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ORIGINAL REPORT

Phase III Trial of Prophylactic Cranial Irradiation Compared With Observation in Patients With Locally Advanced Non–Small-Cell Lung Cancer: Neurocognitive and Quality-of-Life Analysis

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ABSTRACT

Purpose
There are scant data regarding the effects of prophylactic cranial irradiation (PCI) on neurocognitive function (NCF) and quality of life (QOL). Radiation Therapy Oncology Group trial 0214 showed no overall survival (OS) benefit for PCI in stage III non–small-cell lung cancer (NSCLC) at 1 year. However, there was a significant decrease in brain metastases (BM). This analysis focuses on the impact of PCI on NCF and QOL.

Patients and Methods
Patients with stage III NSCLC who completed definitive therapy without progression were randomly assigned to PCI or observation. NCF was assessed with Mini-Mental Status Examination (MMSE), Activities of Daily Living Scale (ADLS), and Hopkins Verbal Learning Test (HVLT). QOL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) core tool (QOL Questionnaire-QLQC30) and brain module (QLQBN20).

Results
There were no statistically significant differences at 1 year between the two arms in any component of the EORTC-QLQC30 or QLQBN20 ($P > .05$), although a trend for greater decline in patient-reported cognitive functioning with PCI was noted. There were no significant differences in MMSE ($P = .60$) or ADLS ($P = .88$). However, for HVLT, there was greater decline in immediate recall ($P = .03$) and delayed recall ($P = .008$) in the PCI arm at 1 year.

Conclusion
PCI in stage III NSCLC significantly decreases the risk of BM without improving 1-year OS. There were no significant differences in global cognitive function (MMSE) or QOL after PCI, but there was a significant decline in memory (HVLT) at 1 year. This study provides prospective data regarding the relative risks and benefits of PCI in this setting and the need to use sensitive cognitive assessments.

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INTRODUCTION

The addition of chemotherapy to radiation therapy and/or surgery for the treatment of locally advanced (LA) non–small-cell lung cancer (NSCLC) improves survival and reduces extracranial distant metastases.[1-5] However, it does not decrease the relatively high rate of brain metastases (BM) and as a result, the brain has emerged as one of the most frequent sites of initial failure.[6-18]

Radiation Therapy Oncology Group (RTOG) recently conducted a study to evaluate the impact of prophylactic cranial irradiation (PCI) in stage III NSCLC—RTOG trial 0214. We showed that PCI significantly decreases the risk of BM from 18% to 7.7% at 1 year. There were no statistically significant differences in overall survival (OS) or disease-free survival (DFS) at 1 year. The article by Gore et al[18b] in this issue is dedicated to discussing the details of OS, DFS, and the impact of PCI on BM.

BM often have a devastating impact on neurocognitive function (NCF) and quality of life (QOL). PCI has been shown to prevent or delay the incidence of BM in NSCLC.[19-21] However, it can also cause toxicity resulting in a decline in NCF and QOL. Therefore, in conjunction with the above

mentioned end points of this study, a detailed assessment of the end points of NCF and QOL was performed to formally assess these important end points in this phase III trial.

PATIENTS AND METHODS

Study Design

We conducted a multicenter, phase III, prospective randomized study. Patients with stage IIIA/B NSCLC without disease progression after completing definitive therapy were randomly assigned to PCI or observation. PCI was delivered to a total dose of 30 Gy/15 fractions, once daily. The primary end point was OS. Secondary end points included DFS, incidence of BM, NCF, and QOL. NCF data collected at baseline, 3, 6, and 12 months after study entry were used for this analysis. Additional time points included 18, 24, 30, 36, and 48 months. QOL data was collected at baseline, 6, and 12 months after study entry with additional time points at 24, 36, and 48 months.

NCF and QOL Instruments

NCF was assessed using the Mini-Mental Status Examination (MMSE), Hopkins Verbal Learning Test (HVLT),[22] and Activity of Daily Living Scale (ADLS).[23] MMSE is a rapidly and easily administered tool used to detect mild dementia.[24] The HVLT is a well-validated and reliable assessment of memory, including encoding, retrieval, and retention of new information over time.[25,26] ADLS complements both the MMSE and HVLT by providing vital information on day-to-day patient function, which is not covered by MMSE, HVLT, or physical examination.[27]

QOL was assessed with the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life QLQ-C30 Questionnaire (QLQ-C30) and BN20. Both the EORTC QLQ-C30 and the BN20 have previously been shown to be reliable and valid instruments in the setting of recurrent high-grade gliomas.[28,29] The QLQ-C30 is a 30-item, self-report questionnaire.[30] Prior studies have demonstrated this questionnaire to have adequate reliability in patients with lung, breast, ovarian, and head and neck cancer,[31-34] as well as other cancer diagnoses.[35,36] The BN20 is a supplemental questionnaire specifically developed for use with the general questionnaire (QLQ-C30) in patients with brain tumors.[29]

Statistical Methods

The reliable change index (RCI)[37] is derived from the SE of measurement SEM[38] for MMSE and HVLT. The SEM is calculated from the test-retest reliability (r) and the standard deviation of test scores (SD): $SEM = SD(1\text{-}r)^{1/2}$. The SE of difference is then calculated: $SE_{diff} = [2(SEM^2)]^{1/2}$. Cognitive failure at 1 year was evaluated by MMSE and the cutoff was calculated using RCI with $r = 0.83$ and $SD = 2$. Patients with MMSE at or below the cutoff at 1 year were considered cognitive failures. NCF deterioration was defined as a more than or equal to cutoff points drop in RCI of HVLT immediate recall (IR) and delayed recall (DR) at 1 year from baseline. This RCI index is derived with $r = 0.74$ and $SD = 4.325$ for IR, and $r = 0.66$ and $SD = 1.975$ for DR. ADLS was scored as independent versus dependent. Patients who require assistance in any one of the six categories were defined as being dependent.

The primary QOL end points were measured on three different QLQ-C30 scales: global health status/QOL; cognitive functioning; and fatigue. Secondary QOL end points were measured on two QLQ-BN20 scales: future uncertainty and communications deficit. A decline for an individual patient was calculated as a decrease in more than 10 points in the scale score from the baseline measurement to the 1-year measurement. Analysis of the percent of patients with failure at 1 year was performed using a two-sample proportions test statistics. Hommel's stage-wise rejective multiple-test procedure[39] was then used to determine if each individual test should be rejected. In a similar way, for ADLS, analysis of the percentage of patients who remained independent at 1 year and were independent at baseline was performed using two-sample t-test statistics. The change score of each instrument from baseline and the score at baseline were tested using a Wilcox rank sum test.[40] All testing was done at the overall significance level of .05. SAS version 9.2 (SAS Institute, Cary, NC) was used to perform these analyses.

RESULTS

This study opened on September 19, 2002, and closed due to inadequate accrual on August 30, 2007. Targeted accrual was 1,058 patients, and accrual was projected to be 29 patients/month. The total accrual for the study was 356 patients. Among 356 patients entered onto this study, nine patients were ineligible and seven patients withdrew consent. Therefore, 340 patients were evaluable for this study (Fig 1).

Table 1 illustrates the compliance to NCF and QOL assessments at baseline and over the first year of follow-up. At least 90% of patients

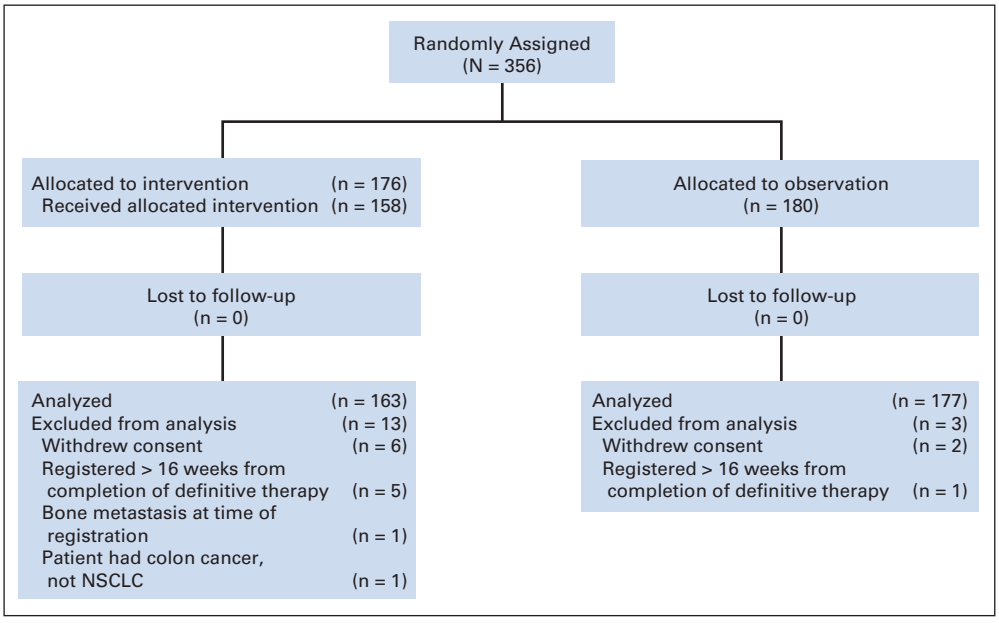

Fig 1. CONSORT diagram. NSCLC, non–small-cell lung cancer.

Table 1. Neurocognitive and QOL Assessment Compliance

Evaluation Status by Treatment Arm and Assessment	Baseline	At 3 Months	At 6 Months	At 12 Months
MMSE				
PCI				
Expected	163	159	152	125
Dead/alive and not evaluated	0/8	4/90	7/89	27/82
Received	155	69	63	43
%	95	43	41	34
Observation				
Expected	177	172	163	139
Dead/alive and not evaluated	0/8	5/86	9/93	24/87
Received	169	86	70	52
%	95	50	43	37
Difference	0	7	2	3
P	1.00	.20	.72	.61
HVLT				
PCI				
Expected	163	159	152	125
Dead/alive and not evaluated	0/11	4/95	7/92	26/84
Received	152	64	60	42
%	93	40	39	34
Observation				
Expected	177	172	163	139
Dead/alive and not evaluated	0/9	5/93	9/100	24/91
Received	168	79	63	48
%	95	46	39	35
Difference, %	2	6	0	1
P	.44	.27	1.00	.86
ADLS				
PCI				
Expected	163	159	152	125
Dead/alive and not evaluated	0/7	4/90	7/82	27/80
Received	156	69	70	45
%	96	43	46	36
Observation				
Expected	177	172	163	139
Dead/alive and not evaluated	0/10	5/86	9/89	24/87
Received	167	86	74	52
%	94	50	45	37
Difference, %	2	7	1	1
P	.40	.20	.86	.87
QLQ-C30/BN20				
PCI				
Expected	163	NA	152	125
Dead/alive and not evaluated	0/16	NA	11/80	26/84
Received	147	NA	72	42
%	90		47	34
Observation				
Expected	177	NA	163	139
Dead/alive and not evaluated	0/15	NA	14/92	24/89
Received	162	NA	71	50
%	92		44	36
Difference, %	2	NA	3	2
P	.52		.59	.73

NOTE. *P* value is from the two-sample z-test to compare the percentage of received forms between the two arms.
Abbreviations: QOL, quality-of-life; MMSE, Mini-Mental Status Examination; PCI, prophylactic cranial irradiation; HVLT, Hopkins Verbal Learning Test; ADLS, Activities of Daily Living Scale; QLQ-C30, Quality-of-Life Questionnaire C30; BN20, brain module N20; NA, not available.

completed a baseline assessment on all NCF and QOL measures. There were no statistically significant differences (SSD) in compliance of these instruments between the two arms.

There were no SSD in change scores at 12 months from baseline between the two arms among any QOL components included in the EORTC QLQ-C30 or QLQ-BN20 (all adjusted *P* values $> .05$). This was the same at baseline and at 6 months from baseline (adjusted *P* values $> .05$).

Table 2 shows the deterioration status as defined by a decrease in more than 10 points in the scale score from baseline to 1 year on the

Table 2. Testing of Deterioration Status From Baseline in European Organisation for the Research and Treatment of Cancer QOL Questionnaire C30

Component by Time Point	PCI				Observation					
	Deterioration		No Deterioration		Deterioration		No Deterioration			
	No.	%	No.	%	No.	%	No.	%	*P**	Adjusted *P*†
6 months										
Global health status/QOL	24	35	45	65	22	32	46	68	.76	.98
Cognitive functioning	24	35	44	65	12	18	56	82	.02	.24
Fatigue	49	21	41	59	22	32	46	68	.27	.98
12 months										
Global health status/QOL	8	22	29	78	16	34	31	66	.20	.98
Cognitive functioning	15	41	22	59	12	25	35	74	.14	.98
Fatigue	13	34	25	66	13	28	34	72	.52	.98

Abbreviations: PCI, prophylactic cranial irradiation; QOL, quality of life.
*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.
†Adjusted using the Hommel's method; adjustment is made within time point.

QLQ-C30. Again, there were no SSD at 6 or 12 months from baseline among any QOL components on either the QLQ-C30 or QLQ-BN20 scale (adjusted *P* values $> .05$). Although a trend for greater decline in patient-reported cognitive functioning with PCI was noted (unadjusted $P = .02$ at 6 months).

The MMSE change scores from baseline indicate no SSD between the two arms at any time point except at 3 months ($P = .01$). The percentage of people who had NCF deterioration by RCI criteria of MMSE are presented in Table 3. The percentage of people who had deteriorated MMSE at 12 months is not SSD between the two arms (Table 3; $P = .60$). However, there is a SSD between the two arms at 3 months ($P = .04$).

For ADLS, the percentages of people who remain independent at 12 months who were independent at baseline were not SSD between the two arms ($P = .88$) nor were they at 3 and 6 months.

However, for HVLT, there was significantly greater deterioration in IR ($P = .03$) and DR ($P = .008$) in the PCI arm at 1 year, the protocol specified end point. Table 4 presents the deterioration status of HVLT using the RCI at 3, 6, and 12 months from baseline between the two arms. In addition, there was a statistically significant greater deterioration in IR in the PCI arm at 3 and 6 months ($P < .0001$ and $P = .045$, respectively) and for DR at 3 months ($P < .001$), but not at 6 months ($P = .81$). The raw scores and change scores for HVLT-IR and DR between the two arms is illustrated in Figure 2.

In an attempt to age stratify the results (> 60, n = 106 [65%] PCI arm; n = 102 [58%] no PCI) no SSD at 1 year in NCF or QOL between patients ≤ 60 or older than 60 years on either arm (all adjusted *P* values $> .05$) was found.

DISCUSSION

A number of randomized and nonrandomized trials have unequivocally shown that PCI is effective in reducing BM in LA-NSCLC. However, unlike small cell lung cancer (SCLC),[41,42] PCI has not been associated with a survival benefit in NSCLC. This study was designed with survival as the primary end point. In a separate report, our study has shown that patients with LA-NSCLC who received no PCI are 2.52 times more likely to develop BM than patients who received PCI. Although PCI decreased the incidence of BM, there was no OS or DFS advantage at 1 year. It is possible that a survival advantage may become evident with longer follow-up. This report focuses on a comprehensive evaluation of NCF and QOL in order to improve our understanding of the effects of PCI on patients with LA-NSCLC.

To date, there is very limited data available regarding the effects of PCI on NCF and QOL in patients with NSCLC with the majority of studies carried out in SCLC. This is due to the lack of intensive NCF and QOL testing in NSCLC trials. This study is the first randomized study of PCI in NSCLC to incorporate prospective NCF and QOL end points. In addition, we have incorporated validated instruments of NCF and QOL using clinically relevant criteria and each patient serves as his/her own control. By doing this, this study can be instrumental in

Table 3. Testing of Deterioration Status From Baseline in Mini-Mental Status Examination During Follow-Up Using Reliable Change Index

Time Point (months)	Prophylactic Cranial Irradiation				Observation				
	Deterioration		No Deterioration		Deterioration		No Deterioration		
	No.	%	No.	%	No.	%	No.	%	*P**
3	23	36	41	64	17	21	65	79	.04
6	17	28	44	72	17	25	52	75	.68
12	9	23	31	78	9	18	41	82	.60

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.

Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

Component by Time Point	PCI				Observation					
	Deterioration		No Deterioration		Deterioration		No Deterioration			
	No.	%	No.	%	No.	%	No.	%	*P**	Adjusted *P*†
3 months										
Recall	28	45	34	55	10	13	66	87	< .001	< .001
Delayed recall	25	44	32	56	7	10	64	90	< .001	< .001
6 months										
Recall	11	19	46	81	3	5	58	95	.02	.045
Delayed recall	8	15	44	85	8	14	50	86	.81	.81
12 months										
Recall	10	26	28	74	3	7	42	93	.01	.03
Delayed recall	10	32	21	68	2	5	38	95	.003	.008

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.
†Adjusted using the Hommel's method; adjustment is made within time point.

better defining the value of PCI in this setting. It is the therapeutic ratio of benefits versus risks that helps determine the advisability of a treatment. These findings can enable us to develop strategies that can potentially increase the benefits and decrease the risks. Potential strategies that can increase the benefits are discussed in more detail in a separate report. It may require better ways of identifying a subgroup of patients with the highest risk of developing BM, such as those with adenocarcinoma, young age, high volume of disease, and predictive markers. These are the patients most likely to benefit from PCI.

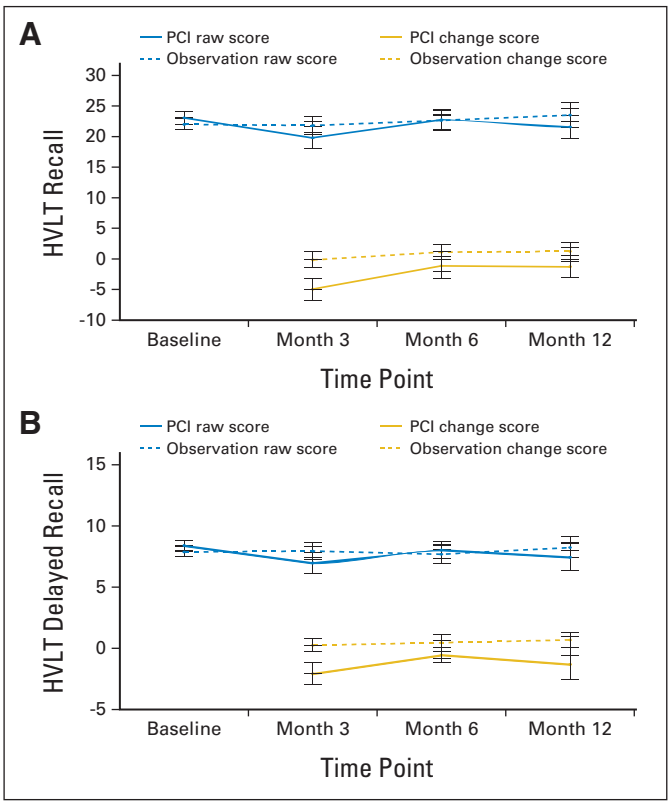

Fig 2. Hopkins Verbal Learning Test (HVLT) recall and delayed-recall raw and change scores. PCI, prophylactic cranial irradiation.

In order to develop strategies to decrease the risks, we must identify and understand those risks. To further identify a subgroup of patients with the highest risk of developing NCF and QOL toxicities, we analyzed the data according to age, however, no clear differences at 1 year emerged in NCF or QOL between patients ≤ 60 or older than 60 years on either arm (all adjusted *P* values > .05). We attempted to identify other patient factors such as hypertension or diabetes, but the data were too limited to allow any meaningful analysis.

In studies of patients with BM, NCF decline correlates with tumor growth[43] and tumor shrinkage (with whole-brain radiation therapy [WBRT]) correlates with preservation of NCF.[44] We attempted to separate those patients who did or did not develop BM. However, due to the small number of patients who developed BM, no significant differences in NCF or QOL could be detected in these patients compared to those without BM.

Prior studies report limited and acceptable adverse effects of PCI on NCF in patients with NSCLC. Stuschke et al[45] studied NCF and brain magnetic resonance imaging in patients with LA-NSCLC after PCI. T2-weighted magnetic resonance imaging revealed white matter abnormalities of higher grade in patients who received PCI than in those who did not. There was a trend toward impaired NCF in patients with higher-degree white matter abnormalities. Impairments in attention and visual memory in long-term survivors was seen in both PCI and non-PCI patient groups.

Pottgen et al[46] performed a battery of NCF tests on 11 long-term survivors of stage IIIA NSCLC treated surgically. Five patients were treated with chemotherapy, thoracic radiation, surgery, and PCI (30 Gy/15 fractions). There was no difference in any of the NCF testing between patients with and without PCI. A slightly reduced NCF in comparison with age-matched normal population was found for patients in both treatment groups.

This study did have a number of limitations. The main limitation in assessing the primary objective of the study was that the accrual goal was not reached thus limiting the power to detect a difference in survival. In terms of assessing the secondary objectives of the impact of PCI on NCF and QOL, the main limitation was the decline in compliance with NCF and QOL testing over time. However, this challenge plagues most studies in patients with advanced cancers, as noted in a systematic review.[47] In addition, since the accrual goal was not

Table 5. Prospective Trials in Lung Cancer

Prospective Trials in Lung Cancer	Total No.	Baseline*	6 Months*	12 Months*	18 Months*	30 Months*
Incorporating NCF						
RTOG 0214 (PCI-NSCLC)	340	324	144	97	—	—
PCI-SCLC (Gregor)	314	125	59	32	—	—
PCI-SCLC (Arriagada)	300	229	—	—	33	23
Incorporating QOL						
RTOG 0214 (PCI-NSCLC)	340	309	143	92		
PCI-SCLC (Slotman)	286	268	79	22		

Abbreviations: NCF, neurocognitive function; RTOG, Radiation Therapy Oncology Group; PCI, prophylactic cranial irradiation; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; QOL, quality of life.
*Actual No. of patients who completed NCF and QOL testing.

reached, power estimates are limited and this is often a problem when trials are powered for clinical end points rather than QOL end points.[48] The compliance rate at 12 months fell to between 34% and 37% for all NCF and QOL measures. However, the majority of the decline was because the windows defined for collection of the data was quite strict (within 2 weeks from specified time point), such that most of the missing data was due to assessments done either too early or too late (rather than never completed at all) and were therefore not included in the analysis. Moreover, the actual number of patients who completed NCF and QOL testing in this study compares favorably when compared to other prospective randomized controlled PCI studies incorporating these end points (Table 5).[49,50,52]

Two randomized controlled trials of PCI in patients with SCLC have examined NCF as an outcome. Arriagada et al[49] found no statistically significant differences between the PCI and observation groups in the relative risks of 2-year cumulative incidence of NCF changes. Gregor et al[50] reported that new cognitive impairments were observed at 6 and 12 months, but there were no notable differences between the PCI and control groups.

In the recently completed randomized study, RTOG 0212 (PCI in SCLC),[51] Wolfson et al found a significant increase at 1 year of NCF decline in the higher-dose PCI arms (36 Gy) compared to the standard-dose PCI arm (25 Gy; $P = .02$). This further supports the NCF findings in our study, comparing PCI (30 Gy) to observation. Of course, the benefit versus risk ratio is quite different in SCLC, in which a survival benefit with PCI exists.

Slotman et al[52] recently reported on QOL assessments in a randomized study of PCI in patients with extensive-stage SCLC. Slotman et al state that only data obtained up to 9 months were included in the analysis because of the small number of patients' data at 1 year. However, even at 9 months, only 38 patients in total completed the QOL assessments. They found that short-term results up to 3 months showed there was a negative impact of PCI on selected QOL scales. The largest mean difference between the two arms was observed for fatigue and hair loss. For global health status, the observed mean difference was 8 points on a scale 0 to 100 at 6 weeks ($P = .018$) and 3 months ($P = .055$). These observed differences were below the cutoff of a 10-point difference for clinical significance. At 6 and 9 months, there was no difference between the two arms with almost identical mean scores. Their 6- and 9-month results are consistent with our 6- and 12-month results showing no difference between the two arms. This study also revealed an OS advantage with the administration of PCI for patients with extensive-stage SCLC.

An interesting finding in our study is that we found that early changes (ie, 3 months) were more dramatic and significant than later changes (ie, 6, 12 months) with respect to NCF (we did not include a time point earlier than 6 months for QOL). For MMSE, although the protocol-specified end point, cognitive failure at 12 months, is not SSD between the two arms ($P = .60$), there is a SSD between the two arms at 3 months ($P = .04$), which was not significant at 6 months ($P = .68$). For HVLT-IR, the most significant change was at 3 months ($P < .001$), which remained significant at 6 months (but to a lesser degree; $P = .045$) and 12 months ($P = .03$), HVLT-DR also had the most significant change at 3 months ($P < .001$), which became not significantly different at 6 months ($P = .81$), but then became significant again at 12 months ($P = .008$), the protocol-specified end point. The differences between MMSE and HVLT may be because the HVLT has better sensitivity than the MMSE in detecting patients with mild dementia.[23] However, the similarities bring up the possibility of recovery with time of diminished recall. For instance, one explanation may be that acutely (up to 3 months) there is an immediate decline from PCI (MMSE, IR, DR); followed by some degree of subacute (6 months) recovery (MMSE, IR, DR); followed by a chronic (12 months) decline (DR) or stabilization (MMSE, IR). It is unknown if the chronic (> 12 months) changes become more long-term or permanent, or if there is some recovery with more time. We will need more follow-up data beyond 12 months to assess these possibilities.

How can we further reduce missing QOL data? RTOG has a pilot study testing a Health Insurance Portability and Accountability Act–compliant, electronic web-based system (Visiontree; VisionTree Software, San Diego, CA) that allows patients to complete the QOL forms online (RTOG 0828).

The results of this study enable us to develop strategies that can potentially decrease the risks associated with PCI. One such strategy is to test agents that protect NCF (RTOG 0614—phase III study testing memantine's ability to reduce cognitive dysfunction from WBRT for BM). Another strategy may be to develop a conformal PCI technique that may spare memory function—hippocampal avoidance (to protect neuronal progenitor cells in this region) as per Gutierrez et al.[53] An additional strategy would be to closely observe patients with imaging and apply WBRT or focused stereotactic radiosurgery as needed.[6,54]

In conclusion, PCI significantly decreases the risk of BM for patients with stage III NSCLC with no significant differences in OS or DFS. At 1 year, there were no significant differences in global cognitive function (MMSE) or QOL after PCI, but there was a significant decline in memory (HVLT). This study more accurately characterizes

NCF and QOL changes in NSCLC patients receiving PCI and demonstrates the need to use sensitive cognitive assessments. RTOG 0214 provides prospective data regarding the relative benefits and risks of PCI in this setting.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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