Final Progress Report for Research Projects Funded by Health Research Grants

Instructions: Please complete all of the items as instructed. Do not delete instructions. Do not leave any items blank; responses must be provided for all items. If your response to an item is "None", please specify "None" as your response. "Not applicable" is not an acceptable response for any of the items. There is no limit to the length of your response to any question. Responses should be single-spaced, no smaller than 12-point type. The report **must be completed using MS Word**. Submitted reports must be Word documents; they should not be converted to pdf format. Questions? Contact Health Research Program staff at 717-783-2548.

1. **Grantee Institution:** American College of Radiology

2. **Reporting Period (start and end date of grant award period):** 1/1/2010 – 12/31/13

3. **Grant Contact Person (First Name, M.I., Last Name, Degrees):** Stephen M Marcus, MS

4. **Grant Contact Person's Telephone Number:** 267-940-9403

5. **Grant SAP Number:** 4100050889

6. **Project Number and Title of Research Project: #2:** Exploration of the RTOG Clinical Trial Database – Beyond Protocol-Specified Endpoints

7. **Start and End Date of Research Project:** 1/1/2010 – 12/31/2013

8. **Name of Principal Investigator for the Research Project:** Kathryn A. Winter, MS

9. **Research Project Expenses**.

   9(A) Please provide the total amount of health research grant funds spent on this project for the entire duration of the grant, including indirect costs and any interest earned that was spent:

   $ 290,425.35

   9(B) Provide the last names (include first initial if multiple individuals with the same last name are listed) of **all** persons who worked on this research project and were supported with health research funds. Include position titles (Principal Investigator, Graduate Assistant, Post-doctoral Fellow, etc.), percent of effort on project and total health research funds expended for the position. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project	Cost
Winter	Dir Stat	3% Yr1;6% Yr 2; 5% yr3; 12% yr 4	$44,998.13
Zhang	Senior Statistician	6% Yr ; 9% Yr 2; 10% Yr3; 6% Yr4	$55,904.77
Bae	Senior Statistician	2% Yr 1	$3,059.80
Moughan	Biostatistician III	5% Yr1; 9% Yrs 2-4	$40,563.76
Hunt	Senior Statistician	6% Yr 1; 3% Yr3; 4% Yr4	$16,518.52
Paulus	Biostatistician I	5% Yr1; 8% Yrs 2-3; 10% Yr4	$30,024.32

9(C) Provide the names of **all** persons who worked on this research project, but who *were not* supported with health research funds. Include position titles (Research Assistant, Administrative Assistant, etc.) and percent of effort on project. For multiple year projects, if percent of effort varied from year to year, report in the % of Effort column the effort by year 1, 2, 3, etc. of the project (x% Yr 1; z% Yr 2-3).

Last Name, First Name	Position Title	% of Effort on Project

9(D) Provide a list of **all** scientific equipment purchased as part of this research grant, a short description of the value (benefit) derived by the institution from this equipment, and the cost of the equipment.

Type of Scientific Equipment	Value Derived	Cost
None		

10. Co-funding of Research Project during Health Research Grant Award Period. Did this research project receive funding from any other source during the project period when it was supported by the health research grant?

Yes_____ No____X_____

If yes, please indicate the source and amount of other funds:

11. Leveraging of Additional Funds

11(A) As a result of the health research funds provided for this research project, were you able to apply for and/or obtain funding from other sources to continue or expand the research?

Yes_____ No____X_____

If yes, please list the applications submitted (column A), the funding agency (National Institutes of Health—NIH, or other source in column B), the month and year when the application was submitted (column C), and the amount of funds requested (column D). If you have received a notice that the grant will be funded, please indicate the amount of funds to be awarded (column E). If the grant was not funded, insert "not funded" in column E.

Do not include funding from your own institution or from CURE (tobacco settlement funds). Do not include grants submitted prior to the start date of the grant as shown in Question 2. If you list grants submitted within 1-6 months of the start date of this grant, add a statement below the table indicating how the data/results from this project were used to secure that grant.

A. Title of research project on grant application	B. Funding agency (check those that apply)	C. Month and Year Submitted	D. Amount of funds requested:	E. Amount of funds to be awarded:
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$
	☐NIH ☐ Other federal (specify:_____ _____) ☐ Nonfederal source (specify: _____)		$	$

11(B) Are you planning to apply for additional funding in the future to continue or expand the research?

Yes_____ No___X_____

If yes, please describe your plans:

12. Future of Research Project. What are the future plans for this research project?

None

13. New Investigator Training and Development. Did students participate in project supported internships or graduate or post-graduate training for at least one semester or one summer?

Yes_____ No___X_____

If yes, how many students? Please specify in the tables below:

	Undergraduate	Masters	Pre-doc	Post-doc
Male				
Female				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
Hispanic				
Non-Hispanic				
Unknown				
Total				

	Undergraduate	Masters	Pre-doc	Post-doc
White				
Black				
Asian				
Other				
Unknown				
Total				

14. Recruitment of Out-of–State Researchers. Did you bring researchers into Pennsylvania to carry out this research project?

Yes_____ No___X_____

If yes, please list the name and degree of each researcher and his/her previous affiliation:

15. Impact on Research Capacity and Quality. Did the health research project enhance the quality and/or capacity of research at your institution?

Yes_____ No___X_____

If yes, describe how improvements in infrastructure, the addition of new investigators, and other resources have led to more and better research.

16. Collaboration, business and community involvement.

16(A) Did the health research funds lead to collaboration with research partners outside of your institution (e.g., entire university, entire hospital system)?

Yes_____ No___X_____

If yes, please describe the collaborations:

16(B) Did the research project result in commercial development of any research products?

Yes_____ No___X_____

If yes, please describe commercial development activities that resulted from the research project:

16(C) Did the research lead to new involvement with the community?

Yes_____ No___X_____

If yes, please describe involvement with community groups that resulted from the research project:

17. <u>Progress in Achieving Research Goals, Objectives and Aims.</u>
List the project goals, objectives and specific aims (as contained in the grant agreement). Summarize the progress made in achieving these goals, objectives and aims <u>for the period</u>

that the project was funded (i.e., from project start date through end date). Indicate whether or not each goal/objective/aim was achieved; if something was not achieved, note the reasons why. Describe the methods used. If changes were made to the research goals/objectives/aims, methods, design or timeline since the original grant application was submitted, please describe the changes. Provide detailed results of the project. Include evidence of the data that was generated and analyzed, and provide tables, graphs, and figures of the data. List published abstracts, poster presentations and scientific meeting presentations at the end of the summary of progress; peer-reviewed publications should be listed under item 20.

This response should be a DETAILED report of the methods and findings. It is not sufficient to state that the work was completed. Insufficient information may result in an unfavorable performance review, which may jeopardize future funding. If research findings are pending publication you must still include enough detail for the expert peer reviewers to evaluate the progress during the course of the project.

Health research grants funded under the Tobacco Settlement Act will be evaluated via a performance review by an expert panel of researchers and clinicians who will assess project work using this Final Progress Report, all project Annual Reports and the project's strategic plan. After the final performance review of each project is complete, approximately 12-16 months after the end of the grant, this Final Progress Report, as well as the Final Performance Review Report containing the comments of the expert review panel, and the grantee's written response to the Final Performance Review Report, will be posted on the CURE Web site.

There is no limit to the length of your response. Responses must be single-spaced below, no smaller than 12-point type. If you cut and paste text from a publication, be sure symbols print properly, e.g., the Greek symbol for alpha (α) and beta (ß) should not print as boxes (□) and include the appropriate citation(s). DO NOT DELETE THESE INSTRUCTIONS.

Project Title and Purpose

Exploration of the RTOG Clinical Trial Database – Beyond Protocol-Specified Endpoints - For over 40 years, the Radiation Therapy Oncology Group (RTOG) has been funded by the National Cancer Institute (NCI) to conduct clinical trials seeking to improve the survival and quality of life of cancer patients. Drawing upon this vast resource of demographic, treatment, outcome, and patient-reported data, the researchers will develop hypotheses and explore correlations that were not defined in the treatment protocols for patients with brain, cervix, gastrointestinal, head and neck, lung, and prostate cancer. These analyses may lead to future protocols and/or better ways to identify high-risk subgroups and screen patients for specific treatment regimens.

Project Overview

RTOG investigators complete analyses and report on the endpoints specified in each NCI-approved protocol. Frequently these analyses raise questions or point to other potential hypotheses that were not included in the original protocol. Likewise, current literature and new

research may point to areas of interest or possible correlations that were unknown during the design of the original protocol.

Specific Aims

The broad objectives of this research proposal are to (i) generate hypotheses and explore correlations that may lead to more efficient clinical trials and more patient-targeted treatments, and (ii) explore novel ways of analyzing the demographic (age, gender, race), treatment (including dose, volume, duration), outcome (survival, disease-free survival, time-to-progression), and quality of life (frequency/severity of adverse events, patient-reported outcomes) data in the RTOG database to potentially develop new tools for determining the best treatment regimen for each patient based upon their personal profile.

Summary

Several analyses (labeled #1-5 below) were conducted during this grant period to address the above stated project and are described in detail.

Progress made on Objective i: Objective i was achieved through analyses #1, #4, and #5. Please refer to page 8 for analysis #1, page 14 for analysis #4, and page 16 for analysis #5.

Progress made on Objective ii: Objective ii was achieved through analyses #1, #2, and #3. Please refer to page 8 for analysis #1, page 10 for analysis #2, and page 12 for analysis #3.

 # 1--Evaluating associations between dosimetric data from radiation therapy to bone marrow and hematologic adverse events.

Intensity modulated radiation therapy (IMRT) can reduce the volume of bone marrow irradiated. Pelvic bone marrow sparing has produced a clinically significant reduction in hematologic toxicity (HT). This analysis investigated HT in Radiation Therapy Oncology Group (RTOG) 0418, a prospective study to test the feasibility of delivering postoperative IMRT for cervical and endometrial cancer in a multi-institutional setting. RTOG 0418 accrued endometrial and cervical cancer patients who were treated with postoperative IMRT to 50.4 Gy to the pelvic lymphatics and vagina. Endometrial cancer patients received IMRT alone, whereas patients with cervical cancer received IMRT and weekly cisplatin (40 mg/m^2). Eligibility criteria for patients with endometrial cancer included International Federation of Gynecology and Obstetrics (FIGO) 1988 stage IB, grade 3 disease; stage IC, grade 1-3 disease; stage IIA, IIB, or IIIC (positive pelvic nodes only) disease; or FIGO stage IB, grade 2 disease in patients who had not undergone lymph node dissection. Concurrent chemotherapy was not allowed for patients with endometrial cancer. Patients with cervical cancer were enrolled if they had high-risk features, which included positive pelvic nodes with negative para-aortic nodes; microscopically positive parametria; or 2 of the following 3 features: one-third or more stromal invasion, lymph-vascular space invasion, and large clinical tumor diameter (>4 cm). Concurrent chemotherapy with weekly cisplatin was given to all patients with cervical cancer. Patients with cervical or endometrial cancer were ineligible for the study if they had a Zubrod performance status of 3 or higher, previous pelvic irradiation, or a weight or lateral body diameter exceeding the limits of the treatment table or

computed tomography (CT) scanner. No specifications were given in the protocol about the volume of bone marrow to be irradiated. The impact of the volume of bone marrow irradiated was evaluated by contouring the pelvic bone for all patients in the study. The total pelvic bone from the superior to the inferior extent of the planning target volume (PTV) was used as a surrogate of bone marrow. Pelvic bone marrow was defined within the treatment field by using a computed tomography density-based auto-contouring algorithm. RTOG 0418 adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events, version 3.0, criteria. Acute toxicity in this analysis was defined as AEs occurring ≤ 90 days from the start of radiation therapy. The X^2 test was used to compare rates of hematologic AEs for patients with a volume of bone marrow irradiation from 10 to 40 Gy (V10-V40) dichotomized at the median. Univariate logistic regression models were used to determine whether there was any correlation between volume of bone marrow irradiation, number of cisplatin cycles, cancer site, age, body mass index (BMI), and hematologic AEs. Two-variable logistic models were also built using these variables.

RTOG 0418 enrolled 83 eligible patients (40 with cervical cancer and 43 with endometrial cancer). Of the 40 patients with cervical cancer, 9 (23%), 13 (33%), and 10 (25%) experienced grade 1, grade 2, and grade 3 HT respectively. Of the 43 patients with endometrial cancer, 6 (14%), 3 (7%), and 7 (16%) experienced grade 1, grade 2, and grade 3 HT respectively. There were no grade 4 or 5 HTs. All grade 3 HTs in the patients with endometrial cancer and all but 1 HT in the patients with cervical cancer were lymphopenias, which are of minimal clinical impact. The median percentage volumes of bone marrow receiving 10, 20, 30, and 40 Gy for all patients were 96%, 84%, 60%, and 37%. The median percentage volumes of marrow treated to 10, 20, 30, and 40 Gy were used as cutoff points for statistical analysis. Among patients with cervical cancer with V40 >37% (median), 75% had grade ≥ 2 HT compared with 40% of patients with V40 ≤37% (p=0.025). Patients with cervical cancer who had a mean bone marrow dose of >34.1 Gy (dichotomized at the median) also had higher rates of grade ≥ 2 HTs than did those with a dose of ≤34.1 Gy (74% vs 43%; p=.049). There was no statistically significant correlation with V10, V20, or V30 with HT. For the cervical cancer patients, the percentage volume of bone marrow receiving 40 Gy (>37% vs ≤37%) did not correlate with the number of cycles of cisplatin (<5 vs ≥ 5) received. In a univariate regression analysis of all patients, the disease site (cervical) correlated with a higher risk of grade ≥ 2 HT, as would be expected given that the cervical cancer patients received chemotherapy whereas the endometrial cancer patients did not. For all patients, V40 >37% showed a trend toward correlation with increased risk of grade ≥ 2 HT (odds ratio [OR] 2.1, 95% CI 0.8-5.0, p=0.12). For patients with cervical cancer, however, V40 >37% was correlated with an increased risk of grade ≥ 2 HT (OR 4.5, 95% CI 1.2-17.4, PZ.029). In the univariate regression analysis, age and BMI were not associated with grade ≥ 2 HT among patients with cervical cancer. In a multivariate regression analysis of patients with cervical cancer, the association of V40 >37% (p=0.032) with grade ≥ 2 HT remained statistically significant after adjustment for BMI. No statistically significant correlations of dose-volume parameters was detected for patients with endometrial cancer who did not receive chemotherapy, as would be expected based on the low rate of HT toxicity in patients receiving pelvic radiation without chemotherapy. Limiting the volume of bone marrow irradiated is associated with reduced rates of HT and may improve tolerance to chemotherapy. For patients receiving chemotherapy and pelvic IMRT, the bone marrow can be contoured, and the median dose and V40 can be evaluated in addition to the volume of bone marrow receiving lower doses with the

goal of reducing HT. Future studies should define the clinical benefit of IMRT in reducing hematologic toxicity and to validate the most critical dosimetric predictors of hematologic toxicity.

 # 2--Evaluating associations between prophylactic cranial irradiation (PCI) and neurocognitive functioning for non-small cell lung cancer (NSCLC) patients and small cell lung cancer (SCLC) patients.

This analysis focused on the impact of prophylactic cranial irradiation (PCI) on self-reported cognitive functioning (SRCF), a functional scale on the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) based on data from two Radiation Therapy Oncology Group (RTOG) protocols. EORTC QLQ-C30 is a 30-item self-report questionnaire containing the following domains (scales): physical functioning (5 items), role functioning (2 items), emotional functioning (4 items), cognitive functioning (2 items), social functioning (2 items), global quality of life (2 items), fatigue (3 items), pain (2 items), nausea and vomiting (2 items), and single items for dyspnea, insomnia, anorexia, constipation, diarrhea and financial impact.

RTOG 0214 randomized patients with locally advanced non-small cell lung cancer to PCI or observation and RTOG 0212 randomized patients with limited-disease small cell lung cancer to high or standard-dose PCI. In both trials, the Hopkins Verbal Learning Test (HVLT)-Recall (HVLT-R) and -Delayed Recall (HTLV-DR) and SRCF were assessed at baseline (after locoregional therapy but before PCI or observation) and at 6 and 12 months after study entry. Because patient follow-up did not always occur at exactly 6 and 12 months' follow-up, data obtained within 4 weeks before or after these time points were included. Data from RTOG 0212 and RTOG 0214 were pooled for this analysis. To minimize the confounding effects of intracranial relapse, all patients who developed an intracranial relapse before follow-up evaluation were excluded. Patients with missing follow-up assessments were excluded from analysis of the applicable time point. Missing data analyses and comparisons of categorical patient characteristics were done using X^2 test statistics, and comparisons of continuous patient characteristics were done using the F statistic from analysis of variance. Baseline comparisons of continuous HVLT scores were done using the Kruskal-Wallis 2-sided rank test to compare means. Follow-up scores were analyzed using the reliable change index method, which allows for changes from baseline to be classified as either a decline, stability, or improvement in function. Logistic regression analysis was used to evaluate whether use of PCI was predictive of decline in HVLT or EORTC QLQ-C30 functional or symptom scale. These models were adjusted for factors that were predictive for decline, such as baseline score, age, gender, education level, marital status, PCI dose, or baseline Zubrod performance status. Baseline score was evaluated continuously and as a categorical variable (impaired vs unimpaired). Baseline HVLT and EORTC QLQ-C30 scores were considered impaired if the score was ≥ 1.5 standard deviations worse than the mean of the normative age-adjusted distribution. For PCI dose, patients were categorized as standard-dose PCI (2.5 Gy x 10 on RTOG 0212 or 2.0 Gy x 15 on RTOG 0214), high-dose PCI (2.0 Gy x 18 or 1.5 Gy x 25 on RTOG 0212), or no PCI. Associations between decline in SRCF, HVLT, or other EORTC QLQ-C30 functional or symptom scale was tested using the Fisher's exact test, with agreement evaluated using the κ correlation statistic. To prevent inflation of type I error, the decision was made a priori to assign

statistical significance for analyses of any EORTC QLQ-C30 functional or symptom scale, including SRCF, to p-values <0.0001. Otherwise, statistical significance was assigned to p-values <0.05. Of the eligible patients pooled from RTOG 0212 and RTOG 0214, 410 (93%) receiving PCI and 173 (96%) undergoing observation completed baseline HVLT or EORTC QLQ-C30 testing and were included in this analysis.

A total of 621 patients were accrued to RTOG 0212 (n=265) and RTOG 0214 (n=356). Of these, 252 patients (95%) on RTOG 0212 and 331 patients (93%) on RTOG 0214 completed either baseline HVLT or EORTC QLQ-C30 testing and were included in this analysis. Of the 410 patients treated with PCI, 158 came from the NSCLC study RTOG 0214, and 252 came from the SCLC study RTOG 0212. All 173 patients who did not receive PCI came from RTOG 0214. Comparison of PCI to observation cohorts demonstrated that patients treated with PCI were more likely to attain an educational level of high school equivalence or higher (p=0.02), compared with patients treated without PCI. Otherwise, PCI and observation cohorts were similar with respect to age, gender, partner status, and baseline Zubrod performance status. Compliance with HVLT and EORTC QLQC30 assessments at 6 and 12 months' follow-up did not differ between PCI and observation cohorts. Patient factors associated with higher baseline HVLT-R scores included female gender (p<0.0001), more advanced education level (p<0.0001), partnered status (p=.04), and age ≤ 60 years (p<0.0001). Patient factors associated with higher baseline HVLTDR scores were female gender (p<0.0001), more advanced education level (p<0.0001), and age ≤ 60 years (p=0.03). Comparisons of baseline EORTC QLQ-C30 scores demonstrated no significant associations of SRCF with any patient factors. Analyses for correlation of SRCF decline with decline in HVLT-R or HVLT-DR demonstrated no significant associations at 6-month (HVLT-R, $\kappa = 0.113$, p=0.05; HVLT-DR, $\kappa = 0.155$, p=0.01) or 12-month follow-up (HVLT-R, $\kappa = -0.023$, p=0.74; HVLT-DR, $\kappa = 0.046$, p=0.50). At 6 and 12 months' follow-up, decline in HVLT-R or HVLT-DR was also not correlated with decline in any other EORTC QLQ-C30 symptom or functional scale. Correlative analyses of SRCF decline with other EORTC QLQ-C30 symptom or functional measures demonstrated fair agreement, with decline in self reported physical functioning at 6 months ($\kappa = 0.241$, p<0.0001) and 12 months ($\kappa = 0.299$, p<0.0001) and increasing fatigue ($\kappa = 0.260$, p<0.0001) and appetite loss ($\kappa = 0.263$, p<.0001) at 6 months. Prophylactic cranial irradiation was associated with a higher risk of decline in SRCF at 6 months (odds ratio 3.60, 95% confidence interval 2.34-6.37, p<0.0001) and 12 months (odds ratio 3.44, 95% confidence interval 1.84-6.44, p<0.0001). Decline on HVLT-Recall at 6 and 12 months was also associated with PCI (p=0.002 and p=0.002, respectively) but was not closely correlated with decline in SRCF at the same time points (p=0.05 and p=0.86, respectively). Pooling data from RTOG 0212 and RTOG 0214 was feasible because of the uniformity of QOL and HVLT instruments and the serial assessment time points (6 and 12 months' follow-up). However, pooling these data raises concerns over the interpretation of data from 2 distinct disease processes. For instance, in this study the observation cohort consisted entirely of patients with NSCLC, whereas the PCI cohort was a mixed population of SCLC and NSCLC patients. To address this concern, we excluded any patients who developed brain relapse before follow-up evaluation. In addition, whereas RTOG 0214 randomized patients to PCI or observation, RTOG 0212 randomized patients to high- or standard-dose PCI. Prior analysis of RTOG 0212 has demonstrated an association between high-dose PCI and increased chronic neurologic toxicity. However, in that analysis, high-dose PCI was not specifically associated with greater HVLT decline. Similarly, to elucidate the HVLT and QOL impact of radiation dose in this pooled

analysis, we separated patients receiving low dose PCI (25 Gy) from those receiving high-dose PCI (36 Gy) on RTOG 0212 and pooled them with all patients receiving PCI (30 Gy in 15 fractions) on RTOG 0214. Comparisons demonstrated no difference between high- and low-dose PCI in terms of HVLT or SRCF decline, which permitted inclusion of these patients into a singular PCI cohort. For lung cancer patients who do not develop brain relapse, PCI is associated with decline in not just HVLT-tested but also SRCF at 6 and 12 months' follow-up. However, HVLT decline and SRCF decline are not closely correlated, suggesting that they may represent distinct elements of the cognitive spectrum.

 # 3--Evaluating associations between longitudinal decline in patient-reported quality of life (QoL) and efficacy (disease relapse and overall survival) following curative treatment for limited-disease small cell lung cancer (LD-SCLC) and locally advanced non-small-cell lung cancer (LA-NSCLC).

This analysis is based on data from two Radiation Therapy Oncology Group (RTOG) protocols. RTOG 0214 randomized patients with locally advanced non-small cell lung cancer to PCI or observation and RTOG 0212 randomized patients with limited-disease small cell lung cancer to high or standard-dose PCI. In both studies, patient-reported outcomes were captured prospectively at baseline (after locoregional therapy but before PCI or observation) and at 6 and 12 months after study entry using the EORTC Core Quality of Life Questionnaire (QLQ-C30) and the EORTC Brain Cancer Module (BN20). EORTC BN20 is a 20-item supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain cancer and containing 4 multi-item scales (future uncertainty, visual disorder, motor dysfunction, communication deficit) and 7 single items (headache, seizure, drowsiness, hair loss, itching, weakness of both legs, and difficulties with bladder control). Scores for the QLQ-C30 and BN20 were converted to lie in a range between 0-100, according to the guidelines of EORTC12. For the functioning scales and global QOL scale, higher scores indicate better functioning, whereas for the symptoms higher scores indicate greater symptom severity. Both instruments have been previously shown to be reliable and valid instruments in the setting of recurrent high-grade gliomas. In addition, QLQ-C30 has demonstrated adequate reliability in patients with lung and other cancer diagnoses. Missing data analyses and comparisons of categorical patient characteristics were done using X^2 test statistics, and comparisons of continuous patient characteristics were done using the F statistic from analysis of variance. Baseline comparisons of continuous EORTC QLQ-C30 and BN20 values were done using the Kruskal-Wallis two-sided rank test to compare means. Due to multiple testing for correlations between patient characteristics and EORTC QLQ-C30 and BN20 scores, only p-values <0.001 were considered statistically significant for those correlations. Follow-up EORTC QLQ-C30 and BN20 differences were categorized as decline or no decline from baseline using the reliable change index (RCI) method17 and comparisons were made using chi-square test statistics. An overall survival event was death due to any cause and was estimated from the date of randomization to the date of death or last follow-up if the patient was still alive. Overall survival rates were estimated using the Kaplan-Meier method, and comparisons tested using the log-rank statistic. The development of at least one brain metastasis was considered a failure for the brain relapse endpoint; the development of at least one distant metastasis, including in the brain, was considered a failure for the distant relapse endpoint. For both relapse endpoints, death without a relevant metastasis was considered a competing risk, and patients still alive without developing

relapse were censored at the date of last follow-up. Time to brain or distant relapse was estimated from the date of randomization to the date relapse was first diagnosed or the date of death or last-follow-up if the patient did not develop relapse. Brain and distant relapse failure rates were estimated using the cumulative incidence method and tested using Gray's test. To determine whether a given QOL measure was independently associated with outcomes, Cox proportional hazards models were used for overall survival, and Fine and Gray's proportional hazards models were used for brain and distant relapse. A p-value<0.05 was considered statistically significant. Baseline EORTC score and any characteristic associated in univariate modeling with a given outcome at a significance level of p<0.05 were included in multivariate modeling. Fisher's exact test was used to test for potential correlations between probabilities of decline in different EORTC functional or symptom scales.

Five-hundred and fifty-two of the eligible patients accrued to RTOG 0212 and RTOG 0214 had baseline QOL assessments and were included in this pooled analysis. Compliance with EORTC QLQ-C30 and BN20 assessments was similar between RTOG 0212 and RTOG 0214 at baseline (p=0.61) but higher in RTOG 0214 at 6 months (p=0.01) and 12 months (p=0.001), with 98% of patients completing QOL questionnaires responding to all questions. Baseline characteristics in patients enrolled on RTOG 0212 and those enrolled on RTOG 0214 were similar, except for more advanced education reported by patients enrolled on RTOG 0212 (p=0.01). Comparisons of baseline EORTC QLQ-C30 scores demonstrate better QOL and symptoms across multiple measures for patients with Zubrod PS 0 compared to Zubrod PS 1. In addition, patients older than 60 reported better emotional functioning (p=0.0001) and less severe pain (p<0.0001), insomnia (p=0.0003) and financial difficulties (p<0.0001), compared to patients 60 years of age or younger. Other significant associations were 1) more severe dyspnea reported amongst patients with NSCLC compared to SCLC (p=0.0004), 2) worse emotional functioning amongst women compared to men (p=0.0001), and 3) less financial difficulty amongst patients with more than a high school education (p=0.0007). Similar comparisons of baseline BN20 scores revealed more severe headaches (p<0.0001), hair loss (p<0.0001) and bladder control (p<0.0001) reported by women; less future uncertainty reported by patients with Zubrod PS 0 (p=0.0008); and, greater future uncertainty (p<0.0001) and more severe headaches (p<0.0001) reported by patients ≤60 years of age (online only). Univariate modeling identified statistically significant associations between an increased risk of distant relapse and decline in patient-reported global health status/QOL at 6 months (median time to distant relapse: improvement/no decline, 12.2 months (95% Confidence Interval (CI), 10.5-12.9 months), vs. decline, 10.6 months (95% CI, 7.1-11.8 months), p=0.02). Median time interval between 6-month QOL assessment and distant relapse was 6.4 months (interquartile range (IQR) 3.9-12.6 mos) for patients with QOL improvement/no decline compared to 6.1 months (IQR 4.9-9.3 months) for patients with QOL decline. Univariate analysis for risk of brain relapse showed no significant associations with decline in any EORTC or BN20 measure. Univariate modeling of other patient characteristics demonstrated significant associations between increased risk of distant relapse and younger age (both as a continuous (p=0.006) and categorical (p=0.006, ≤60 vs. >60) variable) and SCLC histology (p=0.002). Adjusting for age (as a categorical variable), histology and baseline EORTC score on multivariate analysis, decline in patient-reported global health status/QOL at 6 months was significantly associated with an increased risk of distant relapse (Hazard Ratio (HR), 1.60; 95% Confidence Interval (CI), 1.07-2.38, p=0.02). Similar findings were observed when adjusting for age as a continuous variable. Decline in patient-reported global health status/QOL

was associated with inferior overall survival amongst 6-month survivors (median survival time (MST) improvement/no decline, 37.8 months (95% CI, 32.2-58.2 months), vs. decline, 23.7 months (95% CI, 17.9-31.0 months); p<0.0001). Amongst 12-month survivors, inferior overall survival was also correlated with decline in patient-reported global health status/QOL (MST 49.0 months (95% CI, 37.8 months-not reached) vs. 32.1 months (95% CI, 25.4-53.4 months); p=0.02) and cognitive functioning (MST 49.0 months (95% CI, 38.6 months-not reached) vs. 34.1 months (95% CI, 27.0-53.4 months); p=0.04). Other covariates associated with inferior overall survival on univariate modeling were lower baseline global health status/QOL score assessed continuously (p=0.047), single/divorced/widowed status (p=0.02) and education level less than high school (p=0.0001). Adjusting for these factors on multivariate analysis, decline in patient-reported global health status/QOL at 6 months (HR, 2.10; 95% CI, 1.46-3.03, p<0.0001) and 12 months (HR, 2.07; 95% CI, 1.20-3.58, p=0.009) and decline in patient-reported cognitive functioning at 12 months (HR, 1.73; 95% CI, 1.03-2.92, p=0.04) predicted for inferior overall survival. Test for correlation demonstrated no association between decline in patient-reported global health status/QOL and decline in patient-reported cognitive functioning at 12 months (p=0.74). In this pooled secondary analysis of RTOG 0212 and 0214, it was observed that longitudinal decline of global health status/QOL in lung cancer survivors is associated with distant relapse and inferior overall survival. These data emphasize the importance of monitoring patient-reported QOL throughout the longitudinal process of diagnosis, treatment, and early survivorship in lung cancer patients and provide rationale for incorporating QOL monitoring into not just clinical trials, but also clinical practice.

 # 4--Evaluating correlation between PSA complete response after hormonal therapy and treatment outcomes in prostate cancer patients.

This analysis focused on assessing associations between per protocol defined PSA complete response (PSA-CR), measured at the end of external beam radiotherapy (EBRT) and short-term hormonal therapy (STHT), on treatment outcomes and was based on data from RTOG 9413. RTOG 9413 trial accrued men with histologically confirmed adenocarcinoma of the prostate, who had an estimated risk of lymph node involvement higher than 15% but with negative nodes, and PSA < 100 ng/ml. The trial randomized patients to one of four arms, receiving prostate only radiation therapy (PORT) or whole pelvis radiation therapy (WPRT), which was followed by a boost to the prostate only, in combination with neoadjuvant and concomitant hormonal therapy (NCHT) or adjuvant hormonal therapy (AHT). Patients included in this analysis were those treated on the RTOG 9413 protocol that had available baseline testosterone, end of hormonal therapy date and PSA data at the end of hormonal therapy, defined as a PSA evaluation done within 120 days following the completion of hormone therapy. Outcome parameters assessed on this study were biochemical failure (BF), local progression (LP), distant metastasis (DM), disease-free survival (DFS), disease specific survival (DSS) and overall survival (OS). RTOG-ASTRO Phoenix consensus definition (Citation - Roach M, 3rd, Hanks G, Thames H, Jr., *et al.* Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65:965-974.) was used to characterize biochemical failure. For endpoints OS and DFS, the Kaplan-Meier method was used to estimate yearly survival rates. For all other endpoints BF, LP, DM and DSS, the cumulative incidence approach was used to estimate yearly incidence rates[9] and Gray's test[10] was used to test for

differences. Univariate analysis was performed to correlate PSA-CR (PSA ≤0.3ng/ml) after total androgen suppression(TAS) with all endpoints, and the following variables were considered for multivariate analysis: PSA at baseline, Gleason score, treatment arm, age, and baseline testosterone. The Cox proportional hazards regression model was used for univariate and multivariate analyses.

A total of 1070 patients treated on RTOG 9413 protocol were eligible for this analysis. Pre-treatment characteristics, including age, baseline PSA, T stage, Gleason score, baseline testosterone, were balanced between the 4 treatment arms. Median PSA at the end of hormonal therapy for all patients was 0.2 ng/mL (range: 0 – 96.2). A total of 744 patients (70%) reached a PSA-CR at the end of hormonal therapy. With a median follow-up of 7.2 years, higher rates of BF (56% vs. 38%), LP (15% vs. 10%), DM (20% vs. 10%) and worse DFS (28% vs. 40%), DSS (85% vs. 93%) and OS (67% vs. 69%) were observed in those 326 patients who failed to achieve PSA-CR. Univariate analysis showed that 7-year BF, DFS, DM and DSS rates were statistically significant better for patients with end of HT PSA ≤0.3 ng/mL, while LP and OS rates were not statistically significant between both groups. On multivariate analysis, failure to reach a PSA-CR at the end of AHT was an independent predictor for prediction of BF ($p<0.0001$), DFS ($p=0.003$), DM ($p=0.0002$) and DSS ($p=0.0003$). Other factors significantly and independently associated with worse DSS were baseline PSA > 20 ng/mL ($p=0.04$) and Gleason score 8-10 ($p=0.0002$). The only factor associated with poorer OS was baseline PSA >20 ng/mL ($p=0.02$). On a post-hoc analysis of all patients who reached PSA-CR ≤0.3 ng/dL, independent of time to response, univariate analysis showed that 7-year BF, DFS, DM, DSS and now OS rates were statistically significantly better for patients with end of HT PSA ≤0.3 ng/mL. During the follow-up period a total of 357 patients died, 104 patients due to prostate cancer. Among them, 55 patients (53%) achieved PSA-CR at the end of HT. Among the 253 patients who died due to other causes and 712 patients who remain alive, PSA-CR at the end of HT was noticed in 75% and 70% of patients, respectively. In an attempt to identify a PSA value at the end of hormone therapy that would predict risk of death, regression analysis showed that PSA value above 1.0 ng/mL is associated with worse overall and cause specific survival. For 103 patients, multivariate analysis showed that PSA ≥ 1.0 ng/mL at the end of HT ($p<0.0001$), PSA at baseline higher than 20 ng/mL ($p=0.02$) and Gleason score 8 or higher ($p=0.0001$) were associated with worse DSS, while PSA ≥ 1.0 ng/mL at the end of HT ($p=0.0008$), baseline PSA ($p=0.04$) and age ($p<0.0001$) were associated with worse OS.

Failure to obtain PSA-CR of ≤0.3 ng/mL after short-term hormonal therapy and external beam radiotherapy is associated with unfavorable outcomes. In an attempt to individualize therapy based on specific tumor needs, this hypothesis generating analysis suggests that complete responders (i.e., patients with a PSA ≤0.3 ng/dL after short-course ADT and EBRT) could stop treatment earlier, while partial responders (PSA >0.3 ng/dL) would receive longer duration ADT, and non-responders who are at higher risk for cancer specific death (PSA >1.0 or 1.4 ng/dL) should be considered for early intervention with more aggressive systemic therapy. Such important change in current practice must be investigated on a clinical trial.

#5--Using a recursive partitioning analysis (RPA) to analyze the relative contributions of pretreatment characteristics to the survival of patients treated with chemoradiotherapy for unresectable carcinoma of the pancreas.

Statistical Methods

This recursive partitioning analysis (RPA) considers models derived by five splitting methods for censored data described by Zhang and Singer and implemented by Zhang's free "stree" software, http://c2s2.yale.edu/software/stree/, for the overall survival of patients from six RTOG unresectable pancreas cancer studies. Each splitting method (likelihood, log-rank, Kaplan-Meier distance, adaptive normalization, and global normalization) provided a survival tree with patients grouped into as few as seven and as many as eleven mutually exclusive terminal nodes of the tree.

These patient groups were then combined in order to arrive at a simpler model with statistically significantly distinct groups, which are called RPA classes. In this process, overall survival was estimated using the Kaplan-Meier method and compared between groups with the log-rank test. Hazard ratios were derived from the Cox regression model. The final models were decided by taking the statistical and visual comparisons of the terminal node survival distributions into account, along with an attempt to group patients meaningfully when possible.

Statistical Analysis

This analysis used data from seven RTOG unresectable pancreas cancer studies which are described in Table 1: 8505, 8801, 9102, 9209, 9812, 0020, and 0411. All of the studies had treatments which included radiation (RT) and chemotherapy. The following variables were used: age (continuous), gender, t-stage (T1, T2, T3, T4, TX), n-stage (N0, N1, N2, NX), and Zubrod (0, 1). Percent weight loss, largest tumor dimension, and location of primary tumor were not included because they were not collected on all of the studies. For studies that collected Karnofsky performed status (KPS), it was converted to a Zubrod score. Twelve patients with Zubrod scores of 2 (or equivalent KPS scores) were excluded from the analysis, resulting in a data from 593 eligible patients. N-stage was categorized for the RPA as N0 vs. all others and one TX patient was grouped with unknown and missing t-stage patient for the purpose of the RPA.

Table 2 presents baseline characteristics and the distribution of patients across the studies.

Table 3 describes the final models achieved from the different RPA splitting methods. The table lists all variables appearing in the initial full tree, the number of classes in the final model, the hazard ratios and log-rank p-values comparing the ordered classes, and a description of each class with median survival time. In some cases both a two-class and three-class model is provided. Although one would prefer more than two distinct RPA classes, it did not appear possible for a majority of the models. The likelihood survival tree could not be reduced to statistically significantly distinct classes.

Figures 1a through 4b provide the survival curves of the RPA classes for each final model presented in Table 3. Appendix Figures 1-5 present the survival curves corresponding to the full trees resulting from each method.

Table 1
Contributing RTOG Studies
(n*=593)

Study	n (%)	Title
8505	71 (12.0%)	Phase I/II Study of Intraoperative and External Radiotherapy plus 5-FU for Resectable, Unresectable, and Localized Adenocarcinoma of the Pancreas
8801	77 (13.0%)	Phase I/II Study of Prophylactic Hepatic Irradiation plus Local Irradiation and Systemic Chemotherapy with 5-FU in Patients with Unresectable Adenocarcinoma of the Pancreas
9102	27 (4.6%)	Phase III Randomized Trial of Chemoradiotherapy using 5-FU with vs without Electron-Beam Intraoperative Irradiation in Patients with Unresectable, Nonmetastatic Adenocarcinoma of the Pancreas
9209	47 (7.9%)	Phase I/II Study of Hyperfractionated External-Beam Radiotherapy, Prophylactic Hepatic Radiotherapy, and Concurrent 5-FU/Low-Dose CF in Patients with Unresectable Carcinoma of the Pancreas
9812	105 (17.7%)	A Phase II Trial of External Irradiation (50.4 GY) and Weekly Paclitaxel (Taxol) for Non-Metastatic, Unresectable Pancreatic Cancer
0020	184 (31.0%)	A Randomized Phase II Trial of Weekly Gemcitabine, Paclitaxel and External Irradiation (50.4 Gy) Followed by the Farnesyl Transferase Inhibitor R115777 (NSC #702818) for Locally Advanced Pancreatic Cancer
0411	82 (13.8%)	A Phase II Study of Bevacizumab with Concurrent Capecitabine and Radiation Followed by Maintenance Gemcitabine and Bevacizumab for Locally Advanced Pancreatic Cancer

*Eligible patients

Table 2
Pretreatment Characteristics
(n=593)

Age	
Median	62
Min - Max	29 - 84
Gender	
Male	310 (52.3%)
Female	283 (47.7%)
Zubrod	
0: Fully Active	292 (49.2%)
1: Restricted	301 (50.8%)
T-Stage	
T1	50 (8.4%)
T2	102 (17.2%)
T3	193 (32.5%)
T4	232 (39.1%)
TX	1 (0.2%)
Unknown/Missing	15 (2.5%)
N-Stage	
N0	346 (58.3%)
N1	161 (27.2%)
N2	2 (0.3%)
NX	68 (11.5%)
Unknown/Missing	16 (2.7%)
Percent Weight Loss	
None	23 (3.9%)
<=10%	104 (17.5%)
>10%	187 (31.5%)
Unknown/Missing	279 (47.0%)
Largest tumor dimension of primary	
<5cm	192 (32.4%)
>=5cm	158 (26.6%)
Unknown/Missing	243 (41.0%)
Primary Location	
Head	337 (56.8%)
Body,Tail,Neck,Body&Tail ,Head/Body,or Diffuse	172 (29.0%)
Unknown/Missing	84 (14.2%)

Table 3

							RPA Classes					
Method	**Full tree[1]**	**Groups**	**Comparison**	**HR[2]**	**95% CI**	**p-value[3]**	**n**	**RPA I (best)**	**n**	**RPA II**	**n**	**RPA III**
Adaptive Norm.	Age Zubrod T-stage Gender	3	II vs. I III vs. II	2.24 2.18	(1.06, 4.73) (1.58, 3.00)	0.0276 <0.0001	10	Z0, T1, age > 71 **MST=12.9 mo.**	525	Other **MST=8.9 mo.**	42	Z1, T3+, age > 63, female **MST=3.5 mo.**
		2	II vs. I	2.21	(1.60, 3.05)	<0.0001	535	Other **MST=9.0 mo.**	42	Z1, T3+, age > 63, female **MST=4.5 mo.**		N/A
Global Norm.	Age Zubrod T-stage	2	II vs. I	1.33	(1.09, 1.63)	0.0043	446	Other **MST=9.3 mo.**	138	Age > 63 & Z1 **MST=6.4 mo.**		N/A
Log-Rank	N-stage Age T-stage	2	II vs. I	1.46	(1.23, 1.75)	<0.0001	219	N0+T4 & age 53-67 or N1,N2,N3 & age 54-77 **MST=11.3 mo.**	357	Other **MST=7.8 mo.**		N/A
KM Distance	Age Gender N-stage	3	II vs. I III vs. II	1.28 1.72	(1.07, 1.53) (1.21, 2.46)	0.0061 0.0028	231	age 38<-41 or age 75<-77 or age 45<-73 & N1,N2,NX or age <=77 & female **MST=9.8 mo.**	315	Age <=38 or Age 73<-75 or Age 45<-73 & N0 **MST=8.2 mo.**	35	age>77 & female or age 41<-45 **MST=4.7 mo.**
		2	II vs. I	2.19	(1.40, 3.42)	0.0005	561	Other **MST=8.8 mo.**	20	Age>77, fem **MST=4.4 mo.**		N/A
Likelihood	Age N-stage T-stage	Could not find any clear separation of nodes.										

[1] All variables that appeared in the full RPA tree
[2] A hazard ratio greater than one for group A vs. B indicates an increased risk for group compared to group B.
[3] Log-rank test

Figure 1a
Adaptive Normalization Final RPA Model – Three Classes

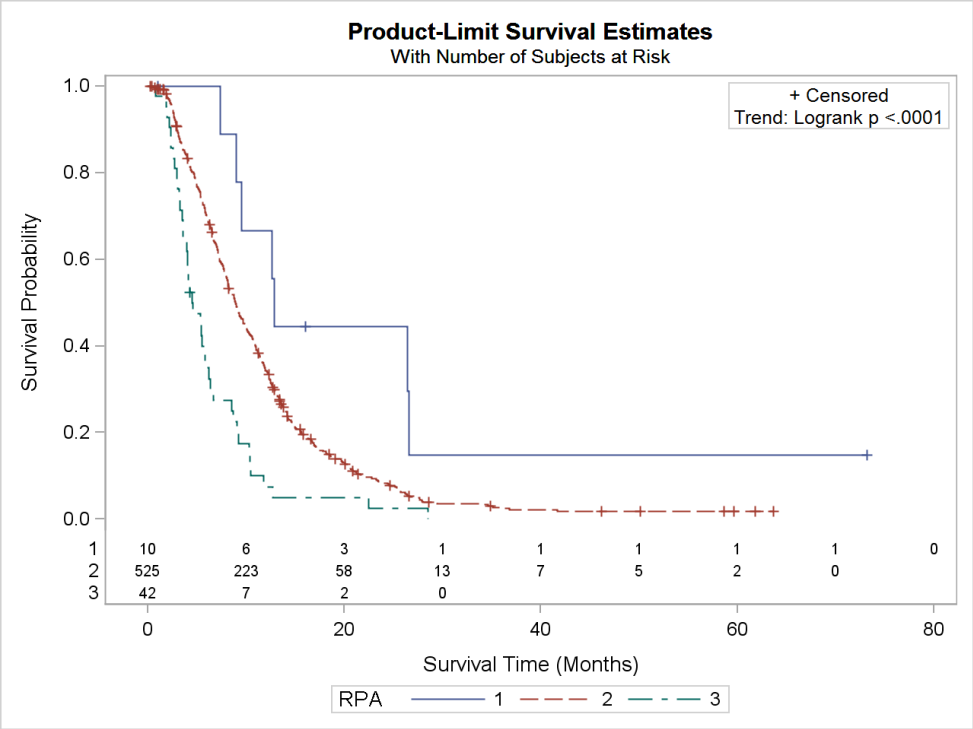


Figure 1b
Adaptive Normalization Final RPA Model – Two Classes

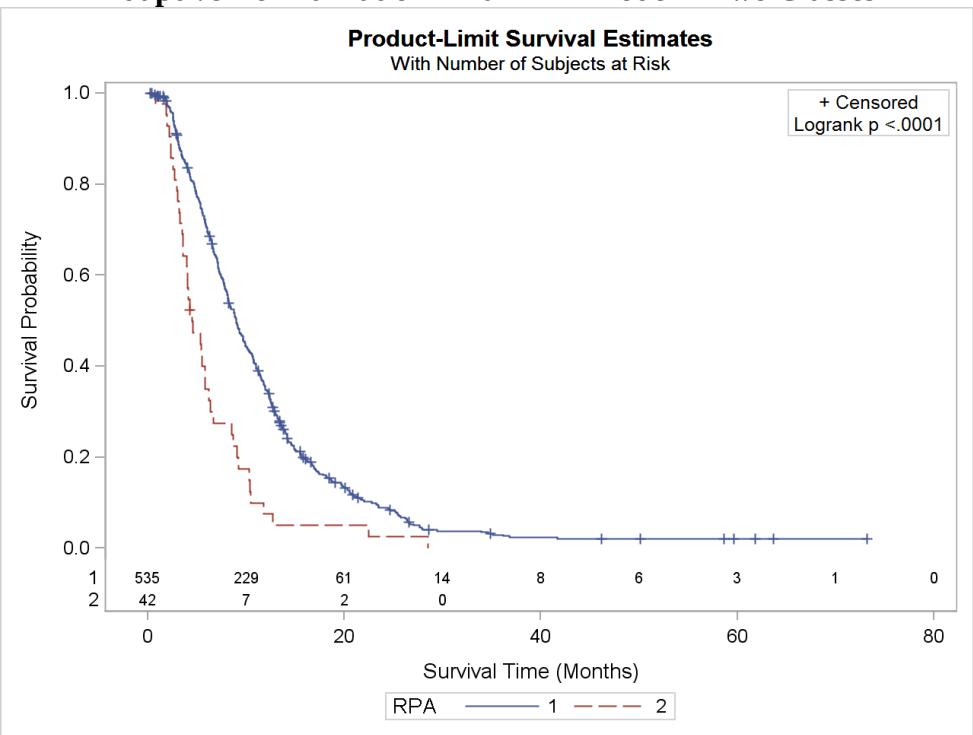


Figure 2
Global Normalization Final RPA Model

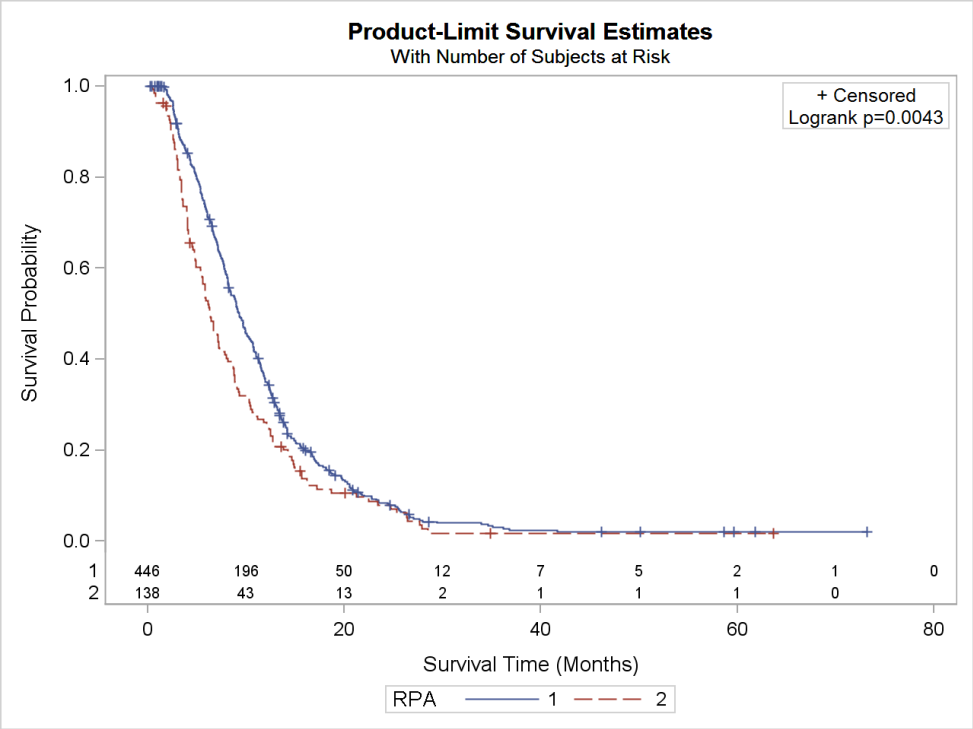


Figure 3
Log-rank Final RPA Model

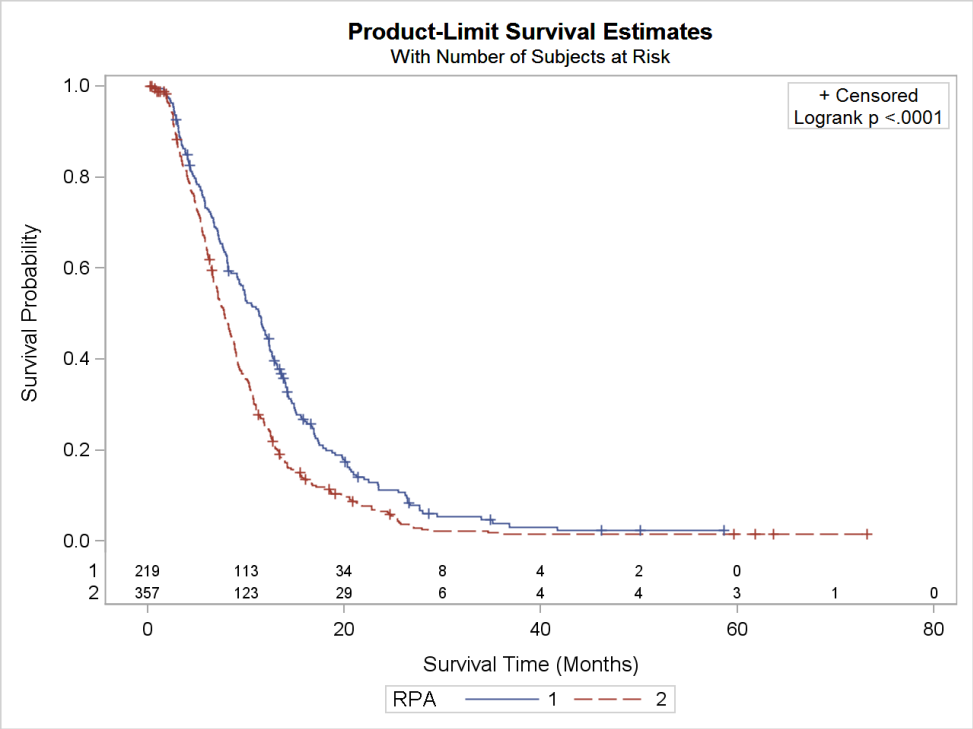


Figure 4a
Kaplan-Meier Distance Final RPA Model – Three Classes

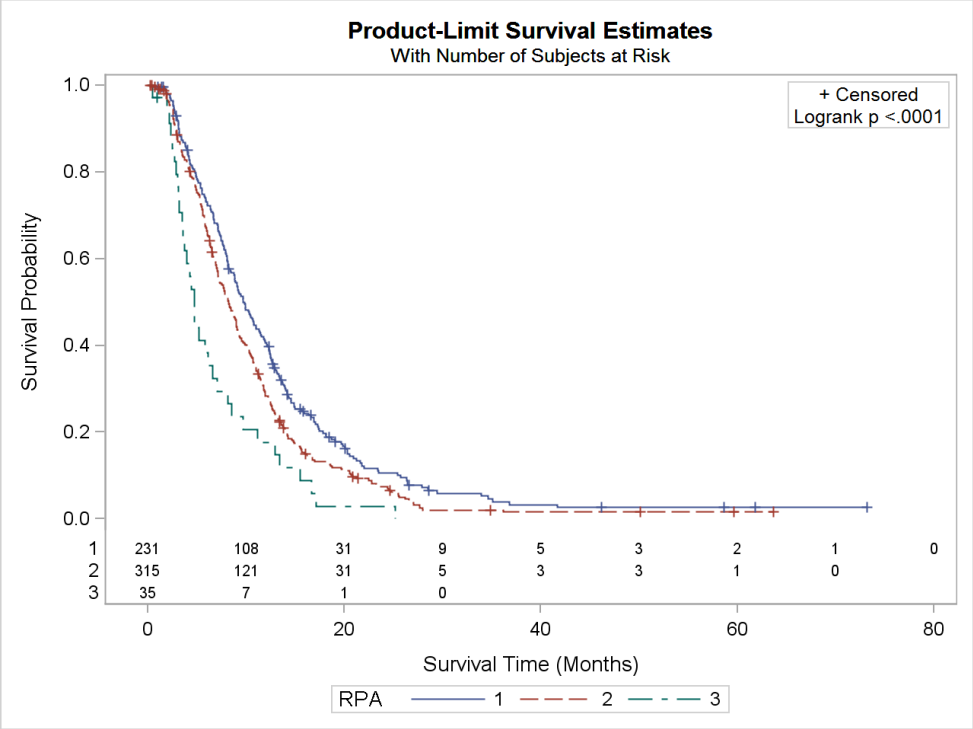
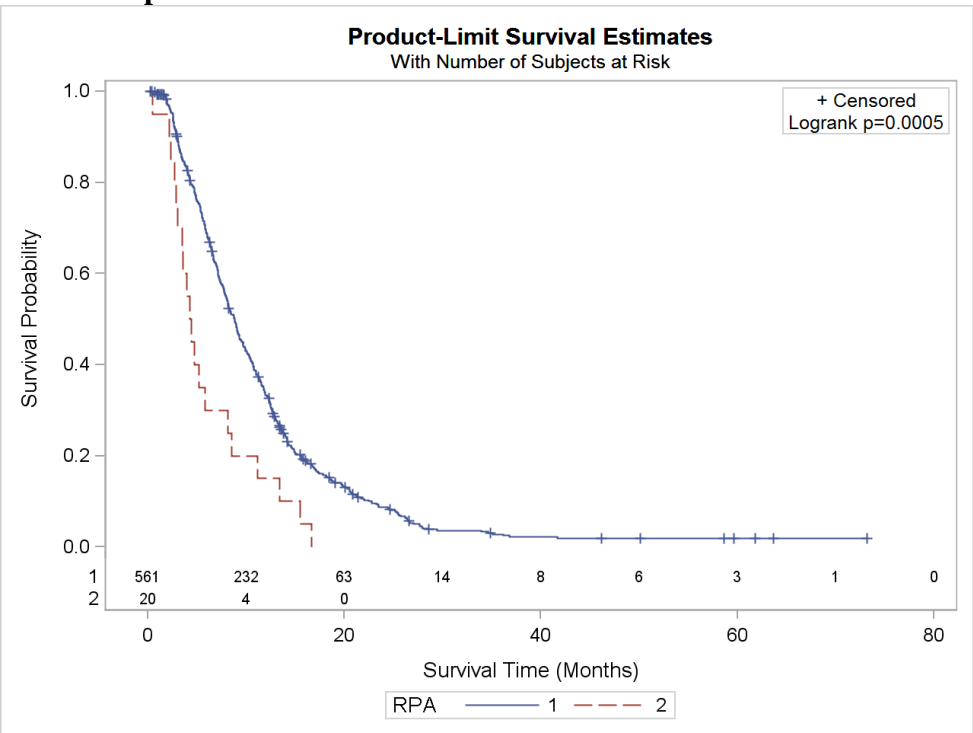
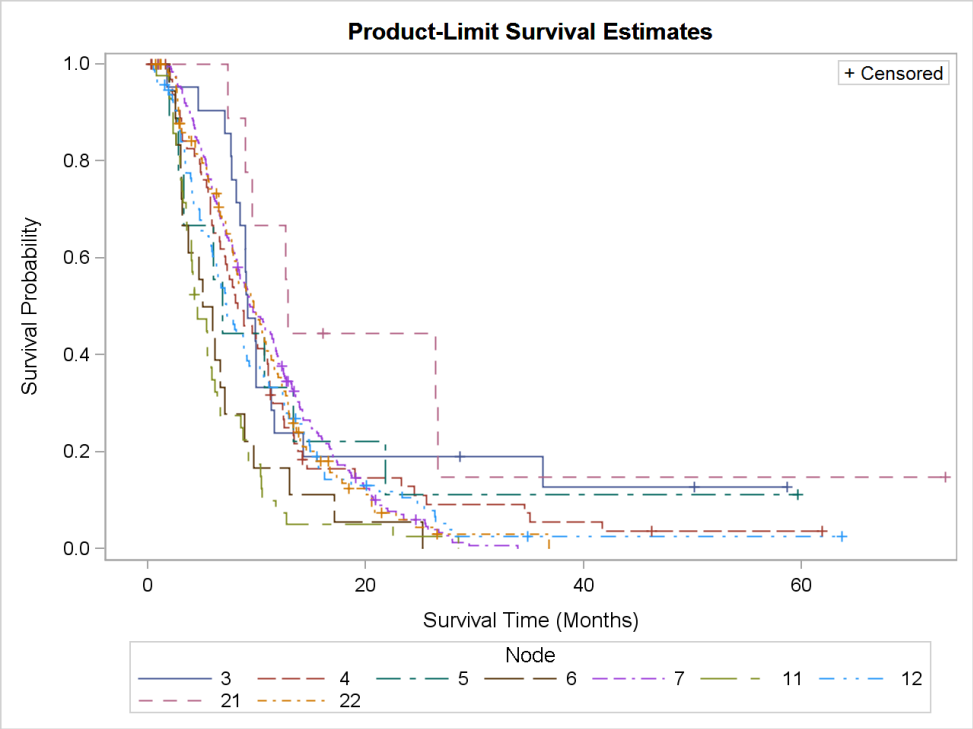


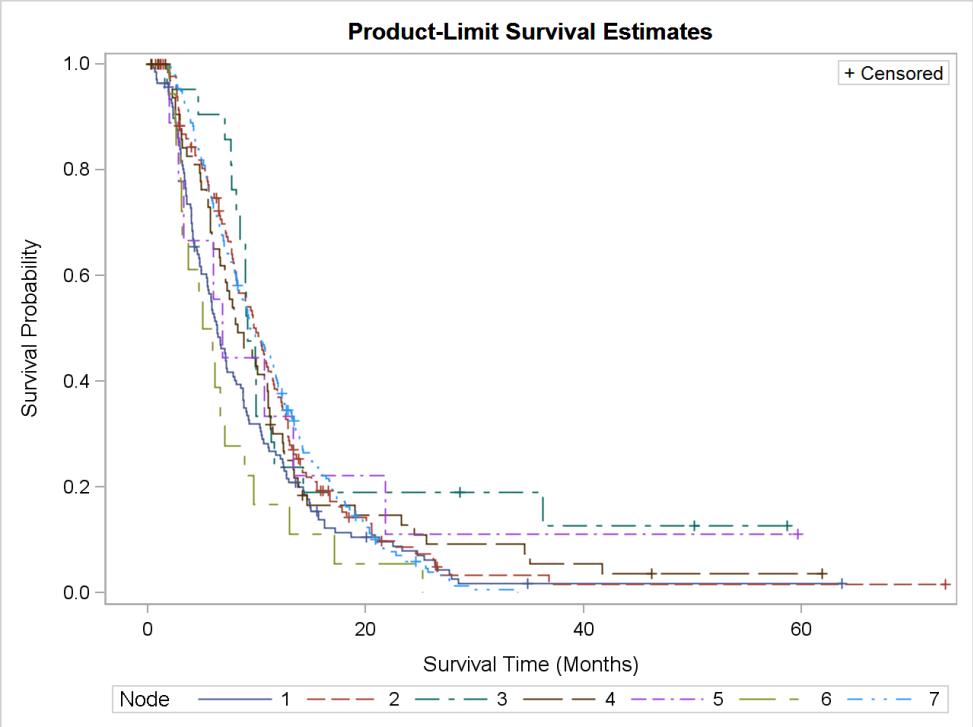
Figure 4b
Kaplan-Meier Distance Final RPA Model – Two Classes



Appendix Figure 1
Adaptive Normalization All Nodes

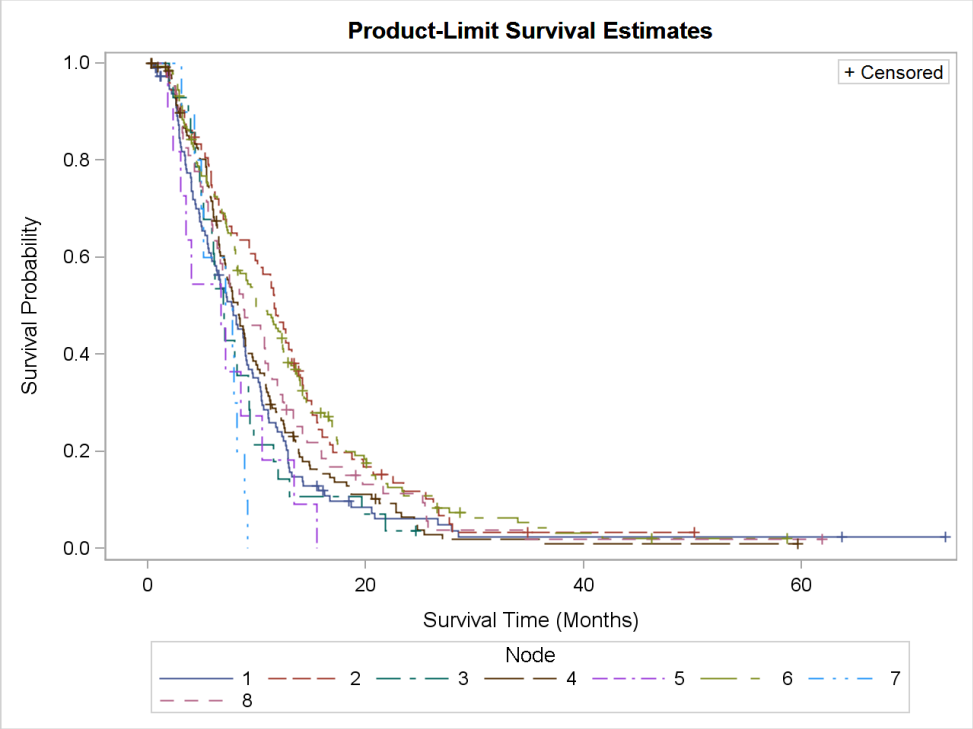


Appendix Figure 2
Global Normalization All Nodes

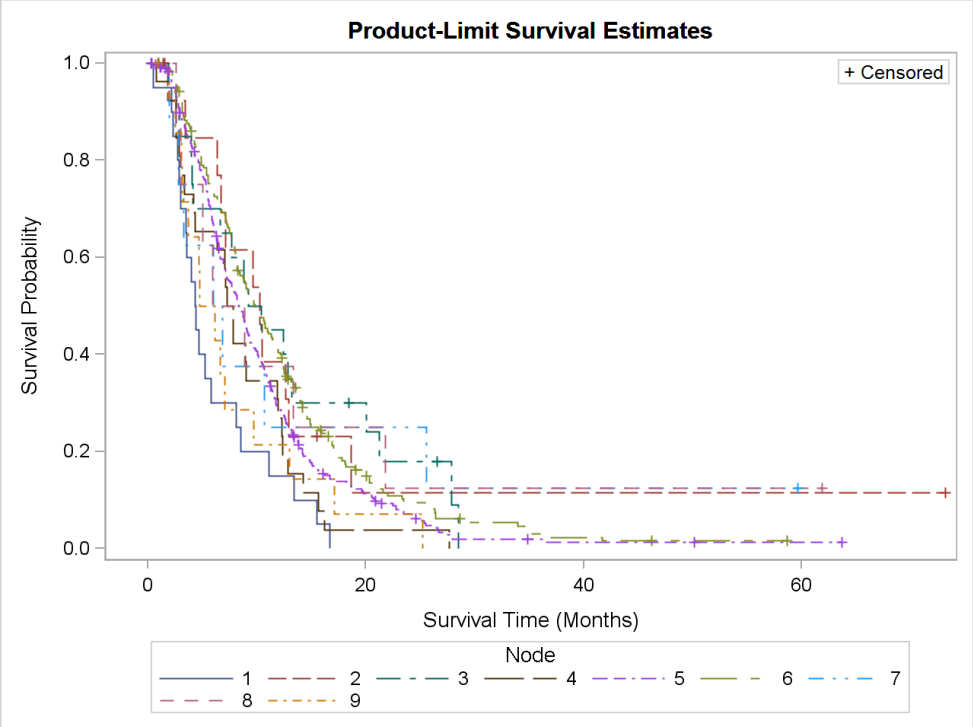


Appendix Figure 3

Log-rank Final RPA All Nodes

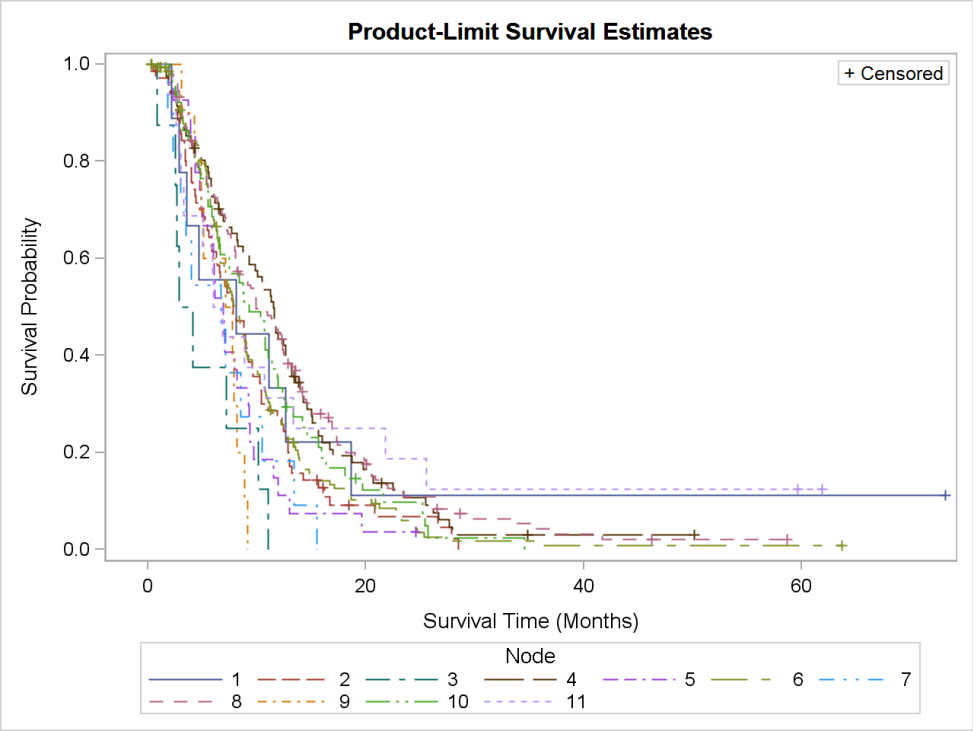


Appendix Figure 4
Kaplan-Meier Distance All Nodes



Appendix Figure 5

Likelihood All Nodes



Abstracts/Presentations

Klopp, A., J. Moughan, Portelance, L; Miller, BE; Salehpour, MR; D'Souza, D; Souhami, L; Small, W; Gaur, R; Jhingran, A. Hematologic Toxicity on RTOG 0418: A Phase II Study of Post-Operative IMRT for Gynecologic Cancer. Amer Soc Thera Rad Onc (ASTRO), October 31-November 4, 2010; San Diego, CA.

Cury, F; Hunt, D; Roach, M; Lawton, C; Gore, E; Hsu, IC; Krisch, RE; Seider, M; Sandler, H; Shipley, WU. PSA response after short-term hormonal therapy plus external beam radiotherapy and outcome in patients treated on RTOG 9413. Amer Soc Thera Rad Onc (ASTRO), October 31-November 4, 2010; San Diego, CA.

Gondi, V; Paulus, R; Bruner, DW; Meyers, CA; Gore, EM; Wolfson, A; Werner-Wasik, M; Choy, H; Movsas, B (2011). Prognostic Significance of QOL Deterioration During Early Lung Cancer Survivorship: Secondary Analysis of RTOG 0212 and 0214. Proc of American Society of Clinical Oncology (ASCO) Annual Meeting, June 3-7, 2011; Chicago, IL

Gondi V, Paulus R, Bruner DW, Meyers CA, Gore EM, Wolfson A, Werner-Wasik M, Choy H, Movsas B Decline in tested and patient-reported cognitive functioning following prophylactic cranial irradiation for lung cancer: Secondary analysis of RTOG 0212 and 0214. Amer Soc Thera Rad Onc (ASTRO) October 2-6, 2011; Miami Beach, FL

18. Extent of Clinical Activities Initiated and Completed. Items 18(A) and 18(B) should be completed for all research projects. If the project was restricted to secondary analysis of clinical data or data analysis of clinical research, then responses to 18(A) and 18(B) should be "No."

18(A) Did you initiate a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__No

18(B) Did you complete a study that involved the testing of treatment, prevention or diagnostic procedures on human subjects?

_____Yes
__X__No

If "Yes" to either 18(A) or 18(B), items 18(C) – (F) must also be completed. (Do NOT complete 18(C-F) if 18(A) and 18(B) are both "No.")

18(C) How many hospital and health care professionals were involved in the research project?

_____Number of hospital and health care professionals involved in the research project

18(D) How many subjects were included in the study compared to targeted goals?

_____Number of subjects originally targeted to be included in the study
_____Number of subjects enrolled in the study

Note: Studies that fall dramatically short on recruitment are encouraged to provide the details of their recruitment efforts in Item 17, Progress in Achieving Research Goals, Objectives and Aims. For example, the number of eligible subjects approached, the number that refused to participate and the reasons for refusal. Without this information it is difficult to discern whether eligibility criteria were too restrictive or the study simply did not appeal to subjects.

18(E) How many subjects were enrolled in the study by gender, ethnicity and race?

Gender:
_____Males
_____Females
_____Unknown

Ethnicity:
_____Latinos or Hispanics

_____Not Latinos or Hispanics
_____Unknown

Race:
_____American Indian or Alaska Native
_____Asian
_____Blacks or African American
_____Native Hawaiian or Other Pacific Islander
_____White
_____Other, specify:_____
_____Unknown

18(F) Where was the research study conducted? (List the county where the research study was conducted. If the treatment, prevention and diagnostic tests were offered in more than one county, list all of the counties where the research study was conducted.)

19. Human Embryonic Stem Cell Research. Item 19(A) should be completed for all research projects. If the research project involved human embryonic stem cells, items 19(B) and 19(C) must also be completed.

19(A) Did this project involve, in any capacity, human embryonic stem cells?
_____Yes
__X__No

19(B) Were these stem cell lines NIH-approved lines that were derived outside of Pennsylvania?
_____Yes
__X__No

19(C) Please describe how this project involved human embryonic stem cells:

20. Articles Submitted to Peer-Reviewed Publications.

20(A) Identify all publications that resulted from the research performed during the funding period and that have been submitted to peer-reviewed publications. Do not list journal abstracts or presentations at professional meetings; abstract and meeting presentations should be listed at the end of item 17. **Include only those publications that acknowledge the Pennsylvania Department of Health as a funding source** (as required in the grant agreement). List the title of the journal article, the authors, the name of the peer-reviewed publication, the month and year when it was submitted, and the status of publication (submitted for publication, accepted for publication or published.). Submit an electronic copy of each publication or paper submitted for publication, listed in the table, in a PDF version 5.0.5 (or greater) format, 1,200 dpi. Filenames for each publication should include

the number of the research project, the last name of the PI, and an abbreviated title of the publication. For example, if you submit two publications for Smith (PI for Project 01), one publication for Zhang (PI for Project 03), and one publication for Bates (PI for Project 04), the filenames would be:

Project 01 – Smith – Three cases of isolated
Project 01 – Smith – Investigation of NEB1 deletions
Project 03 – Zhang – Molecular profiling of aromatase
Project 04 – Bates – Neonatal intensive care

If the publication is not available electronically, provide 5 paper copies of the publication.

Note: The grant agreement requires that recipients acknowledge the Pennsylvania Department of Health funding in all publications. Please ensure that all publications listed acknowledge the Department of Health funding. If a publication does not acknowledge the funding from the Commonwealth, do not list the publication.

Title of Journal Article:	Authors:	Name of Peer-reviewed Publication:	Month and Year Submitted:	Publication Status (check appropriate box below):
1. Hematologic Toxicity in RTOG 0418: A Phase 2 Study of Postoperative IMRT for Gynecologic Cancer	Ann H. Klopp, MD, PhD,Jennifer Moughan, MS, Lorraine Portelance, MD, Brigitte E. Miller, MD, Mohammad R. Salehpour, PhD, Evangeline Hildebrandt, CMD, BS, Jenny Nuanjing, CMD, BS, David D'Souza, MD, Luis Souhami, MD, William Small, Jr., MD, Rakesh Gaur, MD, MPH, and Anuja Jhingran, MD	International Journal of Radiation Oncology biology*physics	Sept 2012	☐Submitted ☐Accepted ☒Published
2. Decline in Tested and Self-Reported Cognitive Functioning After Prophylactic Cranial Irradiation	Vinai Gondi, MD, Rebecca Paulus, MS, Deborah W. Bruner, RN, PhD, FAAN,Christina A. Meyers, PhD, Elizabeth M. Gore,	International Journal of Radiation Oncology biology*physics	December 2012	☐Submitted ☐Accepted ☒Published

for Lung Cancer: Pooled Secondary Analysis of Radiation Therapy Oncology Group Randomized Trials 0212 and 0214	MD, Aaron Wolfson, MD, Maria Werner-Wasik, MD, Alexander Y. Sun, MD, PhD, Hak Choy, MD,and Benjamin Movsas, MD			
3. Prognostic Significance of Decline in Patient-Reported Quality of Life during Early Lung Cancer Survivorship: Pooled Secondary Analysis of RTOG 0212 and 0214	Vinai Gondi, M.D., Rebecca Paulus, B.S., Deborah W. Bruner, R.N., Ph.D., FAAN, Christina A. Meyers, Ph.D., Elizabeth M. Gore, M.D., Aaron H. Wolfson, M.D., Maria Werner-Wasik, M.D., Alexander Y. Sun, M.D., Hak Choy, M.D., and Benjamin Movsas, M.D.	Journal of Clinical Oncology	May 2013	☒Submitted ☐Accepted ☐Published
4. Prostate-specific antigen response after short-term hormone therapy plus external-beam radiotherapy and outcome in patients treated on Radiation Therapy Oncology Group study 9413	Fabio L. Cury MD, Daniel Hunt PhD, Mack Roach III MD, William Shipley MD, Elizabeth Gore MD, I-Chow Hsu MD, Robert E. Krisch MD, Michael J. Seider MD, Howard Sandler MD, Colleen Lawton MD	Cancer	October 2012	☐Submitted ☐Accepted ☒Published

20(B) Based on this project, are you planning to submit articles to peer-reviewed publications in the future?

Yes_____X_____ No_____

If yes, please describe your plans:

The results of the unresectable pancreas cancer recursive partitioning analysis (RPA) will be submitted to a peer-reviewed journal.

21. Changes in Outcome, Impact and Effectiveness Attributable to the Research Project. Describe the outcome, impact, and effectiveness of the research project by summarizing its impact on the incidence of disease, death from disease, stage of disease at time of diagnosis, or other relevant measures of outcome, impact or effectiveness of the research project. If there were no changes, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

The results from the assessment of radiation dose to bone marrow and hematologic toxicities showed that the bone marrow can be contoured and be associated with lower hematologic toxicity. These results will help to guide the bone marrow dosimetric constraints for treating post-operative cervix and endometrial cancer patients in regular practice and for future prospective clinical trials. The results from the analysis looking at associations between prophylactic cranial irradiation (PCI) and self-reported cognitive functioning (SRCF) provides important information that emphasizes the need for being able to find ways to provide prophylactic treatment for brain metastases that limits impact on declining cognitive functioning. Contouring the brain for radiation treatment to spare dose to the hippocampus is a possible solution and is being investigated in prospective clinical trials. The results of evaluating associations between patient-reported quality of life (QoL) and efficacy outcomes further emphasizes the importance of the treating the whole person, not just the tumor. From a clinical trial perspective, it also provides important information about factors other than treatment that can be addressed such that they don't become confounding factors when evaluating treatments. From looking at associations between per protocol defined PSA complete response (PSA-CR) and treatment outcomes, provides information that will be able to be used to help individualize a patient's treatment. For example interventions for non PSA complete responders can be considered earlier on in the patient's care that could have long term impacts. This information could also be used to design a prospective trial further evaluating post initial treatment interventions. The recursive partitioning analysis for unresectable pancreas cancer provides preliminary information that can be further explored with larger datasets.

22. Major Discoveries, New Drugs, and New Approaches for Prevention Diagnosis and Treatment. Describe major discoveries, new drugs, and new approaches for prevention, diagnosis and treatment that are attributable to the completed research project. If there were no major discoveries, drugs or approaches, insert "None"; do not use "Not applicable." Responses must be single-spaced below, and no smaller than 12-point type. DO NOT DELETE THESE INSTRUCTIONS. There is no limit to the length of your response.

None.

23. Inventions, Patents and Commercial Development Opportunities.

23(A) Were any inventions, which may be patentable or otherwise protectable under Title 35 of the United States Code, conceived or first actually reduced to practice in the performance of work under this health research grant? Yes_____ No___X_____

If "Yes" to 23(A), complete items a – g below for each invention. (Do NOT complete items a - g if 23(A) is "No.")

a. Title of Invention:

b. Name of Inventor(s):

c. Technical Description of Invention (describe nature, purpose, operation and physical, chemical, biological or electrical characteristics of the invention):

d. Was a patent filed for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____

If yes, indicate date patent was filed:

e. Was a patent issued for the invention conceived or first actually reduced to practice in the performance of work under this health research grant?
Yes_____ No____
If yes, indicate number of patent, title and date issued:
Patent number:
Title of patent:
Date issued:

f. Were any licenses granted for the patent obtained as a result of work performed under this health research grant? Yes_____ No____

If yes, how many licenses were granted?_____

g. Were any commercial development activities taken to develop the invention into a commercial product or service for manufacture or sale? Yes___ No____

If yes, describe the commercial development activities:

23(B) Based on the results of this project, are you planning to file for any licenses or patents, or undertake any commercial development opportunities in the future?

Yes_____ No___X_____

If yes, please describe your plans:

24. Key Investigator Qualifications. Briefly describe the education, research interests and experience and professional commitments of the Principal Investigator and all other key investigators. *In place of narrative you may insert the NIH biosketch form here; however, please limit each biosketch to 1-2 pages. For Nonformula grants only – include information for only those key investigators whose biosketches were not included in the original grant application.*

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Winter, Kathryn	Director of Statistics
eRA COMMONS USER NAME (credential, e.g., agency login) NONE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Shippensburg University, Shippensburg, PA	B.A.	1993	Mathematics
University of Florida, Gainesville, FL	M.S.	1995	Statistics

A. Personal Statement

I am the Director of Statistics for the Radiation Therapy Oncology Group and have been working in multimodality cancer clinical trials, with a focus on radiation therapy, for over 17 years. During this time I have designed, analyzed, and overseen clinical and translational trials and projects across many disease sites, including prostate cancer, and am the statistical co-author on over 65 peer-reviewed journal articles. Additionally, for the last 6 years in my role as director, I have overseen the day-to-day operations of the RTOG Statistics and Data Management Center. I am the Principal Investigator for four research projects funded by the Pennsylvania Department of Health focusing on correlating biospecimens with clinical data to advance current knowledge regarding the treatment and prognosis of cancer patients. My extensive experience with clinical trial design as well as my current role position me well for my role as a Co-Investigator on this R21 grant, which aims to explore novel statistical tests and designs that have the potential to change the way clinical trials are designed and monitored.

B. Positions and Honors

Positions and Employment

1993-1995 Teaching Assistant, Department of Statistics, Univ. of Florida, Gainesville, FL
1995-1999 Statistician, RTOG Statistical Center, American College of Radiology (ACR), Phila., PA
1999-2006 Senior Statistician, RTOG Statistical Center, ACR, Philadelphia, PA
2001-2002 Adjunct Professor, Department of Mathematics and Computer Science, Saint Joseph's University, Philadelphia, PA
2002-2006 Adjunct Professor, College of Graduate Studies, Thomas Jefferson University, Philadelphia, PA
2006-2007 Acting Senior Director, Research & Operations, RTOG Statistical Center, ACR, Philadelphia, PA
2006-2007 Acting Group Statistician, RTOG Statistical Center, ACR, Philadelphia, PA
2008-2009 Acting Group Statistician, RTOG Statistical Center, ACR, Philadelphia, PA
2007-present Director, RTOG Statistical Center, ACR, Philadelphia, PA

Other Professional Experience

2005-present Statistical Representative, NCI GI Pancreas Task Force
2006-2012 Statistical Representative, NCI GYN Cancer Steering Committee
2006-present RTOG Representative, NCI Group [Biospecimen] Banking Committee
2007-2010 Statistical Representative, NCI CIRB
2007-2012 Statistical Representative, NCI GYN Cervical and Uterine Task Forces

C. Selected Peer-reviewed Publications (from a total of 70)

1. Gaffney D, **Winter K,** et al: Feasibility of RNA Collection for Micro-Array Gene Expression Analysis in the Treatment of Cervical Carcinoma: A Scientific Correlate of RTOG C-0128. Gynecologic Oncology 97(2): 607-611, 2005.
2. Pilepich M, **Winter K,** et al: Androgen Suppression Adjuvant To Definitive Radiotherapy In Carcinomas Of The Prostate - Long Term Results Of Phase III RTOG 85-31. Int J Radiat Onco Biol Phys. 61(5): 1285-1290, 2005.
3. Gaffney DK, **Winter K,** Dicker AP et al: A Phase II Study of Acute Toxicity for Celebrex™ (celecoxib) and Chemoradiation in Patients with Locally Advanced Cervical Cancer: Primary Endpoint Analysis of RTOG 0128. Int J Radiat Onco Biol Phys 67: 104-109, 2007.
4. Regine W, **Winter K**, et al: Fluorouracil vs Gemcitabine Chemotherapy Before and After Fluorouracil-Based Chemotherapy Following Resection of Pancreatic Adenocarcinoma: A Randomized Controlled Trial. *JAMA*, **299,** 1019-1026, 2008.
5. Arthur D, **Winter K**, et al: A Phase II Trial of Brachytherapy Alone After Lumpectomy for Select Breast Cancer: Tumor Control and Survival Outcomes of RTOG 95-17. *Int J Radiat Oncol Biol Phys*, 72, 467-473, 2008. PMCID: PMC2604132
6. Ajani J, **Winter K**, et al: (Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal: A Randomized Controlled Trial. *JAMA*, 299, 1914-1921, 2008.
7. Weidhaas, J, Li S, **Winter K**, et al: Changes in Gene Expression Predicting Local Control in Cervical Cancer: Results from RTOG 0128. *Clin Cancer Res*, 15, 4199-4206, 2009. PMCID: PMC2758917
8. Tucker S, Dong L, Bosch W, Michalski J, **Winter K**, Mohan R, Purdy J, Kuban D, Lee A, Cheung M, Thames H and Cox, J: Late Rectal Toxicity on RTOG 94-06: Analysis Using a Mixture Lyman Model. *Int J Radiat Oncol Biol Phys*, 78, 1253-1260, 2010. PMCID: PMC2963659
9. Kachnic L, **Winter K**, Wasserman T, Minsky B, Ginsberg R, Pisansky T, Martenson J, Komaki R, Okawara G, Rosenthal S and Kelsen D: A Comparative Longitudinal Quality of Life Study Between High Dose and Conventional Dose Radiation in RTOG 94-05 (Int 0123): A Phase III Trial of Combined Modality Therapy for Esophageal Cancer. *Gastrointest Cancer Res*, 4 (2):45-52, 2011.
10. Wong S, **Winter K**, Meropol N, Anne R, Kachnic L, Rashid A, Watson J, Mitchell E, Pollock J, Lee R, Haddock M, Erickson B and Willett C: RTOG 0247: A Randomized Phase II Study of Neoadjuvant Capecitabine and Irinotecan or Capecitabine and Oxaliplatin with Concurrent Radiation Therapy for Locally Advanced Rectal Cancer. *Int J Radiat Oncol Biol Phys*, 82 (4):1367-1375, 2012. PMCID: PMC3208721
11. Kachnic L, **Winter K,** Myerson R, Goodyear M, Willins J, Esthappen J, Haddock M. Rotman M, Parikh P, Willett C: RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal. *Int J Radiat Onco Biol Phys* 2013, 86, (1), 27-33. PMCID: PMC3619011 [Available on 2014/5/1]