Author's response to reviews

Title: Quality of Life Assessment: An Independent Predictor of Survival in Non-Small Cell Lung Cancer

Authors:

Donald P Braun (donald.braun@ctca-hope.com)
Digant Gupta (gupta_digant@yahoo.com)
Edgar D Staren (edgar.staren@ctca-hope.com)

Version: 2 Date: 9 January 2011

Author's response to reviews:

January 09, 2011

Dear Dr. Norton,

Greetings,

Thank you for your correspondence in connection with our manuscript entitled “Quality of Life Assessment: An Independent Predictor of Survival in Lung Cancer - MS: 4844240744723740” for consideration in “BMC Cancer”.

We have addressed the reviewers’ concerns in our revised manuscript, which is being resubmitted to “BMC Cancer”. Attached below, for your perusal, is a detailed description (highlighted in red and CAPS) of how we have addressed the reviewers’ comments in our revised manuscript. The changes in the resubmitted manuscript have also been highlighted in red for easy identification.

We thank you once again for your interest in our manuscript. Please let us know if you have any further questions and we will be more than happy to clarify.

We look forward to hearing back from you soon.

Yours Sincerely,

Digant Gupta, MD, MPH
Cancer Treatment Centers of America
Midwestern Regional Medical Center
2520 Elisha Avenue
Zion, IL 60099, USA
Phone: 847-872-4040
Reviewer's report
Title: Quality of Life Assessment: An Independent Predictor of Survival in Lung Cancer
Version: 1 Date: 29 November 2010
Reviewer: Richard Fielding

Reviewer's report:
Title: Quality of Life Assessment: An Independent Predictor of Survival in Lung Cancer

Abstract:
1. Re-write Results section to emphasize adjusted findings rather than the unadjusted bivariate results as is currently the case. AS SUGGESTED, THE RESULTS SECTION OF THE ABSTRACT HAS BEEN RE-WRITTEN TO EMPHASIZE THE ADJUSTED FINDINGS.

2. Include findings of differences in QoL of on vs. off treatment patients. OPTIONAL

3. The content of the Conclusions should be in the Results, and a new Conclusion focusing on the very limited predictive effect of physical status and importance of QoL for patients (see below) AS SUGGESTED, WE HAVE MODIFIED THE CONCLUSION SECTION OF OUR ABSTRACT AND MANUSCRIPT TO REFLECT THE KEY FINDINGS OF OUR STUDY. PLEASE NOTE WE HAVE INCLUDED THE RESULTS OF UNIVARIATE AND MULTIVARIATE ANALYSES FOR GLOBAL QOL SCALE IN OUR REVISED MANUSCRIPT. PLEASE REFER TO OUR RESPONSE TO YOUR POINT #9 BELOW.

Background:
4. Paragraph 3: whereas several studies have shown a number of studies that link QoL to cancer survival, such studies are not without problems, mainly that of reverse causality: patients with more aggressive disease or who are less responsive to treatment feel worse, and hence report poorer QoL. Moreover, some of the more rigorously controlled studies in this area have failed to demonstrate that QoL is an independent risk factor once reverse causality is taken into account. Some mention of this lack of unanimity in the literature is needed in the present paper. Otherwise, if it is a given that QoL predicts outcomes, then where is the value of another “me too” paper describing the same phenomenon? THE DISCUSSION ON LACK OF UNANIMITY IN THE LITERATURE HAS BEEN INCLUDED IN THE DISCUSSION SECTION IN
RESPONSE TO YOUR POINT #8 BELOW. SOME DISCUSSION ON THIS ISSUE HAS ALSO BEEN INCLUDED IN THE LIMITATIONS OF OUR STUDY.

5. Moreover, there are other issues related to choice of instrument that could be mentioned concisely in the Background (see Montazeri et al, H&QoLO., 2009). These include generic vs. symptom specific instruments’ relative sensitivity and other methodological concerns that litter this field. Montazeri’s paper could also be referenced, providing as it does a review of the issue. AS ADVISED, WE HAVE REFERENCED MONTAZERI ET AL. PAPER IN THE BACKGROUND SECTION TO REFLECT THE IMPORTANCE OF THE CHOICE OF INSTRUMENT ON STUDY RESULTS.

Methods:

6. Other issues that have been identified as potentially important in such QoL-survival studies are the inclusion of socioeconomic data in multivariate models. In the USA this should include information on health insurance coverage (access to treatment), and possibly employment and education status. If these data are not available to adjust the multivariate models a note should be included in the limitations section of the paper to this effect and indicating these possible problems. (I note in the Limitations SES is mentioned but no discussion of insurance cover/access is raised). AS RECOMMENDED, THE LACK OF INFORMATION ON ADDITIONAL CONFOUNDERS OF THE QOL-SURVIVAL ASSOCIATION HAS BEEN ACKNOWLEDGED IN THE LIMITATIONS. SPECIAL MENTION WAS MADE OF THE MONTAZERI ET AL. PAPER THAT SUGGESTES QOL DATA MIGHT BE MARKERS OF THE SOCIOECONOMIC STATUS OF CANCER PATIENTS.

Discussion:

7. The authors make a good point in emphasizing the value of QoL to patients being as great as that of survival. Good quality life is a major treatment challenge in optimal cancer care and with targeted therapies, prolonged disease is shifting the equation more in this direction. However, lung cancer remains a serious challenge to survival-extending therapies, making QoL issues even more pertinent. OPTIONAL

8. Page 14: This section needs substantially more work. Instead of simply saying study A found X, study B found Y, and so on, some effort should be made to make sense of these findings and account for the highly variable quality of the evidence they present. Many studies of QoL outcomes have failed to provide adequate controls for confounding, and in particular reverse causality; some (as the authors indicate in the subsequent paragraph, are only case series. In most of these studies, it is not that QoL independently predicts survival, but that QoL reflects progress of the underlying disease. The present study strongly suggests this also, with only physical QoL and symptoms predicting survival after adjustment for disease factors. THANK YOU FOR THESE INSIGHTS. AS ADVISED, WE HAVE MADE SUBSTANTIAL REVISIONS TO THIS SECTION INCLUDING THE DISCUSSION OF INADEQUATE CONTROL OF CONFOUNDING WITH REVERSE CAUSALITY IN PARTICULAR.
9. The authors seem to emphasize throughout that their study shows that QoL independently predicts survival, but this interpretation is not justified, given that only physical status predicts outcome. The Physical subscale of the EORTC is in effect reflecting the physical status of the patient, which in turn is a reflection of the disease progress. THANK YOU FOR POINTING THIS OUT. WE REALIZE THAT WE SHOULD HAVE REPORTED THE RESULTS OF OVERALL (GLOBAL) QOL AS WELL IN OUR MANUSCRIPT. WE HAVE NOW INCLUDED THE RESULTS OF UNIVARIATE AND MULTIVARIATE ANALYSES FOR GLOBAL QOL SCALE. PLEASE REFER TO TABLES 4 AND 6. WE FOUND THAT GLOBAL QOL WAS ALSO INDEPENDENTLY PROGNOSTIC OF SURVIVAL. THE RESULTS AND DISCUSSION SECTIONS HAVE ALSO BEEN UPDATED ACCORDINGLY.

In this regard the authors have produced identical findings to another large longitudinal study that we published in 2007 (Fielding & Wong, EJC, 2007). Yet there is no mentioned of these or other findings that reach similar conclusions. Some effort should be made to represent or account for dismissing alternate findings. AS RECOMMENDED, YOUR STUDY (FIELDING & WONG, EJC, 2007) HAS BEEN DISCUSSED IN THE CONTEXT OF OUR STUDY FINDINGS. WE THINK YOUR STUDY PROVIDES VALUABLE INSIGHTS ON THE IMPORTANCE OF COMPLETE ADJUSTMENT OF POTENTIAL CONFOUNDERS IN ORDER TO REALLY UNDERSTAND AND UNRAVEL THE QOL-SURVIVAL ASSOCIATION IN CANCER. WE HAVE RE-EMPHASIZED THIS POINT IN THE LIMITATIONS PARAGRAPH OF OUR REVISED PAPER.

10. The authors’ conclusions are therefore contentious. Claiming that it is vital to measure QoL to determine when interventions should be undertaken to improve QoL is fair enough and not disputed. Making the patient as comfortable and able as possible is probably the most important issue in advanced lung cancer. However, other disease indicators (weight loss, appetite, other physical symptoms) provide probably the same information on likely survival that the physical scales of QoL instruments do. THE CONCLUSION SECTION HAS BEEN REVISED SIGNIFICANTLY IN THE LIGHT OF NEW ANALYSES REPORTED ON GLOBAL QOL AND ITS RELATIONSHIP WITH SURVIVAL.

11. A strength of the study is the sample size. THIS HAS BEEN INCLUDED IN THE PARAGRAPH ON STRENGTHS.

12. References 26 and 38 are duplicates. Ref 43 includes an typo (%). THANK YOU. WE FOUND SOME MORE DUPLICATES WHICH HAVE NOW BEEN REMOVED. TYPO HAS ALSO BEEN CORRECTED.

Major compulsory revisions.
Points 1, 3, 4, 8, 9, 10

Minor compulsory revisions.
Points 5, 6, 11, 12
Optional revisions.
Points 2, 7

Reviewer’s report
Title: Quality of Life Assessment: An Independent Predictor of Survival in Lung Cancer
Version: 1 Date: 19 December 2010
Reviewer: Thida Win

Reviewer’s report:
Quality of Life Assessment: An Independent Predictor of Survival in Lung Cancer

1. Well defined question and answer well. THANKS.

2. Method is appropriate and well described, however, it was not clear, when and how receive the follow up information and quality of data. PLEASE SEE OUR EXPLANATION BELOW.

3. The data is sound, however, quality is in question as not prospectively collected. WE DO ACKNOWLEDGE THE FACT THAT OUR STUDY BECAUSE OF ITS RETROSPECTIVE NATURE IS NOT BASED ON PRIMARY RESEARCH DATA. HOWEVER, THE QOL DATA USED FOR THE PURPOSE OF ANALYSIS WERE COLLECTED USING A VALIDATED QUESTIONNAIRE BY A WELL-TRAINED CLINICAL COORDINATOR. DATA WERE SYSTEMATICALLY COLLECTED AND ENTERED IN AN EXCEL SPREADSHEET THAT WAS MAINTAINED BY THE OFFICE OF CLINICAL RESEARCH. SEVERAL QUALITY CHECKS WERE PERFORMED FROM TIME TO TIME TO ENSURE COMPLETENESS AND ACCURACY OF DATA. THIS INFORMATION HAS NOW BEEN INCLUDED IN THE REVISED MANUSCRIPT.

4. The manuscript adhere to the relevant standards for reporting and data deposition. THANKS.

5. Discussion and conclusions are well balanced and adequately supported by the data. THANKS.

6. Limitations of the work are clearly stated. THANKS.

7. Good discussion regarding background literature. THANKS.

8. Title and abstract accurately convey the message. THANKS.

9. Good writing style. THANKS.

Recommendation: Discretionary Revisions, as very interesting study, added value to current literature. Recommend more reassurance regarding data quality. PLEASE SEE OUR EXPLANATION ABOVE.
Reviewer's report
Title: Quality of Life Assessment: An Independent Predictor of Survival in Lung Cancer
Version: 1 Date: 22 December 2010
Reviewer: Madelon Pijls-Johannesma

Reviewer's report:
This paper reports whether QoL at admission can predict survival in lung cancer patients. Nevertheless, overall QoL was not reported in the analysis. This paper is focusing on the impact on different QoL domains on survival. It is incorrect to interpret these domains as QoL, although there most domains highly correlate with QoL, QoL as measured with the EORTC-QLQ-C30 should be determined by the subscale global health status/QoL. Though, it seems that the conclusion drawn by the results does not give a direct answer to the primary aim of this study. THANK YOU FOR THIS SUGGESTION. WE REALIZE THAT OUR ANALYSIS IS INCOMPLETE WITHOUT INCLUSION OF THE RESULTS FOR GLOBAL QOL. AS A RESULT, WE HAVE INCLUDED THE RESULTS OF UNIVARIATE AND MULTIVARIATE ANALYSES FOR GLOBAL QOL SCALE. PLEASE REFER TO TABLES 4 AND 6. WE FOUND THAT GLOBAL QOL WAS ALSO INDEPENDENTLY PROGNOSTIC OF SURVIVAL. THE RESULTS AND DISCUSSION SECTIONS HAVE ALSO BEEN UPDATED ACCORDINGLY.

PLEASE NOTE: SINCE THE GLOBAL QOL SCALE OF THE QLQ-C30 IS HIGHLY CORRELATED WITH OTHER SCALES, IT WAS NOT INCLUDED IN PROGNOSTIC INDICATOR ANALYSES WHEN OTHER VARIABLES FROM QLQ-C30 WERE USED, IN ORDER TO ACHIEVE MODEL STABILITY. INSTEAD, GLOBAL QOL WAS ANALYZED SEPARATELY AFTER ADJUSTING FOR CLINICAL AND DEMOGRAPHIC FACTORS.

Besides at the end of the introduction, it seems that main goal is to investigate the efficacy of the QLQ-C30. THE GOAL OF THIS STUDY WAS TO INVESTIGATE WHETHER QOL, AS MEASURED BY EORTC QLQ-C30, CAN PREDICT SURVIVAL IN LUNG CANCER PATIENTS. AS RECOMMENDED, WE HAVE RE-PHRASED THE GOAL OF THE STUDY TO AVOID ANY CONFUSION.

Next, a very heterogeneous group of patients was investigated. Does this cohort consist of only NSCLC or were also SCLC patients included? ONLY NSCLC WERE INCLUDED. THIS HAS BEEN CLARIFIED IN THE METHODS SECTION OF THE REVISED PAPER AS WELL AS IN THE ABSTRACT.

Stage I-IV do have different prognosis, it would have been useful if analysis were also performed for each individual subgroup, e.g. stage I-II, stage III and stage IV. Altogether, the goal of this paper is not clearly described and the analyses are insufficient. IN RESPONSE TO YOUR EARLIER SUGGESTION, WE HAVE INCLUDED THE ANALYSES FOR GLOBAL QOL IN OUR REVISED
MANUSCRIPT. MOREOVER, WE MADE SURE WE CONTROLLED FOR TUMOR STAGE IN THE MULTIVARIATE ANALYSIS. PLEASE SEE TABLES 5 AND 6. AFTER ADJUSTING FOR TUMOR STAGE, GENDER, AND PRIOR TREATMENT HISTORY, WE STILL FOUND PHYSICAL FUNCTION AND GLOBAL QOL TO BE SIGNIFICANTLY ASSOCIATED WITH SURVIVAL.

Specific comments

Introduction:

If the aim is to investigate the impact of QoL on survival than this should also be the main subject of this section. Most is written about QoL assessment and the EORTC-QLQ-C-30. Unless I misunderstood the general aim of the paper, these subjects do have a link with the general aim but are actually not the scope of this subject. AS SUGGESTED, THE INTRODUCTION SECTION HAS BEEN REVISED TO FOCUS MORE ON THE MAIN TOPIC OF QOL AND CANCER SURVIVAL.

In the first paragraph it is written ‘The vast majority do not have curative treatment options…….’ Especially for this group of patients QoL assessment is important. Although the minority, also 163 stage I/II patients are included. I assume these patients were treated with curative intent. WE AGREE. AS A RESULT, WE HAVE MODIFIED THE ABOVE SENTENCE IN THE INTRODUCTION TO SAY “THE VAST MAJORITY OF PATIENTS, ESPECIALLY THOSE WITH ADVANCED DISEASE, DO NOT HAVE CURATIVE TREATMENT OPTIONS…….”

Since a difference in prognosis is expected this group should not be analyzed together with the other patients, since survival is a primary endpoint. WE AGREE. THEREFORE, WE MADE SURE WE CONTROLLED FOR TUMOR STAGE IN THE MULTIVARIATE ANALYSIS. PLEASE SEE TABLES 5 AND 6. AFTER ADJUSTING FOR TUMOR STAGE, GENDER, AND PRIOR TREATMENT HISTORY, WE STILL FOUND PHYSICAL FUNCTION AND GLOBAL QOL TO BE SIGNIFICANTLY ASSOCIATED WITH SURVIVAL.

Method:

In the section ‘Prespecified Baseline Clinical Factors’ baseline clinical factors were described. It would be valuable to also add performance status and the existence of co-morbidities since these variables do have a high impact on QoL. UNFORTUNATELY, WE DID NOT HAVE DATA ON PERFORMANCE STATUS, COMORBIDITIES AND OTHER POTENTIAL CONFOUNDERS. A LIMITATION ACKNOWLEDGING THIS IS INCLUDED IN THE DISCUSSION SECTION IN THE SECOND TO LAST PARAGRAPH.

“Data analysis and Statistical Methods”; It is mentioned that HR was used for survival, however the RR was reported in the tables 4 and 5. SORRY FOR THIS TYPO. RR HAS BEEN REPLACED WITH HR IN TABLES 4 AND 5 AS WELL AS THROUGHOUT THE MANUSCRIPT.

Results:
‘Relationship between QoL and other covariates’: A difference for fatigue and pain was reported between metastatic and locoregional disease and also regarding physical, role and social functioning scores between previously treated and newly diagnosed disease. The interpretation in the next sentence should move to the discussion section. AS SUGGESTED, THE INTERPRETATION HAS BEEN MOVED TO THE DISCUSSION SECTION.

Tables:
Please describe in the footnote of table 2 and 3 the interpretation of high and low scores. These are different for functional and symptom scales. AS SUGGESTED, A FOOTNOTE HAS BEEN INCLUDED UNDER TABLES 2 AND 3.