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## Decline in Tested and Self-Reported Cognitive Functioning Following Prophylactic Cranial Irradiation for Lung Cancer: Pooled Secondary Analysis of RTOG Randomized Trials 0212 and 0214

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### Summary

Prior studies have demonstrated an association between prophylactic cranial irradiation (PCI) and subsequent decline in the Hopkins Verbal Learning Test (HVLT). In this analysis, prophylactic cranial irradiation is also associated with a higher rate of decline in self-reported cognitive functioning (SRCF). This study provides novel observations regarding the absence of a close correlation between decline in HVLT and decline in SRCF, suggesting that they may represent distinct elements of the cognitive spectrum.

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**Purpose**—Prophylactic cranial irradiation (PCI) has been associated with decline in tested cognitive functioning, using the Hopkins Verbal Learning Test (HVLТ). The purpose of this study was to assess the impact of PCI on self-reported cognitive functioning (SRCF), a functional scale on EORTC QLQ-C30.

**Methods and Materials**—RTOG 0214 randomized patients with locally advanced non-small cell lung cancer to PCI or observation. RTOG 0212 randomized patients with limited-disease small cell lung cancer to high- or standard-dose PCI. In both trials, HVLТ-recall (R) and -delayed recall (DR) and SRCF were assessed at baseline (following locoregional therapy but before PCI or observation) and at 6 and 12 months (mos). Patients developing brain relapse prior to follow-up evaluation were excluded. Decline was defined using the reliable change index method and correlated with receipt of PCI versus observation using logistic regression modeling. Fisher's exact test correlated decline in SRCF with HVLТ decline.

**Results**—Of the eligible patients pooled from RTOG 0212 and RTOG 0214, 410 (93%) receiving PCI and 173 (96%) undergoing observation completed baseline HVLТ or EORTC QLQ-C30 testing and were included in this analysis. PCI was associated with a higher risk of decline in SRCF at 6 mos (Odds Ratio (OR), 3.60, 95% confidence interval (95%CI), 2.34-6.37,  $p<0.0001$ ) and 12 mos (OR 3.44, 95%CI 1.84-6.44,  $p<0.0001$ ). HVLТ-R decline at 6 and 12 mos 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).

**Conclusions**—In lung cancer patients who do not develop brain relapse, PCI is associated with decline in HVLТ-tested and self-reported cognitive functioning. Decline in HVLТ and decline in SRCF are not closely correlated, suggesting that they may represent distinct elements of the cognitive spectrum.

## Keywords

Lung cancer; cognitive functioning; RTOG 0212; RTOG 0214; prophylactic cranial irradiation

## Introduction

Recent clinical trials have demonstrated cognitive impairment as an adverse effect of cranial irradiation, based on recall and delayed recall testing using the Hopkins Verbal Learning Test (HVLТ). For instance, RTOG 0214 was a phase III trial of prophylactic cranial irradiation (PCI) versus observation in patients with locally-advanced NSCLC [1]. RTOG 0214 tested HVLТ as a secondary endpoint and observed greater decline in HVLТ in the PCI cohort as compared to the observation cohort at 1-year follow-up [2]. Similar findings have been demonstrated in the setting of brain metastases [3].

However, whether receipt of cranial irradiation is associated with subsequent decline in self-reported cognitive functioning (SRCF), as assessed using quality of life (QOL) questionnaires, remains ill defined. Slotman et al. attempted to address this question in a phase III trial of PCI versus observation for extensive-disease small cell lung cancer and observed a two-fold increase in the proportion of patients experiencing SRCF decline with PCI, although this result did not reach statistical significance [4]. Similarly, RTOG 0214 demonstrated a trend for greater decline in SRCF with PCI, but this finding lost statistical

significance on multivariate analysis [2]. One potential reason for the absence of statistical significance in these findings may have been limited sample size, as RTOG 0214 was not able to reach target accrual and both trials reported significant non-compliance with QOL follow-up.

To overcome this limitation, we pooled neurocognitive and quality of life data from RTOG 0214 with data from RTOG 0212, a phase II trial of high-dose versus standard-dose PCI for limited-stage small cell lung cancer. In addition to using HVLТ for cognitive function testing, both RTOG trials utilized the same QOL instrument, EORTC Core Quality of Life Questionnaire (QLQ-C30), in which self-reported cognitive functioning is specifically assessed as a two-item functional scale.

## Methods and Materials

The details regarding patient eligibility and treatment on RTOG 0212 and RTOG 0214 have been previously described [1,5]. Briefly, eligibility for RTOG 0212 was limited to patients with limited-disease SCLC with complete response to chemotherapy and consolidative chest radiotherapy; Zubrod performance status of 1; and, RTOG neurologic function class of 1 or 2. Eligibility on RTOG 0214 was limited to patients with stage IIIA/B NSCLC with stable disease or complete/partial response after potentially curative therapy; no evidence of brain or extracranial metastases; and, resolution to grade 2 of any acute or subacute grade 3 toxicities from prior therapy. All patients signed an institutional review board-approved, study-specific consent form.

RTOG 0212 randomized patients to standard-dose PCI (25 Gy in 10 daily fractions) or high-dose PCI (36 Gy). Those randomized to the high-dose PCI underwent a second randomization to receive PCI in 18 daily fractions of 2.0 Gy per fraction or 24 twice-daily fractions of 1.5 Gy per fraction [5]. RTOG 0214 randomized patients to PCI (30 Gy in 15 daily fractions) or observation [1] (Figure 1). Both trials are registered with ClinicalTrials.gov, numbers NCT00057746 (RTOG 0212) and NCT00048997 (RTOG 0214).

## QOL and HVLТ Assessments

In both studies, self-reported outcomes were captured prospectively using the EORTC QLQ-C30. EORTC QLQ-C30 is a 30-item self-report questionnaire containing multiple QOL domains (scales) [6]. For this analysis, global quality of life as well as each symptom and functional scale, including SRCF, were analyzed separately. Specifically, SRCF is a two-item functioning scale captured with questions pertaining to concentration and memory. As with other functional scales, higher scores indicate better functioning. EORTC QLQ-C30 scores were converted to lie in a range between 0-100, according to the guidelines of EORTC [7]. EORTC QLQ-C30 has been previously shown to be a reliable and valid instrument in patients with lung and other cancer diagnoses [6,8].

Both trials tested cognitive function prospectively using HVLТ, a well-validated and reliable assessment of list-learning memory, including encoding, retrieval and retention of new information over time [9]. HVLТ incorporates 6 different forms, helping to mitigate practice

effects of repeated administrations. Each form includes 12 nouns (targets) with 4 words drawn from 3 semantic categories, which differ across the 6 forms. The test involves memorizing a list of 12 targets for 3 consecutive trials (Recall) and recalling the 12 targets after a 20-minute delay (Delayed Recall). Raw scores can range from 0-36 for HVL-Recall (HVL-R) and 0-12 for delayed recall (HVL-DR).

In both studies, baseline HVL and EORTC QLQ-C30 were completed following definitive loco-regional therapy but before the initiation of PCI or observation. Serial follow-up HVL and EORTC QLQ-C30 testing was performed at 6 and 12 months after study entry. Since patient follow-up did not always occur at exactly 6 and 12 months follow-up, data obtained within 4 weeks before or after these time points were included. Data collected at additional time points of 24, 36 and 48 months after study entry were not included in this analysis due to substantial long-term non-compliance. Each patient served as his/her own control, as the difference in scores obtained at baseline and at 6 and 12 months after randomization were calculated.

### Statistical Methods

Data from RTOG 0212 and RTOG 0214 were pooled for this exploratory analysis, evaluating whether receipt of PCI predicted for decline in HVL and/or SRCF. To minimize the confounding effects of intracranial relapse, all patients who developed an intracranial relapse prior to follow-up evaluation were excluded. Patients with missing follow-up assessments were excluded from analysis of the applicable time point. Comparisons of categorical patient characteristics were done using chi-square test statistics, and comparisons of continuous patient characteristics were done using the F-statistic from analysis of variance.

Baseline comparisons of continuous HVL scores were done using the Kruskal-Wallis two-sided rank test to compare means. Follow-up scores were analyzed using the reliable change index (RCI) method [10], which allows for changes from baseline to be classified as either a decline, stability, or improvement in function. Logistic regression analysis [11] was used to evaluate whether use of PCI was predictive of decline in HVL 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 HVL and EORTC QLQ-C30 scores were considered impaired if the score was 1.5 standard deviations (SDs) worse than the mean of the normative age-adjusted distribution [12,13]. For PCI dose, patients were categorized as standard dose PCI (2.5 Gy  $\times$  10 on RTOG 0212 or 2.0 Gy  $\times$  15 on RTOG 0214), high dose PCI (2.0 Gy  $\times$  18 or 1.5 Gy  $\times$  25 on RTOG 0212) or no PCI. Associations between decline in SRCF, HVL, or other EORTC QLQ-C30 functional or symptom scale was tested using the Fisher's exact test, with agreement evaluated using the Kappa correlation statistic [14,15].

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  $<0.05$ .

Statistical Analysis Software® (SAS Institute, Cary, NC) version 9.2 was used for all statistical analyses.

## Results

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 HVLТ or EORTC QLQ-C30 testing and were included in this analysis (Figure 2). 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 to patients treated without PCI (Table 1). Otherwise, PCI and observation cohorts were similar with respect to age, gender, partner status, and baseline Zubrod performance status. Compliance with HVLТ and EORTC QLQ-C30 assessments at 6 and 12 months follow-up did not differ between PCI and observation cohorts (Figure 2).

Higher baseline HVLТ-R and HVLТ-DR scores were observed among patients receiving PCI ( $p=0.02$  and  $p=0.02$ , respectively) and high-dose PCI ( $p=0.004$  and  $p=0.01$ , respectively) (Table e1; [www.redjournal.org](http://www.redjournal.org)). Patient factors associated with higher baseline HVLТ-R scores included female gender ( $p<0.0001$ ), more advanced education level ( $p<0.0001$ ), partnered status ( $p=0.04$ ), and age  $\geq 60$  ( $p<0.0001$ ). Patient factors associated with higher baseline HVLТ-DR scores were female gender ( $p<0.0001$ ), more advanced education level ( $p<0.0001$ ), and age  $\geq 60$  ( $p=0.03$ ). Comparisons of baseline EORTC QLQ-C30 scores demonstrated no significant associations of SRCF with any patient factors.

At 6 and 12 months follow-up, PCI was associated with higher rates of decline in HVLТ-R, HVLТ-DR, and SRCF (Figure 3). No other associations were observed between PCI and decline in global health status/quality of life or other EORTC QLQ-C30 functional or symptom scales (data not shown). For HVLТ-R and -DR, baseline impairment was associated with lower rates of decline at 6 months ( $p=0.0003$  and  $p=0.001$ , respectively) and 12 months ( $p=0.002$  and  $p=0.03$ ). Similar results were observed when baseline score was assessed continuously (data not shown). For SRCF, baseline score assessed continuously or categorically (impaired vs. unimpaired) was not associated with subsequent decline at 6 or 12 months. Age  $>60$  was associated with higher rates of HVLТ-DR decline at 12 months ( $p=0.02$ ).

In a multivariate logistic regression model of HVLТ-R decline at 6 and 12 months, both receipt of PCI ( $p=0.002$  and  $p=0.002$ , respectively) and baseline HVLТ-R impairment ( $p=0.0002$  and  $p=0.003$ , respectively) remained independently predictive (Table 2). Association between PCI and HVLТ-DR trended to statistical significance (6 months,

$p=0.08$ ; 12 months,  $p=0.06$ ) after adjusting for baseline impairment. Similar results were observed when baseline score was assessed continuously (data not shown).

Analyses for correlation of SRCF decline with decline in HVLТ-R or HVLТ-DR demonstrated no significant associations at 6 months (HVLТ-R, Kappa 0.113,  $p=0.05$ ; HVLТ-DR, Kappa 0.155,  $p=0.01$ ) or 12 months follow-up (HVLТ-R, Kappa -0.023,  $p=0.74$ ; HVLТ-DR, Kappa 0.046,  $p=0.50$ ) (Table 3). At 6 and 12 months follow-up, decline in HVLТ-R or HVLТ-DR was also not correlated with decline in any other EORTC QLQ-C30 symptom or functional scale (data not shown). 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,  $p<0.0001$ ) at 6 months (Table 3).

## Discussion

In this analysis of pooled HVLТ and quality of life data from RTOG 0212 and RTOG 0214, we observed at least a three-fold elevated risk of decline in SRCF 6 and 12 months following PCI as compared to observation in lung cancer patients who did not develop brain relapse. This adverse quality of life effect of PCI was selective for SRCF and was not similarly appreciated with global health status/quality of life or any other EORTC QLQ-C30 symptom or functional scale. Similar results, presented in abstract form [16], have been observed in the EORTC trial of adjuvant whole-brain radiotherapy versus observation following surgical resection or radiosurgery for 1 to 3 brain metastases. Using the EORTC QLQ-C30 questionnaire to examine health-related quality of life, patients who underwent whole-brain radiotherapy were noted to have decline in SRCF at 12 months follow-up. The summation of these and our findings provides the first evidence of a cognitive functioning-specific quality of life detriment to cranial irradiation and emphasizes the importance of counseling patients on cranial irradiation-induced cognitive decline not just captured on intensive memory testing but also self-reported.

Another salient finding of this study is the poor agreement between HVLТ and SRCF in detecting decline in cognitive functioning, raising important questions about our current understanding of cognitive decline following cranial irradiation. Firstly, prior studies have shown a decline in list-learning recall and delayed recall, as captured by HVLТ, between 3 and 12 months after cranial irradiation [2,3,17]. However, the findings from our study question whether this HVLТ decline is pertinent to self-reported quality of life and/or perceptible to patients. Secondly, prior studies have demonstrated a potentially selective effect of cranial irradiation on HVLТ and not on other cognitive domains, assessed using conventional cognitive tests [17]. However, our study demonstrates an effect of PCI on SRCF in the absence of a close correlation between SRCF and HVLТ. This finding suggests that cranial irradiation may induce decline in another as yet unidentified cognitive domain that may be more closely correlated with SRCF. To address both of these questions and further enhance our understanding of the cognitive effects of cranial irradiation, future prospective trials of cranial irradiation should expand beyond HVLТ and the two-item

cognitive function scale of EORTC QLQ-C30 to more comprehensively assess the multiple dimensions of human cognition.

Independent of the effects of PCI or age, patients with baseline impairment in HVLTR or DR were significantly less likely to develop subsequent HVLTR decline. This may be due in part to the limited score range of HVLTR. The reliable change index defines decline as an absolute score reduction outside a test's standard error. However, to achieve this absolute score reduction, patients who start at a substantially lower baseline score would require a larger percentage decrease in their follow-up score. This becomes especially problematic in HVLTR-DR, for instance, where the score range is 0-12 and where baseline impairment for ages 70-86 is defined as a score less than 4.50 [12]. These findings highlight the importance of investigating cognitive tests with larger score ranges, as is currently being done on RTOG 0925 and RTOG 0933.

At 6 and 12 months, statistically significant correlations were observed between SRCF decline and decline in self-reported physical functioning. In addition, SRCF decline was correlated with increasing fatigue and appetite loss at 6 months, but these associations were lost at 12 months. These findings suggest that SRCF decline may be due, in part, to declining performance status, iatrogenic causes (e.g., pain medications), or extra-cranial disease progression. However, the absence of any effects of PCI on self-reported physician functioning, fatigue and appetite loss, and the relatively low kappa statistics suggesting fair strength of agreement [18], indicate that PCI-associated decline in SRCF is likely not explained by these effects alone.

The results of this study should be placed within the context of the established intracranial control and survival benefits of PCI in certain clinical settings of small cell lung cancer. Prior studies of whole brain radiotherapy in patients with brain metastases have observed an association between intracranial tumor progression and neurocognitive function [17,19]. Similar studies have not been conducted in the PCI setting. In this study, an attempt to evaluate HVLTR and EORTC QLQ-C30 decline in patients who developed brain relapse was limited due to substantial non-compliance following brain relapse. However, given the aforementioned findings in the brain metastasis setting, it is reasonable to assume that the emergence of intracranial metastases may also have potentially adverse neurocognitive effects.

The findings of this study do contrast with those reported by Li et al. [20], who observed a significant correlation between neurocognitive function and quality of life at baseline and 4 months following whole-brain radiotherapy in patients with brain metastases. However, both our study and Li et al. were similar in observing no such correlation at 6 months follow-up. In addition, our study has a number of methodological differences from the Li et al. study. Firstly, the first follow-up evaluation in our study was 6 months, preventing an evaluation of potential correlations at earlier time points. Secondly, our study correlated decline of HVLTR with decline in quality of life, whereas Li et al. correlated raw HVLTR and quality of life scores. Lastly, Li et al. examined all patients with brain metastases following whole-brain radiotherapy, irrespective of intracranial progression. Our study specifically excluded patients with brain relapse to avoid the confounding effects of intracranial disease.

Pooling data from RTOG 0212 and RTOG 0214 was feasible due to the uniformity of quality of life 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 two distinct disease processes. For instance, in this study, the observation cohort consisted entirely of patients with NSCLC, while the PCI cohort was a mixed population of SCLC and NSCLC patients. To address this concern, we excluded any patients who developed brain relapse prior to follow-up evaluation. In addition, while 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 quality of life 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.

In conclusion, 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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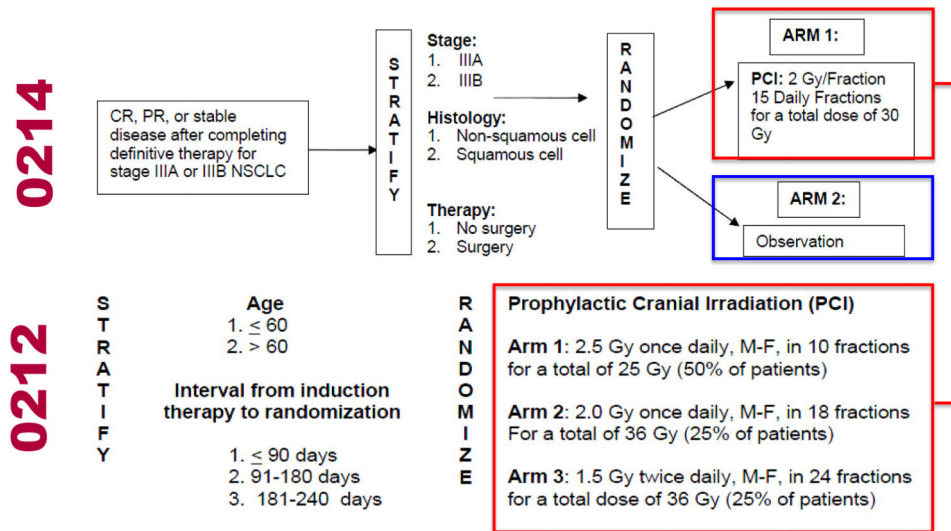
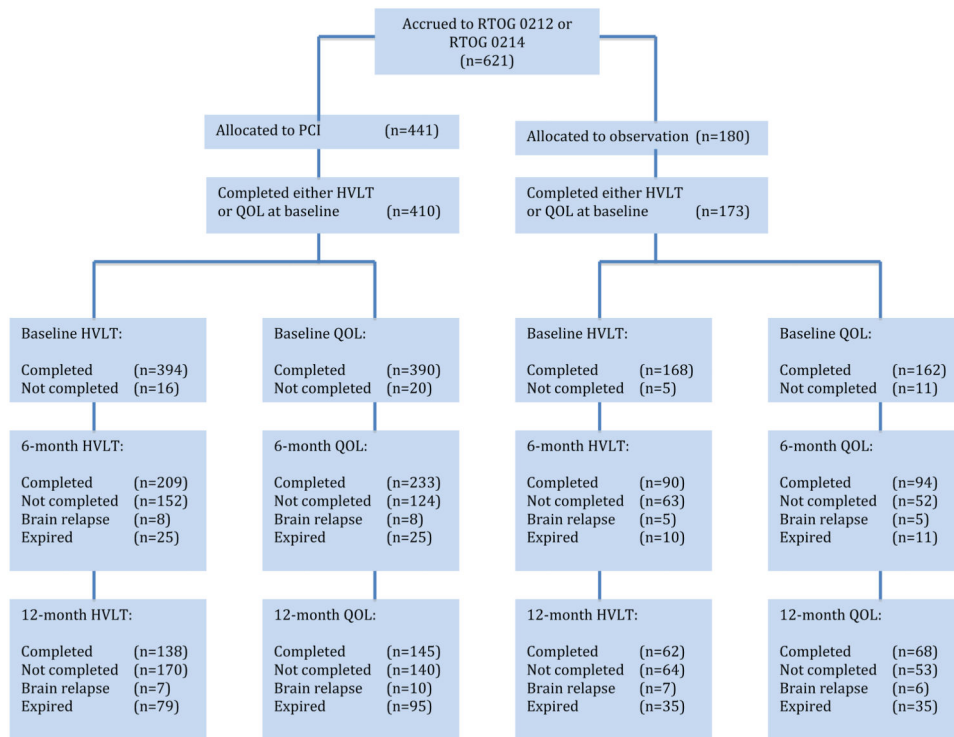
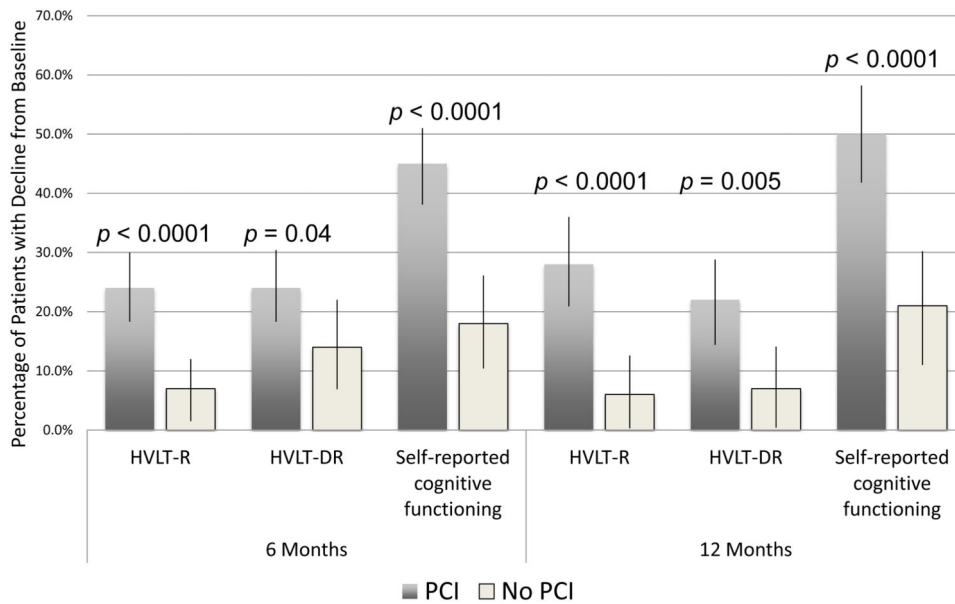


Figure 1. Study schema



**Figure 2. CONSORT Flowchart**

PCI: prophylactic cranial irradiation; HVL: Hopkins Verbal Learning Test; QOL: quality of life.



**Figure 3. Prophylactic cranial irradiation (PCI) is associated with decline in both tested and self-reported cognitive functioning**

HVLT-R: Hopkins Verbal Learning Test-Recall; HVLT-DR: Hopkins Verbal Learning Test-Delayed Recall. Black bars represent 95% confidence intervals. For HVLT-Recall and -Delayed Recall comparisons, statistical significance was assigned to  $p < 0.05$ . For SRCF comparisons, statistical significance was assigned to  $p < 0.0001$  to prevent inflation of type I error from multiple testing of EORTC QLQ-C30.

**Table 1**  
**Patient Characteristics**

	PCI (n=410)	No PCI (n=173)	<i>p</i> value
Age			0.87
Median	62	62	
Range	39-86	39-83	
Gender			0.44
Male	242 (59%)	108 (62%)	
Female	168 (41%)	65 (38%)	
Education Level			0.02
< High School	96 (25%)	57 (35%)	
High School	146 (39%)	44 (27%)	
> High School	137 (36%)	61 (38%)	
Unknown	31	11	
Partner Status			0.07
Partnered	258 (65%)	125 (73%)	
Not Partnered	140 (35%)	47 (27%)	
Unknown	12	126	
Zubrod Performance Status*			0.09
0	133 (50%)	102 (59%)	
1	123 (46%)	67 (39%)	
2-3	9 (3%)	4 (2%)	

\* Baseline Zubrod performance was collected on 105 (43.2%) of the patients enrolled on RTOG 0212 and all patients enrolled on RTOG 0214.

Abbreviations: PCI, prophylactic cranial irradiation.

**Table 2**

Logistic regression models of association of PCI with decline in HVL-T-Recall, HVL-T-Delayed Recall, and self-reported cognitive function.

Factor	Decline in ...					
	HVL-T-Recall		HVL-T-Delayed Recall		Self-Reported Cognitive Function	
	6 months	12 months	6 months	12 months	6 months	12 months
No PCI (RL) vs. PCI	3.91	4.96	1.89	2.49	3.60	3.44
Odds Ratio	1.68-9.08	1.84-13.38	0.94-3.81	0.96-6.48	2.34-6.37	1.84-6.44
95% CI	0.002	0.002	0.08	0.06	<0.0001	<0.0001
<i>p</i>						
Baseline Impairment (RL) vs. No Impairment	4.62	4.13	4.51	3.33	NA*	NA*
Odds Ratio	2.09-10.22	1.63-10.43	1.85-10.97	1.10-10.09		
95% CI	0.0002	0.003	0.0009	0.03		
<i>p</i>	NA*	NA*	NA*	2.52	NA*	NA*
Age 60 (RL) vs. >60				1.06-5.99		
Odds Ratio				0.04		
95% CI						
<i>p</i>						

Abbreviations: HVL-T, Hopkins Verbal Learning Test; PCI, prophylactic cranial irradiation; RL, referent level; 95% CI, 95% confidence interval.

\* N/A: Factor not significant on univariate logistic regression analysis.

For HVL-T-Recall and -Delayed Recall comparisons, statistical significance was assigned to  $p < 0.05$ . For SRCF comparisons, statistical significance was assigned to  $p < 0.0001$  to prevent inflation of type I error from multiple testing of EORTC QLQ-C30.

**Table 3**

Correlations between decline in self-reported cognitive functioning and decline in HVLТ or other EORTC QLQ-C30 functional or symptom scales at 6 and 12 months follow-up.

		Self-Reported Cognitive Functioning		p value*
		Decline	No decline	
<b>HVLТ-Recall</b>	6 Months			0.05
	Decline	24 (9%)	28 (10%)	
	No decline	68 (25%)	147 (55%)	
	<i>Kappa (p**)</i>	<i>0.113 (0.05)</i>		
	12 Months			0.86
	Decline	16 (9%)	25 (14%)	
	No decline	60 (33%)	83 (45%)	
<i>Kappa (p**)</i>	<i>-0.023 (0.74)</i>			
<b>HVLТ-Delayed Recall</b>	6 Months			0.02
	Decline	27 (11%)	27 (11%)	
	No decline	60 (24%)	133 (54%)	
	<i>Kappa (p**)</i>	<i>0.155 (0.01)</i>		
	12 Months			0.54
	Decline	14 (8%)	17 (10%)	
	No decline	52 (31%)	83 (50%)	
<i>Kappa (p**)</i>	<i>0.046 (0.50)</i>			
<b>Global Health Status/QOL</b>	6 Months			0.02
	Decline	45 (14%)	52 (16%)	
	No decline	74 (23%)	150 (47%)	
	<i>Kappa (p**)</i>	<i>0.126 (0.02)</i>		
	12 Months			0.44
	Decline	27 (13%)	33 (16%)	
	No decline	59 (28%)	93 (44%)	
<i>Kappa (p**)</i>	<i>0.055 (0.41)</i>			
<b>Physical Functioning</b>	6 Months			<0.0001
	Decline	46 (14%)	33 (10%)	
	No decline	73 (23%)	170 (53%)	
	<i>Kappa (p**)</i>	<i>0.241 (&lt;0.0001)</i>		
	12 Months			<0.0001
	Decline	38 (18%)	20 (9%)	
	No decline	48 (23%)	106 (50%)	
<i>Kappa (p**)</i>	<i>0.299 (&lt;0.0001)</i>			
<b>Role Functioning</b>	6 Months			0.0002

		Self-Reported Cognitive Functioning		
		Decline	No decline	p value*
	Decline	50 (16%)	45 (14%)	
	No decline	69 (21%)	158 (49%)	
	<i>Kappa (p **)</i>	0.207 (0.0002)		
	12 Months			0.007
	Decline	31 (15%)	24 (11%)	
	No decline	55 (26%)	102 (48%)	
	<i>Kappa (p **)</i>	0.180 (0.006)		
<b>Emotional Functioning</b>	6 Months			0.05
	Decline	27 (8%)	28 (9%)	
	No decline	92 (29%)	175 (54%)	
	<i>Kappa (p **)</i>	0.100 (0.04)		
	12 Months			0.005
	Decline	29 (14%)	21 (10%)	
	No decline	57 (27%)	105 (50%)	
	<i>Kappa (p **)</i>	0.183 (0.004)		
<b>Social Functioning</b>	6 Months			0.0003
	Decline	40 (12%)	31 (10%)	
	No decline	79 (25%)	172 (53%)	
	<i>Kappa (p **)</i>	0.200 (0.0001)		
	12 Months			0.03
	Decline	27 (13%)	23 (11%)	
	No decline	59 (28%)	103 (49%)	
	<i>Kappa (p **)</i>	0.141 (0.03)		
<b>Fatigue</b>	6 Months			<0.0001
	Decline	64 (20%)	57 (18%)	
	No decline	54 (17%)	146 (45%)	
	<i>Kappa (p **)</i>	0.260 (<0.0001)		
	12 Months			0.002
	Decline	42 (20%)	35 (17%)	
	No decline	44 (21%)	91 (43%)	
	<i>Kappa (p **)</i>	0.214 (0.002)		
<b>Nausea and Vomiting</b>	6 Months			0.04
	Decline	27 (8%)	27 (8%)	
	No decline	92 (29%)	176 (55%)	
	<i>Kappa (p **)</i>	0.106 (0.03)		
	12 Months			0.55
	Decline	14 (7%)	16 (8%)	



		Self-Reported Cognitive Functioning		
		Decline	No decline	p value*
	No decline	72 (24%)	110 (52%)	
	<i>Kappa (p**)</i>	<i>0.040 (0.46)</i>		
<b>Pain</b>	6 Months			0.0006
	Decline	49 (15%)	46 (14%)	
	No decline	70 (22%)	156 (49%)	
	<i>Kappa (p**)</i>	<i>0.192 (0.0005)</i>		
	12 Months			0.03
	Decline	33 (16%)	30 (14%)	
	No decline	53 (25%)	96 (45%)	
	<i>Kappa (p**)</i>	<i>0.152 (0.02)</i>		
<b>Dyspnea</b>	6 Months			0.47
	Decline	27 (9%)	38 (12%)	
	No decline	92 (29%)	164 (51%)	
	<i>Kappa (p**)</i>	<i>0.043 (0.40)</i>		
	12 Months			0.87
	Decline	18 (8%)	28 (13%)	
	No decline	68 (32%)	98 (46%)	
	<i>Kappa (p**)</i>	<i>-0.014 (0.82)</i>		
<b>Insomnia</b>	6 Months			0.05
	Decline	34 (11%)	38 (12%)	
	No decline	85 (27%)	163 (51%)	
	<i>Kappa (p**)</i>	<i>0.105 (0.05)</i>		
	12 Months			0.06
	Decline	30 (14%)	29 (14%)	
	No decline	55 (26%)	96 (46%)	
	<i>Kappa (p**)</i>	<i>0.127 (0.06)</i>		
<b>Appetite Loss</b>	6 Months			<0.0001
	Decline	56 (17%)	44 (14%)	
	No decline	63 (20%)	159 (49%)	
	<i>Kappa (p**)</i>	<i>0.263 (&lt;0.0001)</i>		
	12 Months			0.002
	Decline	27 (13%)	16 (8%)	
	No decline	57 (27%)	108(52%)	
	<i>Kappa (p**)</i>	<i>0.209 (0.0008)</i>		
<b>Constipation</b>	6 Months			0.10
	Decline	34 (11%)	41 (13%)	

		Self-Reported Cognitive Functioning		
		Decline	No decline	p value*
	No decline	85 (26%)	162 (50%)	0.009
	<i>Kappa (p**)</i>	0.091 (0.09)		
	12 Months			
	Decline	29 (14%)	22 (10%)	
	No decline	56 (27%)	103 (49%)	
	<i>Kappa (p**)</i>	0.177 (0.006)		
<b>Diarrhea</b>	6 Months			0.58
	Decline	15 (5%)	21 (7%)	
	No decline	104 (32%)	181 (56%)	
	<i>Kappa (p**)</i>	0.026 (0.54)		
	12 Months			0.06
	Decline	13 (6%)	8 (4%)	
No decline	73 (35%)	117 (55%)		
<i>Kappa (p**)</i>	0.099 (0.04)			
<b>Financial Difficulties</b>	6 Months			0.01
	Decline	25 (8%)	21 (7%)	
	No decline	93 (29%)	181 (57%)	
	<i>Kappa (p**)</i>	0.124 (0.008)		
	12 Months			0.11
	Decline	17 (8%)	14 (7%)	
No decline	69 (33%)	110 (52%)		
<i>Kappa (p**)</i>	0.094 (0.09)			

Abbreviations: HVLT, Hopkins Verbal Learning Test.

\* P-value from Fisher's exact test. To prevent inflation from type 1 error due to multiple testing, statistical significance was assigned to p-values <0.0001.

\*\* P-value from Z-test. To prevent inflation from type 1 error due to multiple testing, statistical significance was assigned to p-values <0.0001.