Title

Exploring Radiotherapy Targeting Strategy and Dose: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Stage III NSCLC

Journal

Journal of Thoracic Oncology, 13(8)

ISSN

1556-0864

Authors

Schild, Steven E
Pang, Herbert H
Fan, Wen
et al.

Publication Date

2018-08-01

DOI

10.1016/j.jtho.2018.04.011

Peer reviewed

Exploring Radiotherapy Targeting Strategy and Dose: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer

Steven E. Schild, M.D., Wen Fan, MB, Thomas E. Stinchcombe, M.D., Everett E. Vokes, M.D., Suresh S. Ramalingam, M.D., Jeffrey D. Bradley, M.D., Karen Kelly, M.D., Herbert H. Pang, PhD., Xiaofei Wang, PhD

PII: S1556-0864(18)30537-9

DOI: 10.1016/j.jtho.2018.04.011

Reference: JTHO 940

To appear in: *Journal of Thoracic Oncology*

Received Date: 17 January 2018

Revised Date: 5 April 2018

Accepted Date: 7 April 2018

Please cite this article as: Schild SE, Fan W, Stinchcombe TE, Vokes EE, Ramalingam SS, Bradley JD, Kelly K, Pang HH, Wang X, Exploring Radiotherapy Targeting Strategy and Dose: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer, *Journal of Thoracic Oncology* (2018), doi: 10.1016/j.jtho.2018.04.011.

Exploring Radiotherapy Targeting Strategy and Dose: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer

Steven E. Schild M.D.[1]

Wen Fan MB [2]

Thomas E. Stinchcombe, M.D.[3]

Everett E. Vokes M.D. [4]

Suresh S. Ramalingam M.D. [5]

Jeffrey D. Bradley M.D. [6]

Karen Kelly M.D. [7]

Herbert H. Pang PhD.,[2, 8]

Xiaofei Wang PhD [2, 9]

Supported by National Institutes of Health Grant No. R21-AG042894 (T.E.S., E.E.V., H.H.P., X.W.), Health and Medical Research Fund No.12133251 (H.H.P.), and National Cancer Institute Grant No.P01-CA142538 (X.W.) and a grant from Duke University(WF, XW).

1. Corresponding Author: Department of Radiation Oncology, Mayo Clinic, 5777 E. Mayo Blvd. Phoenix, AZ 85054, Phone 480-342-1262,FAX: 480-342-3972, E-mail: sschild@mayo.edu
2. Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, NC.
3. Duke Cancer Institute, Durham, NC.
4. University of Chicago, Medical Oncology, Chicago, IL.
5. Winship Cancer Institute of Emory University, Atlanta, GA.
6. Washington University, Radiation Oncology, St. Louis, MO.
7. University of California, Medical Oncology, Davis, CA.
8. School of Public Health, HKU Li Ka Shing Faculty of Medicine, Hong Kong SAR, China
9. Alliance Statistics and Data Center, Durham, NC.

Running Title: Radiotherapy Parameters in Combined Modality Therapy of NSCLC

Abstract

Introduction: Concurrent chemoradiotherapy(CRT) is standard therapy for locally-advanced non–small-cell lung cancer(LA-NSCLC)patients. This study was performed to examine thoracic radiotherapy(TRT) parameters and their impact on patient survival.

Methods: We collected Individual patient data(IPD) from 3600LA-NSCLC patients participating in 16 cooperative group trials of concurrent CRT. The primary TRT parameters examined included field design strategy(elective nodal irradiation(ENI) compared to involved field TRT(IF-TRT)), total dose, and biologically effective dose(BED). Hazard ratios(HRs) for overall survival were calculated with univariable and multivariable Cox models.

Results: TRT doses ranged from 60 to 74 Gy with most treatments administered once-daily. ENI was associated with poorer survival than IF-TRT(univariable HR,1.37;95%CI,1.24-1.51,p<0.0001;multivariable HR,1.31;95%CI,1.08-1.59,p=0.002). The median survival of the IF and ENI patients were 24 and 16 months, respectively. Patients were divided into 3 dose groups: low total dose(60 Gy), medium total dose(>60Gy-66Gy) and high total dose(>66Gy-74 Gy). With reference to the low dose group, the multivariable HR's were 1.08 for the medium dose group(95%CI=0.93-1.25) and 1.12 for the high dose group(CI=0.97-1.30).The univariate p=0.054 and multivariable p=0.17. BED was grouped as follows: low(<55.5Gy_{10}), medium(=55.5 Gy_{10}), or high(>55.5 Gy_{10}). With reference to the low BED group, the HR was 1.00(95%CI=0.85-1.18) for the medium BED group and 1.10(95%CI=0.93-1.31) for the high BED group. The univariable p=0.076 and multivariable p=0.16.

Conclusions: For LA-NSCLC patients treated with concurrent CRT, IF-TRT was associated with significantly better survival than ENI-TRT. TRT total and BED dose levels were not significantly associated with patient survival. Future progress will require research focusing on better systemic therapy and TRT.

Introduction

Lung cancer is the most common malignancy resulting in death. In the U.S. alone during 2017, it was estimated that lung cancer was diagnosed in 222,500 patients and resulted in 157,700 deaths.[1] Approximately 20% of all lung cancers are locally advanced or stage III at diagnosis.[2] Non-small cell lung cancer(NSCLC) comprises approximately 85% of all lung cancers with only a minority of patients amenable to resection. Thus, systemic therapy and radiotherapy are used for most patients. [2]

Significant progress has been made since the 1960's in the treatment of locally advanced(stage III) NSCLC(LA-NSCLC).[3, 4] In the 1960's, a randomized trial found that thoracic radiotherapy(TRT) resulted in modestly better patient survival than observation.[5] Prior to the common usage of chemoradiotherapy(CRT), another randomized trial determined that the regimen of 60Gy in 30 daily fractions achieved better local control than lesser TRT doses conventionally fractionationed.[6] In the 1990's, induction chemotherapy followed by TRT achieved better patient survival than TRT alone.[7, 8] Later, randomized trials found that concurrent CRT resulted in better survival then sequential CRT.[9, 10] In 2015, a large trial determined that concurrent chemotherapy with TRT doses of 60Gy in 30 daily fractions resulted in better survival than the same chemotherapy with 74Gy in 37 daily fractions.[11] Thus, progress has been made and patient outcomes have improved.[3, 4] Additionally, a recent randomized trial found that progression free survival was further improved in stage III NSCLC patients if they received immunotherapy(durvalumab) after CRT.[12]

Despite progress, controversies remain in the treatment of LA-NSCLC patients. In the radiation therapy of LA-NSCLC, certain basic questions have not been clearly answered. For example, what dose-fractionation pattern is best? Should TRT only target radiographically visible disease with involved field thoracic radiotherapy(IF-TRT) or should one also irradiate adjacent lymph nodes that have potential microscopic disease but are not radiographically abnormal with elective nodal irradiation(ENI)? In order to address these questions, we performed this pooled analysis of the outcomes of patients participating in the National Cancer Institute(NCI) National Clinical Trials Network(NCTN) trials. The main goal of this analysis was to establish which radiotherapy targeting and dosing strategies were associated with improved patient survival. This information would provide data helpful in designing future trials and developing evidence-based TRT guidelines that define the standard of care in treating LA-NSCLC.

Methods and Materials:

In order to address these fundamental radiation oncology questions regarding the treatment of LA-NSCLC, we performed this pooled analysis of the outcomes of 3600 LA-NSCLC patients participating in 16 trials. These trials are shown in Table 1.

Data-sharing agreements were developed with the various cooperative groups to perform this analysis. Individual patient data(IPD) were obtained for unresectable LA-NSCLC patients in NCTN trials. All therapy was delivered between 1990 and 2012. A centralized database was developed including these patients' data to potentially identify optimal dose-fractionation and target volumes for TRT within various CRT programs.

Only trials including concurrent CRT with or without additional chemotherapy before or after concurrent CRT were included. Excluded were high-risk patients with poor performance status and those treated with targeted therapy without concurrent CRT. The primary end point of this analysis was overall survival. The duration of survival was defined as the period of time between registration or randomization and death. Treatment patterns were divided as follows: induction chemotherapy followed by concurrent CRT, concurrent CRT alone, and concurrent CRT followed by consolidation chemotherapy.

Radiotherapy variables evaluated included nodal coverage strategy(IF-TRT vs ENI-TRT), total TRT dose, and biologically effective dose(BED). IF-TRT most commonly refers to radiotherapy administered to the primary lesion and radiographically involved regional lymph nodes (>1cm in short diameter or metabolically active nodes on positron emission tomography(PET), when available). ENI includes radiotherapy to the primary lesion, radiographically involved nodes, and adjacent uninvolved nodes(most often including the ipsilateral hilum, much of the mediastinum, and in some trials the supraclavicular nodes). The BED formula (shown below) accounts for the efficacy provided by individual dose-fractionation programs related to the overall time radiotherapy is delivered compared to the potential doubling time of tumor cells.[13]

BED=(nd){1+[d/(α/β)]}-(0.693t/α Tpot) [14]

n=the total number of fractions delivered

d=the dose per fraction (Gy)

α/β =10 for acute effects and tumor control and 3 for chronic effects

α =0.3 Gy

t=total days in which radiotherapy is delivered

Tpot=potential doubling time(5.6 days)

The potential doubling time(Tpot) for NSCLC has been reported in the radiobiology literature to range from 2.2 to 8.9 days.[15-17] We used 5.6 days as the Tpot value for the purposes of this analysis. Thus, a break in the TRT decreases the BED and the potential efficacy of the regimen because a greater overall time of RT allows for tumor repopulation to occur.

Statistical Analysis:

The association between radiotherapy and other patient characteristics were tested using the chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. Kaplan-Meier curves were used to estimate survival.[18] The distribution difference of survival for various groups was tested by log-rank test, and the association of radiotherapy related variables with survival were further quantified by unadjusted and adjusted hazard ratios(HRs), estimated with 95%CI's using univariable and multivariable Cox models.[19, 20] Frailty Cox models were used with study trials as random effect to account for the clustering effect of patients within studies and the between-trial variance that could not be captured by covariates.[19, 20] Candidate covariates used for backward selection were: treatment pattern, age group, performance status, sex, race, weight loss, histology, number of chemotherapy agents, and recent trial or not(accrual closed before or after 2000). Treatment pattern and radiotherapy variables were included in all adjusted models because they corresponded to the effects of primary interest. The other variables included in the final model for the

survival analyses were: treatment pattern, age group, performance status, sex, weight loss, and number of chemotherapy agents. The adjusted HRs from the pooled analysis were compared with the adjusted HRs of each trial. The *P* values testing specific effects of these regression models were based on the Wald test. All *P* values reported are two sided and were not adjusted for multiple comparisons. The study was approved by the Duke University Institutional Review Board. Data management and statistical analyses were performed by statisticians at the Duke Department of Biostatistics and Bioinformatics using SAS (version 9.3; SAS Institute, Cary, NC) and R (version 3.2; R Foundation, Vienna, Austria) statistical software.

Results

IPD from 3600 patients participating in 16 trials were included in this pooled analysis**(Figure 1;Table 1).**[9, 21-35] Patient characteristics are found in **Table 2.** The average patient age was 62 years and 64% were men. Zubrod performance status was 0-1 in 99.1% of patients and 88.8% were white. Tumor histologies were described as adenocarcinoma in 33.3%, squamous cell cancer in 35.4% and other in remaining patients. It was quite common during at that time to report the tissue as NSCLC without being more specific. The cohort was split almost evenly between stages IIIa and IIIb disease and 83% had no significant weight loss in the past 6 months. TRT field design(IF vs. ENI) employed was specifically described in each protocol. The majority of patients(2844, 79%) were treated with ENI-TRT(**Table 2**) and this TRT targeting strategy was more common in early trials. Total doses ranged from 60 to 74Gy and most treatment was given daily but some studies included twice-daily TRT arms(**Table 3).**

Seven trials included induction chemotherapy followed by concurrent CRT, four trials included concurrent CRT followed by consolidation chemotherapy, four trials used concurrent CRT alone, and one trial randomly assigned patients between induction chemotherapy followed by concurrent CRT and concurrent CRT. Specific chemotherapy agents used in each trial are found on Table 1. Follow-up ranged from 0.1 to 14 years(median:6.1 years).

The TRT field design(ENI or IF) was stipulated in each trial and evaluated in detail with respect to patient survival. In both the univariable and multivariable models, ENI patients had a statistically significantly worse survival than IF patients (univariable HR,1.37; 95%CI,1.24-1.51,p<0.0001 and multivariable HR,1.31; 95%CI,1.08-1.59,p=0.002). The median survival in the IF and ENI patients were 24 months (95%CI,20.8-26.1) and 16 months (95% CI,15.1-16.9), respectively. The 3- and 5-year survival rates were 37%(95% CI,33.5%-41.1%) and 19%(95%CI,14.0%-23.9%) in IF patients compared to 25%(95%CI,23.6%-26.8%) and 16%(95% CI,14.2%-16.9%) in ENI patients(**Figure 2**).

Total TRT doses ranged from 60 to 74Gy and most treatment was delivered with once daily fractionation(**Table 3).** Patients were divided into 3 dose groups: low total dose: 60Gy(1322 patients,37%), medium total dose: >60Gy-66Gy(1422 patients,39%) and high total dose >66Gy-74Gy (856 patients,24%). The total dose was evaluated with respect to survival. In the multivariable analysis, covariates selected included: total dose group, field design(ENI vs IF-TRT), age, PS, gender, weight loss, stage, number of agents. The association between total radiotherapy dose and survival and was not significant on univariable (p=0.054) or multivariable analysis(p=0.17). With reference to

the low dose group, the univariable HR's were 1.07(95%CI,0.98-1.17) for the medium dose group, and 0.96(95%CI,0.87-1.06) in the high dose group. With reference to the low dose group, the multivariable HR's were 1.08(95%CI,0.93-1.25) for the medium dose group and 1.12 (95%CI,0.97-1.30) for the high dose group. The median survival was 18 months in the low dose group, 16 months in the medium dose group, and 19 months in the high dose group. The 5-year survival was 17% in the low dose group, 16% in the medium dose group and 17% in the high dose group (Figure 3, survival with 95%CI's).

BED was grouped as follows: low(<55.5$Gy_{10,}$,747 patients,21%), medium (55.5Gy_{10},1197 patients,33%), or high(>55.5 Gy_{10} ,1656 patients,46%). The median survival was 19 months for the low BED patients, 18 months for the medium BED patients, and 16 months for the high BED patients. The univariable p=0.076 and multivariable p=0.16. With reference to the low BED group, the univariable HR's were1.03(95%CI,0.93-1.15) for those in the medium BED group and 1.11(95%CI,1.01-1.22) for the high BED. Covariates included BED, fields(ENI vs. IF), age, PS, gender, weight loss, stage and number of systemic agents. With reference to the low BED group, the multivariable HR's were 1.00(95%CI,0.85-1.18) for the medium BED group and 1.10(95%CI,0.93-1.31) for the high BED group. Thus, BED was not significantly associated with survival(**Figure 4**,survival with 95%CI's).

Conclusions:

This study was performed to examine specific radiotherapy parameters used in LA-NSCLC cooperative group trials with the goal of determining if these factors were

associated with survival. This data could be useful when choosing specific targeting strategies(IF-RT vs ENI) and doses of radiation when planning concurrent CRT.

The present study found that CRT employing IF-RT was associated with significantly better survival than ENI with median survival of 24 months and 16 months, respectively. Previous randomized studies that have investigated IF-RT compared to ENI have been relatively small, lacking sufficient power to detect a clearly significant difference in overall survival. Our findings generally agree with the three randomized C-RT trials that compared IF-RT to ENI.[36-38]

Yuan et al. included 200 patients with LA- NSCLC treated with concurrent CRT and randomized to either an IF-TRT or ENI arm. A total of 4 to 6 cycles of cisplatin-based chemotherapy were delivered, and concurrent CRT was started after the second cycle of chemotherapy. Conventionally fractionated (1.8-2Gy daily) three-dimensional TRT was used to deliver 68-74Gy with IF-TRT or 60-64Gy with ENI. The 2- and 5-year survival rates were 26% and 18% for the ENI arm and 39% and 25% for the IF-TRT arm, respectively. Only the 2-year survival rates were significantly different(*P*=0.048). The median survival was 15.0 months with ENI and 20.0 months with IF-TRT.

Yang et al. included 55 LA-NSCLC patients who first received four cycles of induction chemotherapy and then were randomized to ENI(mean dose:58.4Gy) or IF-TRT(mean dose:65.8Gy). The median survival was 15 months with IF-TRT and 13 months with ENI(*P*=0.084).

Chen et al. randomized 85 patients to IF-RT or ENI delivering a median dose of 60Gy in each arm. Induction chemotherapy(paclitaxel and carboplatin) was administered intravenously for 2 cycles. This was followed by CRT with concurrent

weekly paclitaxel. The 2-, and 3-year survival rates were 53%, and 37%, respectively, in IF-RT arm, compared to 34.9%, and 30.3% in ENI arm(P=0.08). The median survival was 28 months with IF-TRT and 17 months with ENI. Debate continued following these randomized trials that reported significant or nearly significant findings.[39-41]

Li et al. evaluated the three randomized trials and three additional retrospective studies in a meta-analysis.[42] This was done to provide better evidence on the incidence of elective nodal failure(ENF) with IF-TRT or ENI. ENF was defined as nodal failure without local failure in initially univolved nodes within regions that received prophylactic irradiation with ENI but were not treated with IF-TRT. When combining all six studies, the incidence of ENF was 5.5 % with IFRT and 3.4 % with ENI(RR=1.15,p=0.64).

Cooperative group trials employed both IF-RT and ENI as it was unknown which was better. These were compared in the present pooled analysis to provide objective evidence regarding survival. On both univariable and multivariable analyses, ENI was associated with poorer survival. This data provides reasonably strong evidence that IF-TRT should be the preferred strategy. Reasons for this difference in survival may be related to toxicity or immunosuppression as IF-TRT avoids irradiating large clinically uninvolved nodal regions mainly within the mediastinum. This decreases the dose delivered to normal surrounding normal tissues such as heart, lungs, esophagus, and the immune system. Of these, the most important may be the heart as exposure to therapeutic irradiation has been associated with severe toxicity and poorer survival.[11, 43, 44] In one large modern trial, multivariable analysis revealed that poorer survival was associated with higher prescribed radiation dose, esophageal toxicity, target volume, and heart V5 and V30(% of heart volume receiving $\geq$5Gy or $\geq$30Gy, respectively).[11] In a

large retrospective study, Speirs reported that the 2-year survival of LA-NSCLC lung cancer patients was 46.8% for those with a heart V50 of <25% versus 26.7% for those with greater heart exposure($p < 0.0001$).[43] Additionally, the dose administered to the immune system(lymphoid system, circulating white blood cells and marrow) appears important. Jin et al. found that the dose to immunologic system was significantly associated with poorer survival of LA-NSCLC patients.[45] Over time, more trials have been written to include IF-TRT due to concerns of toxicity with the recognition that the survival rates reported in studies employing IF-TRT appeared favorable. These findings also led some authors to write guidelines recommending IF-TRT.[11, 46, 47] While this study focused on survival as the primary endpoint, we plan a separate analysis focused specifically on toxicity.

With respect to the evaluation of TRT dose, the present analysis found no significant association between dose and survival. We divided the total dose into 3 dose groups: low total dose:60 Gy, medium total dose:>60Gy-66Gy and high total dose:>66Gy-74 Gy. With reference to the low dose group, the multivariable HR's were 1.08 for the medium dose group and 1.12 for the high dose group. This suggested that the lower dose range appeared numerically more favorable but not significantly so within the context of the concurrent CRT employed within these trials. Numerically greater HR's in higher dose groups agrees, in general, with the findings of Ramroth et al.[48] They performed a meta-analysis including 3795 patients participating in 25 randomized trials comparing TRT doses. They found that when treatment included concurrent CRT, higher TRT doses resulted in significantly worse survival(HR=1.2,p=0.02). They believed that this was due to increased toxicity with

concurrent CRT employing higher TRT doses. Interestingly, they recommended future CRT research focusing on TRT dose-escalation employing newer technology to reduce toxicity.

We also examined the possible relationships between survival and TRT BED. The BED formula accounts for the length and fractionation of a TRT course. Similar to TRT dose, the BED was not significantly associated with patient survival.

It was generally believed that dose and fractionation affect the survival of stage III NSCLC patients. However, with the radiotherapy technology employed in these trials(primarily 3-D TRT and IMRT),escalation of total dose alone with conventional fractionation did not improve survival.[11] It is possible that altered fractionation programs that employ either multiple daily fractions or fewer larger fractions may improve survival. In the past, programs including multiple daily doses of TRT were administered and found to positively impact survival but mainly in patients who received TRT alone.[9, 49] One CRT trial employing hypofractionation reported very favorable results.[46] The best arm included concurrent hypofractioned IF-TRT(66 Gy in 24 daily treatments) and daily cisplatin resulting in a median survival of 33 months and 5-year survival of 37%.

Strengths of the present study were the large size of the cohort(N=3600) and the prospective nature of the original trials. Limitations include the retrospective nature of this analysis. The use of IF-RT was most common in the more modern series. However, the multivariable analysis was designed to adjust for the timing of various trials and several other factors. We didn't compare intensity modulated radiotherapy(IMRT) to 3-D TRT as IMRT was only used for some of the patients who participated in a single trial. Positron emission tomography(PET) was required in only one trial(CALGB 30407) and

was permissible in the other IF-TRT trials(Table 3). However, there was no PET data within our database so we couldn't examine its potential influence on outcome. PET scans can potentially influence outcome through stage migration and were performed more frequently in the recent studies that included IF-TRT.

In conclusion, this pooled analysis of LA-NSCLC patients treated with concurrent CRT found that IF-TRT resulted in significantly better survival than ENI. Additionally, we did not detect a significant association between TRT dose level and survival. Therefore, for the purposes of general practice and trial development, the use of IF-TRT and 60Gy in 2Gy daily fractions should be considered the standard of care for CRT of LA-NSCLC. Future progress in the treatment of LA-NSCLC is dependent on research examining immunotherapy, targeted therapy, improved imaging, adaptive radiotherapy, simultaneous integrated boost techniques, novel dose-fractionation regimens, and charged particle therapy.

Figure Legends

Figure 1: **CONSORT diagram** of clinical trials. IPD, individual patient data; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.*IPD from treatment arms within that investigated targeted therapy alone, administered sequential chemotherapy and radiotherapy, or poor-risk or poor performance status patient population.

Figure 2: Survival of patients with elective nodal irradiation (ENI) or involved field thoracic Radiotherapy (IF-TRT). The 95% confidence intervals are seen as shading.

Figure 3: Survival of patients with various total doses of radiotherapy administered. Patients were divided into 3 dose groups: low total dose: 60 Gy, medium total dose: >60Gy-66Gy and high total dose >66Gy-74 Gy. The 95% confidence intervals are seen as shading.

Figure 4: Survival of patients with various biologically effective dose levels of radiotherapy administered. BED was grouped as follows: low($<55.5Gy_{10,}$), medium ($55.5Gy_{10}$), or high(>55.5 Gy_{10}). The 95% confidence intervals are seen as shading.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7-30.
2. Chen VW, Ruiz BA, Hsieh MC, et al. Analysis of stage and clinical/prognostic factors for lung cancer from SEER registries: AJCC staging and collaborative stage data collection system. *Cancer* 2014;120 Suppl 23:3781-3792.
3. Dillman RO, McClure SE. Steadily improving survival in lung cancer. *Clin Lung Cancer* 2014;15:331-337.
4. Videtic G, Vokes E, Turrisi A, et al. The survival of patients treated for stage III non-small cell lung cancer in North America has increased during the past 25 years. (abstract 2557). *The 39th annual meeting of the American Society of Clinical Oncology*. Chicago Illinois. : ASCO; 2003:291.
5. Wolf J, Patno ME, Roswit B, et al. Controlled study of survival of patients with clinically inoperable lung cancer treated with radiation therapy. *Am J Med* 1966;40:360-367.
6. Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987;59:1874-1881.
7. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210-1215.
8. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990;323:940-945.
9. Curran WJ, Jr., Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. *J Natl Cancer Inst* 2011;103:1452-1460.
10. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692-2699.
11. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *Lancet Oncol* 2015;16:187-199.
12. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. *N Engl J Med* 2017.
13. Fowler JF. Biological factors influencing optimum fractionation in radiation therapy. *Acta Oncol* 2001;40:712-717.
14. Hall EJ. *Radiology for the Radiologist*. Philadelphia: Lippencott, Williams, and Wilkins; 2000.
15. Tinnemans MM, Schutte B, Lenders MH, et al. Cytokinetic analysis of lung cancer by in vivo bromodeoxyuridine labelling. *Br J Cancer* 1993;67:1217-1222.
16. Shibamoto Y, Ike O, Mizuno H, et al. Proliferative activity and micronucleus frequency after radiation of lung cancer cells as assessed by the cytokinesis-block method and their relationship to clinical outcome. *Clin Cancer Res* 1998;4:677-682.
17. Kerr KM, Lamb D. Actual growth rate and tumour cell proliferation in human pulmonary neoplasms. *Br J Cancer* 1984;50:343-349.
18. Kaplan E.L., P. M. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
19. Cox D. Regression models and life tables:. *J R Stat Soc (Series B)* 1972;4:187-202.
20. Hougaard P. *Analysis of multivariate survival data*. New York, NY,: Springer Science+Business Media; 2000.

21. Clamon G, Herndon J, Cooper R, et al. Radiosensitization with carboplatin for patients with unresectable stage III non-small-cell lung cancer: a phase III trial of the Cancer and Leukemia Group B and the Eastern Cooperative Oncology Group. *J Clin Oncol* 1999;17:4-11.
22. Vokes EE, Herndon JE, 2nd, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002;20:4191-4198.
23. Akerley W, Herndon JE, Jr., Lyss AP, et al. Induction paclitaxel/carboplatin followed by concurrent chemoradiation therapy for unresectable stage III non-small-cell lung cancer: a limited-access study--CALGB 9534. *Clin Lung Cancer* 2005;7:47-53.
24. Vokes EE, Herndon JE, 2nd, Kelley MJ, et al. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol* 2007;25:1698-1704.
25. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* 2008;26:2457-2463.
26. Ready N, Janne PA, Bogart J, et al. Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. *J Thorac Oncol* 2010;5:1382-1390.
27. Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. *J Clin Oncol* 2011;29:3120-3125.
28. Schild SE, Stella PJ, Geyer SM, et al. Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2002;54:370-378.
29. Zhao Y, Foster NR, Meyers JP, et al. A phase I/II study of bortezomib in combination with paclitaxel, carboplatin, and concurrent thoracic radiation therapy for non-small-cell lung cancer: North Central Cancer Treatment Group (NCCTG)-N0321. *J Thorac Oncol* 2015;10:172-180.
30. Movsas B, Scott C, Langer C, et al. Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01. *J Clin Oncol* 2005;23:2145-2154.
31. Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010;28:2475-2480.
32. Blumenschein GR, Jr., Paulus R, Curran WJ, et al. Phase II Study of Cetuximab in Combination With Chemoradiation in Patients With Stage IIIA/B Non-Small-Cell Lung Cancer: RTOG 0324. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2011.
33. Bradley JD, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617. *J Clin Oncol (suppl; abstr 7501)* 2013;31.
34. Hoang T, Dahlberg SE, Schiller JH, et al. Randomized phase III study of thoracic radiation in combination with paclitaxel and carboplatin with or without thalidomide in patients with stage III non-small-cell lung cancer: the ECOG 3598 study. *J Clin Oncol* 2012;30:616-622.

35. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008;26:2450-2456.
36. Chen M, Bao Y, Ma HL, et al. Involved-field radiotherapy versus elective nodal irradiation in combination with concurrent chemotherapy for locally advanced non-small cell lung cancer: a prospective randomized study. *Biomed Res Int* 2013;2013:371819.
37. Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *American Journal of Clinical Oncology* 2007;30:239-244.
38. Yang K, Cao F, Wang J, et al. Improved local control without elective nodal radiotherapy in patients with unresectable NSCLC treated by 3D-CRT. *Front Med China* 2007;1:381-385.
39. Belderbos JS, Kepka L, Kong FM, et al. Elective nodal irradiation (ENI) in locally advanced non-small-cell lung cancer (NSCLC): evidence versus opinion? *Int J Radiat Oncol Biol Phys* 2009;74:322; author reply 322-323.
40. Schild SE. Elective Nodal Irradiation (ENI) doesn't appear to provide a clear benefit for patients with unresectable non-small-cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2008;72:311-312.
41. Kelsey CR, Marks LB, Glatstein E. Elective nodal irradiation for locally advanced non-small-cell lung cancer: it's called cancer for a reason. *Int J Radiat Oncol Biol Phys* 2009;73:1291-1292.
42. Li R, Yu L, Lin S, et al. Involved field radiotherapy (IFRT) versus elective nodal irradiation (ENI) for locally advanced non-small cell lung cancer: a meta-analysis of incidence of elective nodal failure (ENF). *Radiat Oncol* 2016;11:124.
43. Speirs CK, DeWees TA, Rehman S, et al. Heart Dose Is an Independent Dosimetric Predictor of Overall Survival in Locally Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol* 2017;12:293-301.
44. Wang K, Eblan MJ, Deal AM, et al. Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy. *J Clin Oncol* 2017;35:1387-1394.
45. Jin JY, Hu C, Xiao Y, et al. Higher Radiation Dose to Immune System is Correlated With Poorer Survival in Patients With Stage III Non–small Cell Lung Cancer: A Secondary Study of a Phase 3 Cooperative Group Trial (NRG Oncology RTOG 0617). *International Journal of Radiation Oncology, Biology, Physics* 2017;99:S151–S152
46. Walraven I, van den Heuvel M, van Diessen J, et al. Long-term follow-up of patients with locally advanced non-small cell lung cancer receiving concurrent hypofractionated chemoradiotherapy with or without cetuximab. *Radiother Oncol* 2016;118:442-446.
47. De Ruysscher D, Faivre-Finn C, Moeller D, et al. European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol* 2017;124:1-10.
48. Ramroth J, Cutter DJ, Darby SC, et al. Dose and Fractionation in Radiation Therapy of Curative Intent for Non-Small Cell Lung Cancer: Meta-Analysis of Randomized Trials. *Int J Radiat Oncol Biol Phys* 2016;96:736-747.
49. Mauguen A, Le Pechoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788-2797.

Table 1: Clinical trials included in the analysis [8, 21-35]

Cooperative group trial #	Accrual period	Phase	Treatment	# of patients (% of total patients)	Paradigm
CALGB 9130[a]	1991-1994	3	Induction cisplatin/vinblastine → carboplatin + TRT 60 Gy	134 (3.7)	Induction → Concurrent
CALGB 9431[b]	1996-1998	2	Induction cisplatin-based therapy →cisplatin-based + TRT 66 Gy	177 (4.9)	Induction → Concurrent
CALGB 9534	1996-1999	2	Induction carboplatin and paclitaxel →carboplatin and paclitaxel 66 Gy	41 (1.1)	Induction → Concurrent
CALGB 39801	1998-2002	3	Induction carboplatin and paclitaxel →carboplatin and paclitaxel +TRT 66 Gy vs carboplatin and paclitaxel + TRT 66 Gy	338 (9.4)	Induction → Concurrent vs concurrent
CALGB 30105[c]	2002-2004	2	A: Induction carboplatin and paclitaxel →carboplatin and paclitaxel +TRT 74 Gy B: Induction carboplatin and gemcitabine →gemcitabine + TRT 74 Gy	68 (1.9)	Induction → Concurrent
CALGB 30106[d]	2002-2005	2	Induction chemotherapy carboplatin, paclitaxel and gefitinib followed concurrent carboplatin, paclitaxel, and gefitinib + TRT 66 Gy	52 (1.4)	Induction → Concurrent
CALGB 30407[c]	2005-2008	2	A: Concurrent carboplatin and pemetrexed + TRT 70 Gy → consolidation pemetrexed B: Concurrent carboplatin, pemetrexed, cetuximab+ TRT 70 Gy→consolidation pemetrexed	103 (2.9)	Concurrent → Consolidation
NCCTG 942452	1994-1999	3	Cisplatin and etoposide with TRT A: 60 Gy in 30 daily fractions B: Split course 30 Gy in 20 fractions BID followed by 2 week break and 30 Gy in 20 fractions BID	246 (6.8)	Concurrent
NCCTG N0321	2005-2011	1/2	Carboplatin, paclitaxel and bortezomib+ TRT 60 Gy	52 (1.4)	Concurrent

RTOG 9410	1994-1998	3	Cisplatin and vinblastine with TRT 63 Gy (once daily) vs cisplatin and etoposide with twice daily TRT to 69.6 Gy	375 (10.4)	Concurrent
RTOG 9801	1998-2002	3	Carboplatin and paclitaxel→ concurrent weekly carboplatin and paclitaxel with TRT 69.6 Gy	227 (6.3)	Induction → Concurrent
RTOG 0117[e]	2004-2007	2	Concurrent carboplatin and paclitaxel with TRT 74 Gy	45 (1.3)	Concurrent
RTOG 0324	2004-2005	2	Concurrent carboplatin, paclitaxel, cetuximab with TRT 63 Gy→consolidation carboplatin, paclitaxel, and cetuximab	92 (2.6)	Concurrent →consolidation
RTOG 0617	2007-2011	3	Carboplatin and paclitaxel +/- cetuximab with TRT of 60 or 74 Gy→ consolidation carboplatin and paclitaxel +/- cetuximab	540 (15)	Concurrent →consolidation
ECOG E3598	2000-2006	3	Induction carboplatin and paclitaxel→ concurrent carboplatin, paclitaxel +/- thalidomide with TRT 60 Gy	580 (16.1)	Induction →concurrent
SWOG S0023	2001-2005	3	Cisplatin and etoposide with concurrent TRT to 61 Gy followed by docetaxel and then randomized to gefitinib or placebo	530 (14.7)	Concurrent → consolidation

Abbreviations; TRT: thoracic radiation

[a] Only patients receiving concurrent chemoradiotherapy included.

[b] Patients received cisplatin with gemcitabine, paclitaxel or vinorlebine induction therapy followed by same cisplatin-based therapy with concurrent TRT

[c] Randomized phase 2 trial design

[d] Patients with performance status of 2 excluded

[e] Only patients with stage 3 disease included

Table 2: Patients' Characteristics

	Subgroup Summary			
	ENI (N=2844)	IF-TRT (N=756)	Total (N=3600)	p value
Treatment Pattern				<0.0001
concurrent CRT &consolidation chemotherapy	622 (21.9%)	688 (91.0%)	1310 (36.4%)	
concurrent CRT & induction chemotherapy	808 (28.4%)	68 (9.0%)	876 (24.3%)	
concurrent CRT alone	1414 (49.7%)	0 (0.0%)	1414 (39.3%)	
Age				<0.0001
N	2844(79%)	756(21%)	3600	
Mean (SD)	61.6 (9.6)	63.4 (9.4)	62.0 (9.6)	
Range	(20.0-86.0)	(32.0-84.0)	(20.0-86.0)	
Gender				0.2385
Missing	1 (.03%)	0 (.0%)	1(.03%)	
Female	1006 (35.4%)	285 (37.7%)	1291 (35.9%)	
Male	1837 (64.6%)	471 (62.3%)	2308 (64.1%)	
Race				0.0131
Missing	97 (2.7%)	9 (.25%)	106(2.9%)	
Black or African American	228 (8.3%)	86 (11.5%)	314 (9.0%)	
Other	57 (2.1%)	20 (2.7%)	77 (2.2%)	
White	2462 (89.6%)	641 (85.8%)	3103 (88.8%)	
Performance Status				<0.0001
Missing	16 (.4%)	0 (0%)	16(.4%)	
0	1239 (43.8%)	418 (55.3%)	1657 (46.2%)	
1	1558 (55.1%)	338 (44.7%)	1896 (52.9%)	
>= 2	31 (1.1%)	0 (0.0%)	31 (0.9%)	
Histology				<0.0001
Missing	10 (.27%)	2 (.06%)	12(.3)	
Adeno	898 (31.7%)	298 (39.5%)	1196 (33.3%)	
Other	972 (34.3%)	150 (19.9%)	1122 (31.3%)	
Squamous	964 (34.0%)	306 (40.6%)	1270 (35.4%)	
Stage				<0.0001
Stage IIIA	1252 (44.0%)	480 (63.5%)	1732 (48.1%)	
Stage IIIB	1592 (56.0%)	276 (36.5%)	1868 (51.9%)	
Weight loss in last 6 months				<0.0001
Missing	144 (4%)	115 (3.2%)	259(7.2)%	
>5/10% weight loss	544 (20.1%)	26 (4.1%)	570 (17.1%)	
$\leq$ 5/10% weight loss	2156 (79.9%)	615 (95.9%)	2771 (82.9%)	

TRT Total Dose Pattern				<0.0001
60	1012 (35.6%)	310 (41.0%)	1322 (36.7%)	
61	530 (18.6%)	0 (0.0%)	530 (14.7%)	
63	284 (10.0%)	0 (0.0%)	284 (7.9%)	
66	608 (21.4%)	0 (0.0%)	608 (16.9%)	
69.6	410 (14.4%)	0 (0.0%)	410 (11.4%)	
70	0 (0.0%)	103 (13.6%)	103 (2.9%)	
74	0 (0.0%)	343 (45.4%)	343 (9.5%)	
BED				<0.0001
46.73	125 (4.4%)	0 (0.0%)	125 (3.5%)	
54.57	530 (18.6%)	0 (0.0%)	530 (14.7%)	
54.95	92 (3.2%)	0 (0.0%)	92 (2.6%)	
55.5	887 (31.2%)	310 (41.0%)	1197 (33.3%)	
55.7	192 (6.8%)	0 (0.0%)	192 (5.3%)	
60.64	608 (21.4%)	0 (0.0%)	608 (16.9%)	
61.19	410 (14.4%)	0 (0.0%)	410 (11.4%)	
64.61	0 (0.0%)	103 (13.6%)	103 (2.9%)	
67.76	0 (0.0%)	343 (45.4%)	343 (9.5%)	

Abbreviations: IF: Involved field, TRT: thoracic Radiotherapy, ENI: elective nodal irradiation, BED: biologically effective dose

Table 3: Trials included in this analysis and radiotherapy parameters

group	trial	TRT strategy: (ENI vs. IF-TRT)	total dose (Gy) in one arm	# fractions in the first arm	total dose (Gy) in the other TRT arm (when one existed)*	# fractions in the other TRT arm (when one existed)*
CALGB	9130	ENI	60	30		
CALGB	9431	ENI	66	33		
CALGB	9534	ENI	66	33		
CALGB	39801	ENI	66	33		
CALGB	30105	IF-TRT	74	37		
CALGB	30106	ENI	66	33		
CALGB	30407	IF-TRT	70	35		
NCCTG	942452	ENI	60	30	60	40 BID
NCCTG	N0321	ENI	60	30		
RTOG	9410*	ENI	63	34	69.6	58 BID
RTOG	9801	ENI	69.6	58 BID		
RTOG	O117	IF-TRT	74	37		
RTOG	O324	ENI	63	35		
RTOG	O617	IF-TRT	60	30	74	37
ECOG	E3598	ENI	60	30		
SWOG	S0023	ENI	61	32		

Abbreviations: CALGB(Cancer and Leukemia Group B, Now the ALLIANCE), NCCTG (North Central Cancer Treatment Group, Now, the ALLIANCE), RTOG (Radiation Therapy and Oncology Group, Now, NRG), ECOG(Eastern Cooperative Oncology Group, now the ECOG-ACRIN), SWOG:(South West Oncology Group), ENI, Elective Nodal Irradiation, IF-TRT=involved field thoracic radiotherapy, BID=twice daily, *Most trials did not have a second radiotherapy arm. Unless specified, TRT was given once daily.

Figure 1: CONSORT diagram of clinical trials

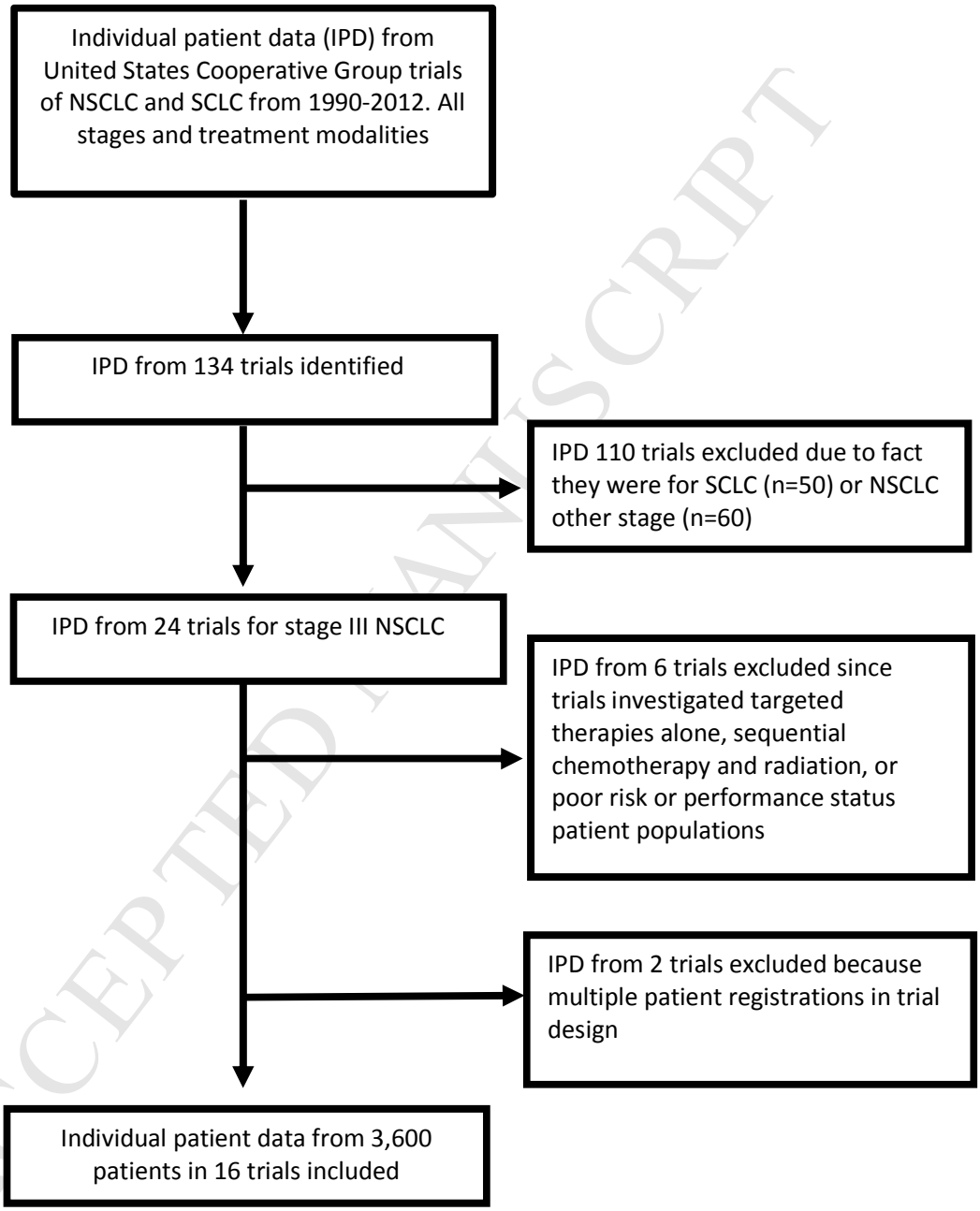


Figure 2

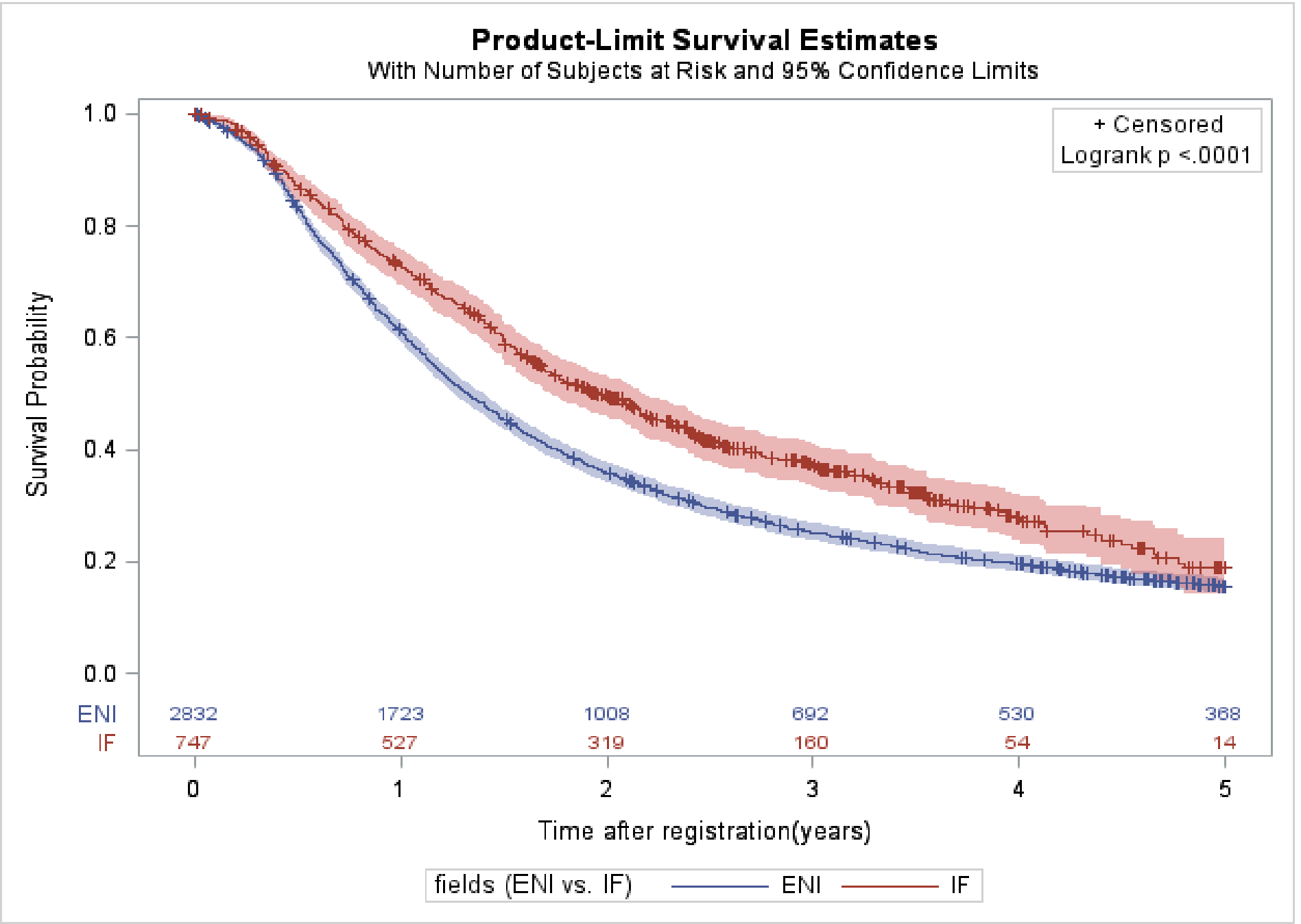

Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
+ Censored
Logrank p <.0001
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
ENI 2832 1723 1008 692 530 368
IF 747 527 319 160 54 14
0
1
2
3
4
5
Time after registration(years)
fields (ENI vs. IF) ENI IF

Figure 3

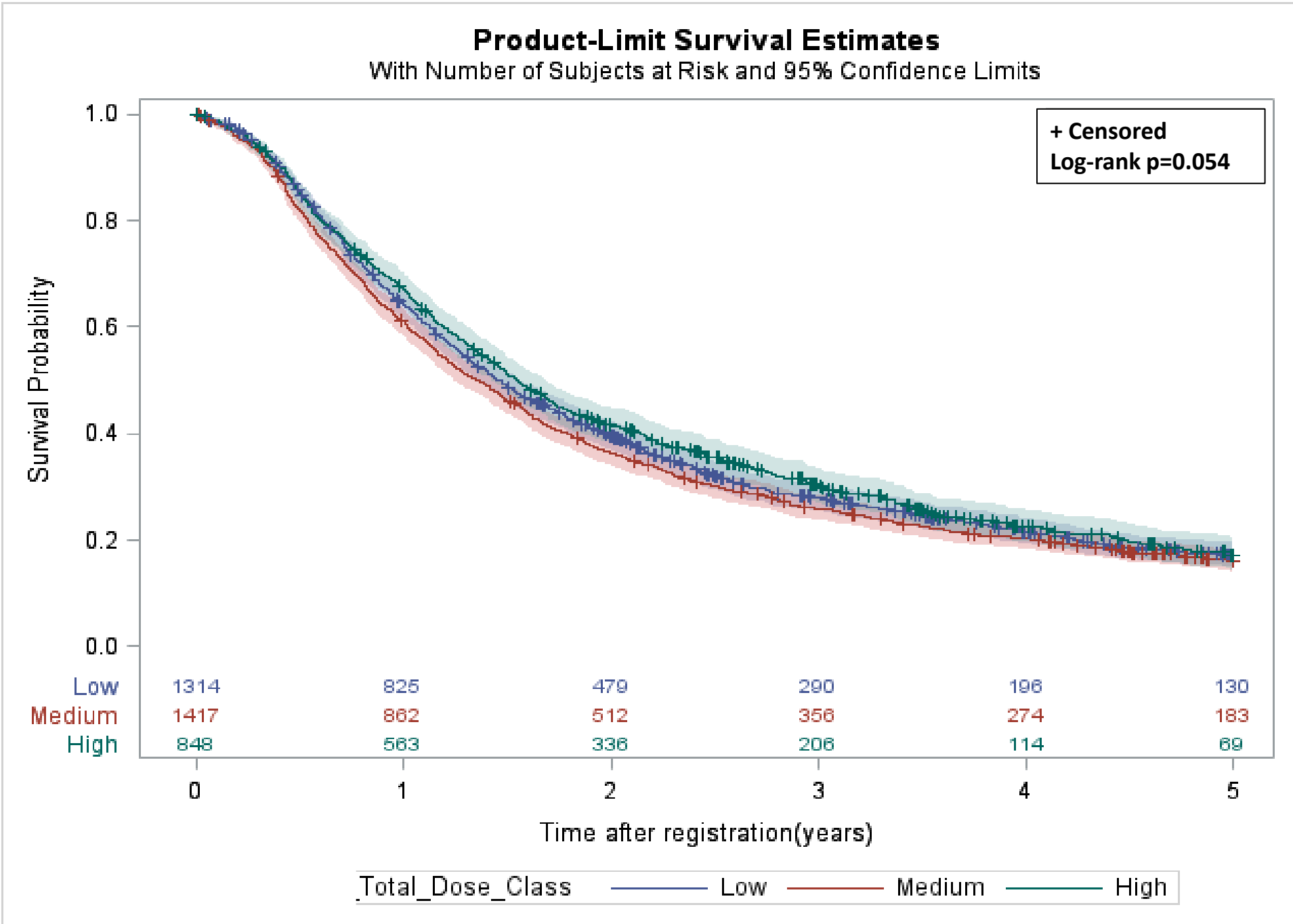
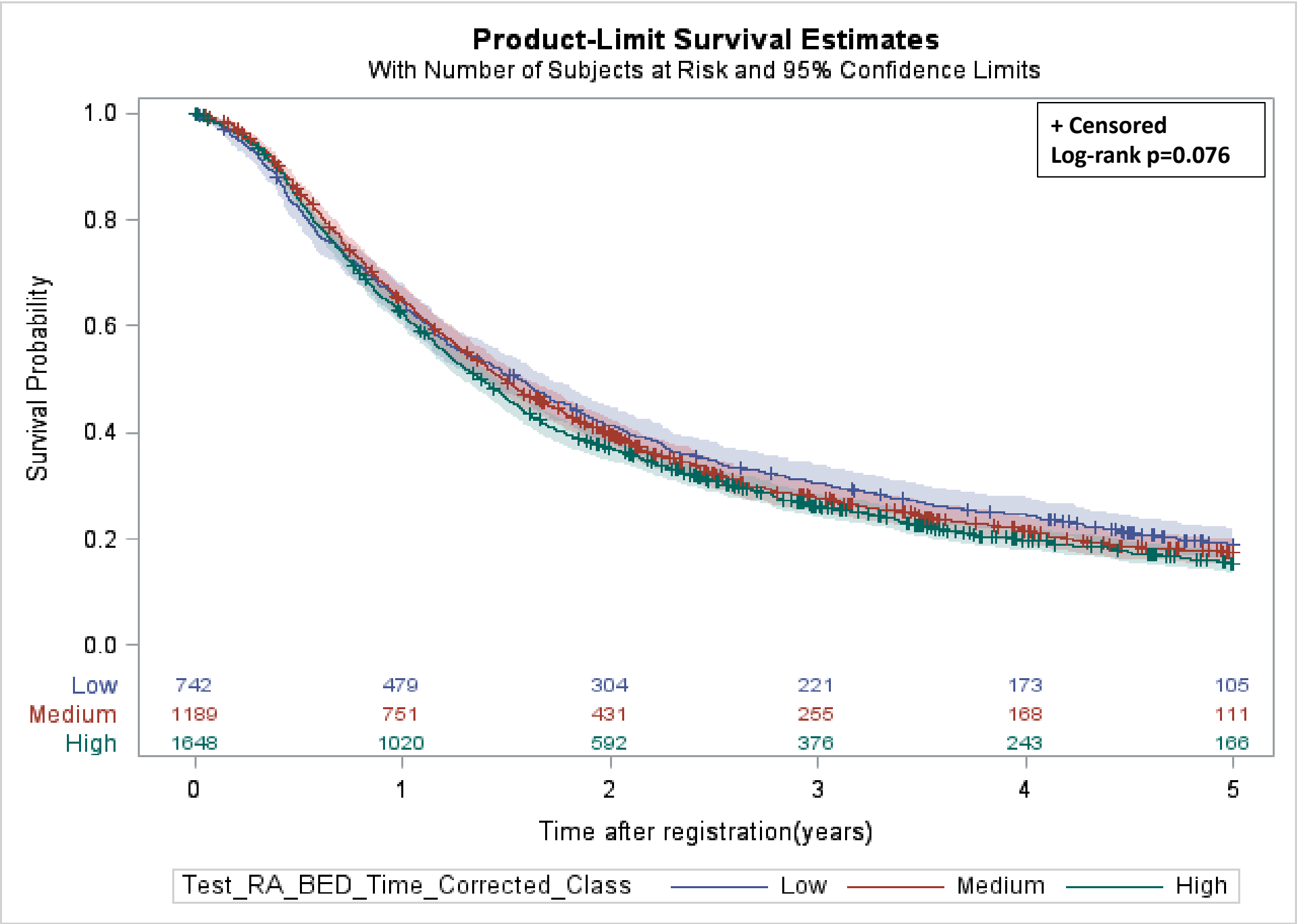

Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
+ Censored
Log-rank p=0.054
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Low 1314 825 479 290 196 130
Medium 1417 862 512 356 274 183
High 848 563 336 206 114 69
0
1
2
3
4
5
Time after registration(years)
Total_Dose_Class
Low
Medium
High

Figure 4


Product-Limit Survival Estimates
With Number of Subjects at Risk and 95% Confidence Limits
+ Censored
Log-rank p=0.076
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
Low 742 479 304 221 173 105
Medium 1189 751 431 255 168 111
High 1648 1020 592 376 243 166
0
1
2
3
4
5
Time after registration(years)
Test_RA_BED_Time_Corrected_Class
Low
Medium
High

"Exploring Radiotherapy Targeting Strategy and Dose: A Pooled Analysis of Cooperative Group Trials of Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer"

DISCLOSURES

Dr. Schild writes and edits for UpToDate on various subjects related to radiation therapy. He is paid $5000-6000 per year.

Dr. Fan has nothing to disclose.

Dr. Stinchcombe has nothing to disclose.

Dr. Vokes reports personal fees from AbbVie, personal fees from Amgen, personal fees from Ariad, personal fees from AstraZeneca, personal fees from Bayer, personal fees from Biolumina, personal fees from BMS, personal fees from Boehringer-Ingelheim, personal fees from Celgene, personal fees from Eli Lilly, personal fees from Serono EMD, personal fees from Genentech, personal fees from Leidos, personal fees from Merck, personal fees from Regeneron, personal fees from Synta, personal fees from Takeda, personal fees from VentiRx, personal fees from Novartis, outside the submitted work.

Dr. Ramalingam reports personal fees from Astra Zeneca, Amgen, Bristol Myer Squibb, Merck, Takeda, Genentech, Roche, Lilly, outside the submitted work.

Dr. Bradley reports grants and personal fees from Mevion Medical Systems, Inc., grants, personal fees and other from ViewRay, Inc., personal fees and other from Varian Medical Systems, outside the submitted work.

Dr. Kellly has nothing to disclose.

Dr. Pang has nothing to disclose.

Dr. Wang has nothing to disclose.