant differences in any demographics or treatment factors between RT dose arms, except for more stage IIIB patients in the high-dose arm at the end of chemoradiation therapy. There were no significant differences in treatment arms, pretreatment characteristics, or survival rates between patients with completed or missing QOL assessments at baseline. Moreover, there were no significant differences in the associations between treatment arms and pretreatment characteristics, or treatment arms and survival between patients with or without QOL, suggesting that the data are missing at random.

Table 2 summarizes the baseline LCS and FACT-TOI scores and the changes over time at 3 and 12 months by radiation dose and technique. The results at the end of chemoradiation are provided in eTable 1 in the Supplement, and the FWB and PWB data are listed in eTable 2 in the Supplement. There were no significant differences in baseline QOL scores by RT dose or technique (Table 2).

At the end of concurrent chemoradiation therapy, 173 (55%) of the 313 patients with baseline QOL data completed the next QOL assessment, with similar completion rates in the 60-Gy and 74-Gy arms (57% vs 53%; $P = .57$). The decline in LCS at the end of chemoradiation tended to be higher in the 74-Gy arm, although not significantly so (33% vs 46%; $P = .08$; effect size [ES], −0.31). Compared with the end of chemoradiation measurement, more patients (219, or 70% of those with baseline QOL data) completed QOL assessment at 3 months after baseline (the primary QOL time point), and 9 patients (3%) died prior to this assessment. The proportion of completed forms at 3 months was also similar between RT dose arms (67% vs 73%; $P = .31$). The proportion of patients who reported a CMD in the LCS was significantly higher in the 74-Gy arm than in the 60-Gy arm at 3 months (45% vs 30%; $P = .02$), corresponding to a moderate ES of 0.38 (Table 2 and Figure 2). At 12 months after baseline, 73 patients (23%) of the 313 who completed the baseline QOL were not alive; 137 patients (44%) completed QOL assessment, corresponding to a completion rate of 57% among living patients. The proportion of completed forms at 12 months was again similar between the RT dose arms (54% vs 61%; $P = .33$). The decline in QOL at 12 months between the RT dose arms was similar for FACT-TOI and for all the subscales. These results continued to hold in multivariate analysis after adjusting for potential confounding variables, including cetuximab usage, RT dosimetric factors, treatment parameters, and baseline characteristics.

Within an exploratory analysis (see eTable 3 and eTable 4 in the Supplement), several dosimetric factors appeared to be significantly associated with CMD in QOL in both univariate and multivariate logistic regression models as follows: lung V20 (the percentage of the lung receiving >20 Gy) was associated with CMD in PWB, FWB and TOI at end of chemoradiation; esophagus V60 (the percentage of the esophagus receiving >60 Gy) and planning target volume (PTV) were associated with CMD in PWB and TOI at 3 months. Heart V5 (the percentage of the heart receiving >5 Gy) was associated with CMD in FWB at 12 months. The variations in radiation doses (between intensity-modulated RT [IMRT] and 3-dimensional conformal RT [3D-CRT]) for the lung, esophagus, and heart were not significantly different among patients completing the QOL forms at baseline (see eTable 4 in the Supplement) or any subsequent time point. Of note, conditional survival of patients with early CMD in the LCS at the end of chemoradiation was nonsignificantly lower than those without (18-month survival rates, 54% vs 71%; log-rank $P = .27$).

Intensity-modulated RT was used in 44% and 46% of patients with baseline QOL data in the 60-Gy and 74-Gy arms, respectively ($P = .72$; Table 1). Of note, this study was stratified,
but not randomized, by radiation technology (IMRT vs 3D-CRT). Overall there were no significant differences in patient demographics or treatment factors between IMRT and 3D-CRT (Table I), with the following exceptions: significantly more patients with higher-stage disease (43% vs 31% stage IIIB; \( P = .04 \)) and larger PTVs (median 509 vs 409 mL; \( P < .001 \)) were treated using IMRT than 3D-CRT. When analyzing results by radiation technology (Table 2 and Figure 2), we found that patients who received IMRT had significantly less CMD in LCS at 12 months than those treated with 3D-CRT (21% vs 46%; \( P = .003 \); ES, 0.37). Similar results at 12 months were found with FACT-TOI (57% vs 36%; \( P = .01 \); ES, 0.34). Radiation technique remained significantly associated with CMDs in LCS (odds ratio [OR], 0.29 [95% CI, 0.13-0.69]; \( P = .01 \)) and TOI (OR, 0.42 [95% CI, 0.20-0.90]; \( P = .03 \)) at 12 months in multivariate logistic regression models.

Beyond RT dose level, baseline QOL (PWB, FWB, and FACT-TOI) was also significantly associated with survival

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**Figure 1. Study Participants’ Enrollment and Progress Flowchart**

- **Baseline**
  - 186 Randomized to standard dose (60 Gy)
  - 10 Data not received
  - 15 Not completed
    - 2 Patients refused for other reason
    - 1 Institutional error
    - 3 Unknown or other reason
  - 9 Completed after start of treatment
  - 161 With baseline PRO/QOL component

- **End of Chemoradiation**
  - 46 Data not received
  - 3 Died prior to assessment
  - 40 Not completed
    - 1 Patient refused due to illness
    - 3 Patients refused due to other reason
    - 14 Institutional error
    - 6 Unknown or other reason
  - 19 Completed too early or too late
  - 97 With end-of-chemoradiation QOLA
  - 92 With both baseline and end-of-chemoradiation QOLA

- **3-Month Follow-up**
  - 24 Data not received
  - 5 Died prior to assessment
  - 39 Not completed
    - 1 Patient refused due to illness
    - 3 Patients refused due to other reason
    - 14 Institutional error
    - 6 Unknown or other reason
  - 15 Completed too early or too late
  - 118 With 3-month QOLA
  - 108 With both baseline and 3-month QOLA

- **12-Month Follow-up**
  - 13 Data not received
  - 34 Died prior to assessment
  - 1 Withdrew consent to further QOL assessments
  - 63 Not completed
    - 2 Patients refused due to illness
    - 13 Patients refused for other reason
    - 23 Institutional error
    - 14 Unknown or other reason
  - 11 Completed too early or too late
  - 75 With 12-month QOLA
  - 70 With both baseline and 12-month QOLA

- **End of Chemoradiation (Continued)**
  - 40 Data not received
  - 4 Died prior to assessment
  - 43 Not completed
    - 2 Patients refused due to illness
    - 2 Patients refused for other reason
    - 17 Institutional error
    - 10 Unknown or other reason
  - 12 Completed too early or too late
  - 87 With end-of-chemoradiation QOLA
  - 81 With both baseline and end-of-chemoradiation QOLA

- **3-Month Follow-up (Continued)**
  - 16 Data not received
  - 8 Died prior to assessment
  - 1 Withdrew consent to further QOL assessments
  - 31 Not completed
    - 2 Patients refused due to illness
    - 2 Patients refused for other reason
    - 12 Institutional error
    - 5 Unknown or other reason
  - 10 Completed too early or too late
  - 118 With 3-month QOLA
  - 111 With both baseline and 3-month QOLA

- **12-Month Follow-up (Continued)**
  - 8 Data not received
  - 48 Died prior to assessment
  - 1 Withdrew consent to further QOL assessments
  - 44 Not completed
    - 3 Patients refused due to illness
    - 5 Patients refused for other reason
    - 14 Institutional error
    - 15 Unknown or other reason
  - 7 Completed too early or too late
  - 73 With 12-month QOLA
  - 67 With both baseline and 12-month QOLA

**PRO** indicates patient-reported outcome; **QOL** quality of life; **QOLA** QOL assessment.
### Table 1. Characteristics by RT Dose and Type for Patients Consenting to QOL Assessment

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<th>RT Dose</th>
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<th>RT Type</th>
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<th></th>
<th>Total</th>
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<td>60 Gy (n = 186)</td>
<td>74 Gy (n = 174)</td>
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<td>3D-CRT (n = 190)</td>
<td>IMRT (n = 162)</td>
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<td>(n = 360)</td>
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<td>Standard, 60 Gy</td>
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<td>82 (50.6)</td>
<td>186 (51.7)</td>
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<td>80 (49.4)</td>
<td>174 (48.3)</td>
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<td>Cetuximab</td>
<td>85 (45.7)</td>
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<td>64 (38-82)</td>
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<td>154 (88.5)</td>
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<td>149 (92.0)</td>
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<td>108 (62.1)</td>
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<td>94 (58.0)</td>
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<td>IIIB/N3</td>
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<td>66 (37.9)</td>
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<td>409.2 (99.0-1836.4)</td>
<td>508.3 (103.3-1851.2)</td>
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<td>(n = 174)</td>
<td>(n = 174)</td>
<td>(n = 130)</td>
<td>(n = 304)</td>
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<td>&lt;High school</td>
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<td>21 (13.0)</td>
<td>29 (15.6)</td>
<td>17 (11.8)</td>
<td>46 (13.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High school</td>
<td>77 (45.8)</td>
<td>65 (40.1)</td>
<td>77 (41.4)</td>
<td>65 (45.1)</td>
<td>142 (43.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;High school</td>
<td>66 (39.3)</td>
<td>76 (46.9)</td>
<td>80 (43.0)</td>
<td>62 (43.1)</td>
<td>142 (43.0)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>Married or partnered</td>
<td>118 (65.6)</td>
<td>117 (68.8)</td>
<td>123 (64.4)</td>
<td>112 (70.4)</td>
<td>235 (67.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Single, widowed, or divorced</td>
<td>62 (34.4)</td>
<td>53 (31.2)</td>
<td>68 (35.6)</td>
<td>47 (29.6)</td>
<td>115 (32.9)</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AJCC, American Joint Committee on Cancer; IMRT, intensity-modulated RT; NA, not applicable; NOS, not otherwise specified; PET, positron emission tomography; PS, performance status; PTV, planning target volume; QOL, quality of life; RT, radiation therapy; 3D-CRT, 3-dimensional conformal RT.

*Unless otherwise noted, data are reported as number (percentage) of study participants.*

*The differences between 3D-CRT and IMRT for these factors (AJCC stage and PTV volume) were significantly different (P < .03), but all other comparisons were not significantly different (P > .10).*
separately in univariate and multivariate Cox regression models. Table 3 summarizes a multivariate Cox proportional hazard analysis between baseline FACT-TOI (continuous) and survival, with adjustment for cetuximab use, PTV, and heart V5. Every 10 points higher on the FACT-TOI at baseline (for a given patient compared with another) corresponded to a 10% decreased risk of death (hazard ratio, 0.901; \(P = .046\)). Other significant variables on multivariate analysis included PTV and heart V5.

### Discussion

Despite few differences in clinician-reported toxic effects between RT dose arms, the patient-reported outcomes clearly demonstrated a clinically meaningful decline (CMD) in QOL on the high-dose radiation arm at 3 months, confirming the primary QOL hypothesis. Prior studies have demonstrated a disconnect between the patient and clinician perspectives;
clinicians often underestimate the level of symptom burden. The only clinically relevant clinician-based toxic effect found to be significantly different between RT dose arms was severe esophagitis. However, while the rate of severe esophagitis at 3 months in the high-dose arm was only 21%, more than 50% of patients reported a CMD in FACT-TOI at 3 months.

Interestingly, in the RTOG 0617 clinical outcomes report, the significant factors associated with survival on multivariate analysis were RT dose level, PTV, heart dose, and severe esophagitis. When incorporating QOL into the model, we found that baseline QOL (FACT-TOI), rather than esophagitis, was significantly associated with survival, in addition to RT dose level, PTV, and heart dose (Table 3). Prior studies have shown that QOL is significantly associated with survival in lung cancer and other cancers. In this study, every 10 points higher in the QOL (FACT-TOI) score at baseline (for a given patient compared with another) corresponded to a 10% decreased risk of death. Similarly, in another locally advanced NSCLC randomized trial, a 10-point higher baseline global QOL score corresponded to a decrease in the hazard of death by 10%. This clinically relevant finding suggests that QOL may be considered a stratification factor in future locally advanced NSCLC trials.

This analysis raises a question about an association between early decline in QOL in the high-dose radiation arm and the survival decrement found in this study. Of note, patients with a CMD in LCS early on (at the completion of chemoradiation) were found to have a nonsignificantly lower 18-month survival (54%) compared with those without CMD in LCS (71%). In another trial, a decline in LCS was significantly associated with lower survival in lung cancer. Other important factors to consider include tumor volume and heart dose. Tumor volume is a well-known negative prognostic factor for survival. Heart dose also appears to be a factor that may partly explain the decline in overall survival and poorer QOL in the high-dose arm. From a dosimetric perspective, lung V20 and esophagus V60 correlated with CMD in LCS at early time points (within 3 months), possibly due to the acute radiation effects of inflammation in these organs. Only heart V5 significantly correlated with CMD with longer follow-up (at 12 months), suggesting that chronic radiation cardiac effects may be clinically relevant and deserve further study. Thus far, no single covariate explains the large survival gap between the 2 RT dose arms, suggesting that the answer to this complex issue is likely multifactorial.

The main limitation of this analysis, which affects many QOL studies, is the issue of missing data. In this study, approximately 70% of patients completed QOL assessment at 3 months, and 57% of living patients completed QOL assessment at 12 months. While these QOL completion rates are reasonable for a locally advanced lung cancer trial, it raises the possibility that there could be nonrandom factors underlying the missing QOL data. Although matched at baseline, patients who were sicker or who had poorer QOL during the study period (or who died at earlier time points) could disproportionately have not completed the QOL tools. However, in this study, there were no significant differences in the associations between treatment arms and pretreatment characteristics or treatment arms and survival between patients with or without QOL data. Moreover, among patients who completed QOL assessment, there were essentially no significant differences in demographics or treatment factors included in this analysis.

Figure 2. Decline in Patient-Reported Quality of Life by Type and Dose of RT

![Figure 2](https://example.com/figure2.png)

Table 3. Multivariate Cox Model of Overall Survival

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Comparison</th>
<th>Standard-Dose Dead/Total</th>
<th>High-Dose Dead/Total</th>
<th>HR (95 CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation level</td>
<td>High dose vs standard dose (RL)</td>
<td>97/155</td>
<td>106/147</td>
<td>1.42 (1.07-1.87)</td>
<td>.01</td>
</tr>
<tr>
<td>Cetuximab assignment</td>
<td>No cetuximab vs cetuximab (RL)</td>
<td>90/133</td>
<td>133/169</td>
<td>0.90 (0.68-1.19)</td>
<td>.44</td>
</tr>
<tr>
<td>PTV</td>
<td>Continuous</td>
<td>203/302</td>
<td>203/302</td>
<td>1.001 (1.000-1.001)</td>
<td>.04</td>
</tr>
<tr>
<td>Heart V5</td>
<td>Continuous</td>
<td>203/302</td>
<td>203/302</td>
<td>1.007 (1.002-1.012)</td>
<td>.01</td>
</tr>
<tr>
<td>FACT-TOI</td>
<td>Continuous</td>
<td>203/302</td>
<td>203/302</td>
<td>0.901 (0.813-0.998)</td>
<td>.046</td>
</tr>
</tbody>
</table>

**Abbreviations:** FACT, Functional Assessment of Cancer Therapy; heart V5, volume of heart receiving 5 Gy or more radiation; HR, hazard ratio; PTV, planning target volume; RL, reference level; TOI, Trial Outcome Index.

*a For high-dose group or no cetuximab group.

*b Two-sided P value.

*c Baseline FACT-TOI, every 10 points.

*d For standard-dose group or cetuximab group.
(including use of cetuximab) between arms at any QOL assessment time.

Other than patient attrition (as is to be expected in a lung cancer trial), the main reason for missing data was institutional error (such as the QOL form not being administered or collected on time). To reduce missing QOL data, RTOG has tested an electronic web-based strategy. This novel approach almost eliminated institutional error as the cause of missing data by using real time email reminders.

A strength of this QOL analysis is that the results were not simply based on differences that were statistically significant but, more importantly, on changes that were clinically meaningful using a validated QOL instrument. The results emphasize the importance of having a predefined clinically meaningful change by which to interpret QOL findings.

As QOL assessment provides data directly from the patient perspective, it provides an opportunity to explore potential strategies that might not have otherwise been appreciated. While RTOG 0617 was stratified, but not randomized, to compare IMRT with 3D-CRT, less CMD in the LCS at 1 year was associated with the use of IMRT (P = .003), despite the fact that IMRT was used to treat patients with higher stages of disease and larger tumor volumes. Retrospective studies have suggested dosimetric and/or clinical benefits of IMRT (over 3D-CRT) in stage III NSCLC. When performed carefully with motion control and image-guided RT, as in this study, IMRT facilitates integrated RT dose painting to tumor regions while minimizing the dose delivered to surrounding normal tissues. As previously reported, overall, the use of IMRT vs 3D-CRT did not affect survival in this study, and a detailed analysis of this issue will be published separately. To our knowledge, RTOG 0617 is the largest prospective study incorporating QOL as an end point in patients treated with modern techniques of IMRT or 3D-CRT for stage III NSCLC.

Conclusions

The QOL analysis of RTOG 0617 demonstrates that baseline QOL was significantly associated with survival on multivariate analysis. This analysis suggests that improved RT techniques may enhance the therapeutic window for patients with lung cancer. Finally, despite few differences in clinician-reported toxic effects between RT dose arms, the patient-reported outcomes demonstrated significantly worse QOL in the high-dose arm at 3 months, confirming the primary QOL hypothesis.


The Importance of Quality of Life Assessment

Charles R. Thomas Jr, MD, PhD

Dose escalation of an antineoplastic modality such as radiotherapy (RT) may result in an increased therapeutic ratio with the use of effective strategies to mitigate normal tissue toxic effects. Successful execution of dose escalation using external beam RT (EBRT) approaches has yielded unintended outcomes.1,2 While increased disease control and survival are a focus of such strategies to increase the therapeutic ratio, quality of life (QOL), as measured by appropriate patient-related outcomes tools, are nearly as important. To that end, Movsas et al3 in this issue of JAMA Oncology, document that an attempt to deliver nearly a quarter higher total dose (74 Gy vs 60 Gy) of EBRT given concomitantly with a platinum-taxane doublet for locally advanced non-small-cell lung cancer (LA-NSCLC) results in a clinically meaningful decrement in QOL at 3 months.3

However, the Radiation Therapy Oncology Group 0617 trial is not the definitive treatise regarding the RT dose-escalation question for LA-NSCLC. The QOL assessments, as well as the survival results, likely were influenced by numerous factors that are difficult to control for in a multi-institutional, cooperative group clinical trial setting. Emerging data on molecular signatures that may predict radiosensitivity and/or radioresistance of tumor, as well as normal tissues, may be helpful in future assessment of baseline patient characteristics for those enrolled in prospective, large-scale cancer clinical trials of RT-based treatment. Moreover, not all modes of potential RT delivery and dose escalation are equal. Currently, radiation oncologists see patients on a weekly basis and basically assess symptoms as a “snapshot in time.” This is fraught with recall bias and other factors that contribute to a diminished appreciation of real-time patient-related outcomes, which should ideally be recorded on a continuous 24/7 basis to assess QOL during treatment. Movsas and colleagues are to be congratulated for executing a trial that will help in the design of next-generation QOL trials for LA-NSCLC.