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CLINICAL INVESTIGATION

"Hope" Drives Quality of Life in Patients With Brain Metastases, But, the "Hope Center" Remains Elusive: An Analysis of NRG-CC003

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Purpose: NRG-CC003 randomized 393 patients with small cell lung cancer to prophylactic cranial irradiation (PCI) with or without hippocampal avoidance (HA). "Hopefulness" is a cognitive construct with 3 components: goals, pathways, and agency. Hope is measurable with validated instruments. Since hope is cognitive in nature, the existence of a "hope center" in the brain

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—most likely in the hippocampus—has been hypothesized. One exploratory objective of NRG-CC003 posited that if hope levels were better maintained in patients randomized to PCI + HA, then the hippocampus would be implicated in the mechanism of hopefulness.

Methods and Materials: PCI consisted of 10 fractions of 2.5 Gy. The Adult Hope Scale (AHS) was administered at time-zero and at 6 months. Regarding patient-reported outcome measures, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 was administered at baseline and at 3, 6-, 12-, 18- and 24-month intervals. Comparisons of AHS scores by arm were made using Wilcoxon−Mann−Whitney tests, and correlation of AHS with EORTC QLQ-C30 by Pearson correlation coefficients.

Results: Approximately 95% completed the AHS at baseline and 67% filled out the questionnaire at 6 months paralleling the completion rates of the conventional tools for QOL and neurocognition. When comparing hope levels (change from baseline to 6 months) there was no significant difference ($P > .05$) between the 2 arms of the trial. There was a correlation for the components of hopefulness with QOL; specifically, between change in agency score and QLQ-C30 global health status ($\rho = 0.27$, $P < .0001$) as well as between change in pathways score and QLQ-C30 global health status ($\rho = 0.16$, $P = .022$).

Conclusions: It is feasible to study hopefulness in the context of prospective trials conducted within the National Clinical Trials Network. The hippocampus could not be implicated as a critical structure in a central pathway that coordinates hopefulness. For the first time, validated tools established a relationship between hope and quality of life among cancer patients.

Introduction

The NRG-CC003 trial[1] was a phase 2/3 study in which patients with small cell lung cancer (SCLC) were randomly assigned to prophylactic cranial irradiation with or without hippocampal avoidance (PCI vs HA-PCI). Previously, NRG Oncology conducted a single-arm trial (RTOG 0933) which demonstrated that protecting the hippocampus during whole brain radiation therapy for brain metastases preserved memory and quality of life.[2] The unique design of NRG-CC003 allowed us to pose mechanistic questions pertaining to, arguably, the most important existential resource[3,4] cherished by patients: hope.

Nearly 4 decades ago, Snyder[5] published a cluster of articles in which Hope Theory was elaborated. Hence, a concept which was deemed amorphous was operationalized. Snyder's[5] model presupposed 3 prerequisites for hope to thrive: goals, pathways, and agency. A goal is an objective worthy of pursuit. Goals are best when both meaningful and possible. Pathways reflect strategies for achieving goals. Hopeful people intuit multiple pathways to circumvent obstacles that arise. Finally, agency is the motivation to pursue a pathway toward a particular goal. Snyder's group[6-8] also developed validated scales to measure hope. Because the model was cognitive, it was presumed that hope was rooted in the brain and the hippocampus was considered the lead candidate for the neural basis of hope.[9,10]

Prior to inaugurating NRG-CC003, a priori permission was granted by the leadership of NRG Oncology to append a hope instrument to the protocol. Because hope had never been evaluated by any of the member groups of the National Clinical Trials Network (NCTN), a decision was made to proceed cautiously; merely 1 tool to gauge hopefulness was added and measurements were made at only 2 timepoints (baseline and 6 months from initiating irradiation).

The decision by NRG Oncology to include an unorthodox measure in a battery of relatively standardized patient-reported outcome measures, enabled hope to be statistically regarded as both a dependent and an independent variable. In the context of hope as a dependent variable, a thought-provoking hypothesis was proposed. Specifically, if at 6months hope levels were better maintained among those randomized to HA, then circumstantial evidence would be available to both implicate the hippocampus in a central pathway for hope, and to demonstrate its radiation dose dependence. Conversely, for the condition wherein hope is viewed as an independent variable, correlation could be made between hope and a variety of traditional endpoints including QOL. Although researchers have speculated about the latter relationships in the past,[11] conclusions were consistently weakened by the fact that validated tools were not employed. Furthermore, the reports contained relatively small numbers of patients who were assessed only by retrospective means. Accordingly, we embarked on the present analysis because it enabled a systematic, prospective evaluation of hope using a standardized tool administered at prespecified timepoints. This effort constituted the first attempt by a group within the NCTN to incorporate a validated measure to assess hope in a prospective trial.

Methods and Materials

Eligibility

Details on patient eligibility and treatment have been described.[12] In brief, eligibility for NRG-CC003 stipulated histologic proof of SCLC. All patients had Zubrod performance status of 0 to 2. Patients were defined as having limited-stage SCLC after undergoing work-up that included history/physical examination and no progression at any site with conventional imaging. Absence of brain metastases at "time zero" was documented by gadolinium contrast-enhanced magnetic resonance imaging of the brain.

Radiation treatment

In the control arm of the study, the whole brain was treated with 3-dimensional radiation therapy; however, the hippocampus was not protected. In the experimental arm of the study, whole brain radiation therapy with HA was delivered with intensity-modulated radiation therapy. In both arms, 2.5 Gy was administered daily for a total dose of 25 Gy in 10 fractions. Megavoltage beams of ≥6 MV were prescribed. Immobilization in the supine position was mandatory. Verification imaging was required. Treating physicians demonstrated proficiency on pre-enrollment benchmark cases to be considered "credentialed." Normal structure constraints and compliance criteria are delineated at ClinicalTrials.gov NCT #02635009. The concurrent use of memantine (20 mg target dose)[13] was optional.

Quality of life

Patient-reported outcomes were captured prospectively. The primary measure of quality of life was the EORTC QLQ-C30[14] which was assessed at baseline and then at 3-, 6-, 12-, 18-, and 24-months. Hope was measured with the Adult Hope Scale (AHS), a 12-item scale (4 items comprising the "agency subscale score," 4 items comprising the "pathways subscale score," and 4 distractors) used to measure "trait hope."[6] The AHS was administered at baseline and at 6 months. Completion of the AHS requires ∼5 minutes. Underlying depression was assessed using the 2-item Patient Health Questionnaire 2 (PHQ-2).[15] The primary endpoint measure of neurocognitive function was the Hopkins Verbal Learning Test - Revised (HVLT-R).[16] Here, too, the cadence of administration included baseline assessment followed by re-evaluation at 3, 6, 12, 18, and 24- months. These validated instruments have all undergone psychometric testing with acceptable reliability as well as validity and can discriminate among patients.

Statistical analysis

Subscale scores of the AHS were calculated by the average of the item scores: agency (items 2, 9, 10, and 12) and pathways (items 1, 4, 6, and 8). The PHQ-2 was used to assess depression between treatment arms. Scores range from 0 to 6, with scores ≥3 indicating depressive symptoms. Pretreatment characteristics were compared between groups using *t* test and categorical variables employing chi-square tests. Comparisons of AHS scores by arm were made using Wilcoxon −Mann−Whitney tests, and correlation of AHS with EORTC QLQ-C30 by Pearson correlation coefficients. Generalized linear models were used to determine the association of pathways and agency score at 6 months with treatment arm, while adjusting for religion (endorse a religion vs not), depression (baseline PHQ-2 score indicating depressed vs not depressed), and stratification factors: SCLC stage (limited vs extended), age (<60 vs ≥60), and planned concurrent memantine use (yes vs no). Similarly, models were run to determine the association of baseline agency and pathway score with each Neurocognitive Function Test (NCF) test. Multiple imputation using Markov chain Monte Carlo algorithms was conducted to impute missing scores for the dependent variable as sensitivity analyses.

Compliance with ethical standards

Before embarking on NRG-CC003, all patients signed an institutional review board-approved, study-specific consent form.

Results

NRG-CC003 opened to accrual in December 2015 and was closed to enrollment in June 2022. Of the 418 screened patients, 196 were randomized to PCI alone and 197 to HA-PCI (Fig. 1). Patient characteristics are displayed in Table 1; baseline characteristics were similar between the allocated groups. The median age was 64 years (range, 34-85). Most patients were white (90.3%). Forty-one per cent of patients had a Zubrod score of 0; 70% had limited-stage disease; and 54.5% had—at most—a high school level education. Approximately half (49%) of the patients in the experimental arm took memantine, whereas 44.4% of patients receiving PCI alone took memantine. A little more than one-quarter of patients classified themselves as either Protestant (24.7%) or Catholic (28.0%) in childhood.

The primary endpoint of neurocognitive deterioration for NRG-CC003 as assessed by HVLT-R Delayed Recall at 6 months was not significantly different between the study arms (30.0% [PCI alone] vs 26.0% [HA-PCI]; $P = .31$). This finding has been interpreted in a separate report.[12]

Figure 1 displays compliance with patient-reported outcome measures. At baseline, 94.9% of patients completed the AHS. Of patients who were alive with consent at 6 months, 66.7% completed the AHS. Similar rates of compliance were recorded at baseline and at 6 months for the EORTC-QLQ30 and HVLT-R instruments, respectively.[12]

At baseline, those professing a formal religious affiliation were more likely to complete the AHS when compared with those who did not (75.3% vs 55.0%; $P = .043$; Table 2A); however, this difference was not significant in patients who completed the AHS at 6 months (74.6% vs 74.0%; $P = .89$; Table 2B).

There were no significant differences between treatment arms (PCI vs HA-PCI) at baseline in both agency and pathway scores (Fig. 2). Likewise, the change from baseline to 6 months was also not significantly different between arms ($P = .42$ for agency,; $P = .24$ for pathway; Fig. 2).

The pathways score at 6 months is predicted by baseline pathways score, stage of illness, religion, and depression (ie, patient with limited SCLC, religious patients, as well as patients who were not depressed, respectively, had more

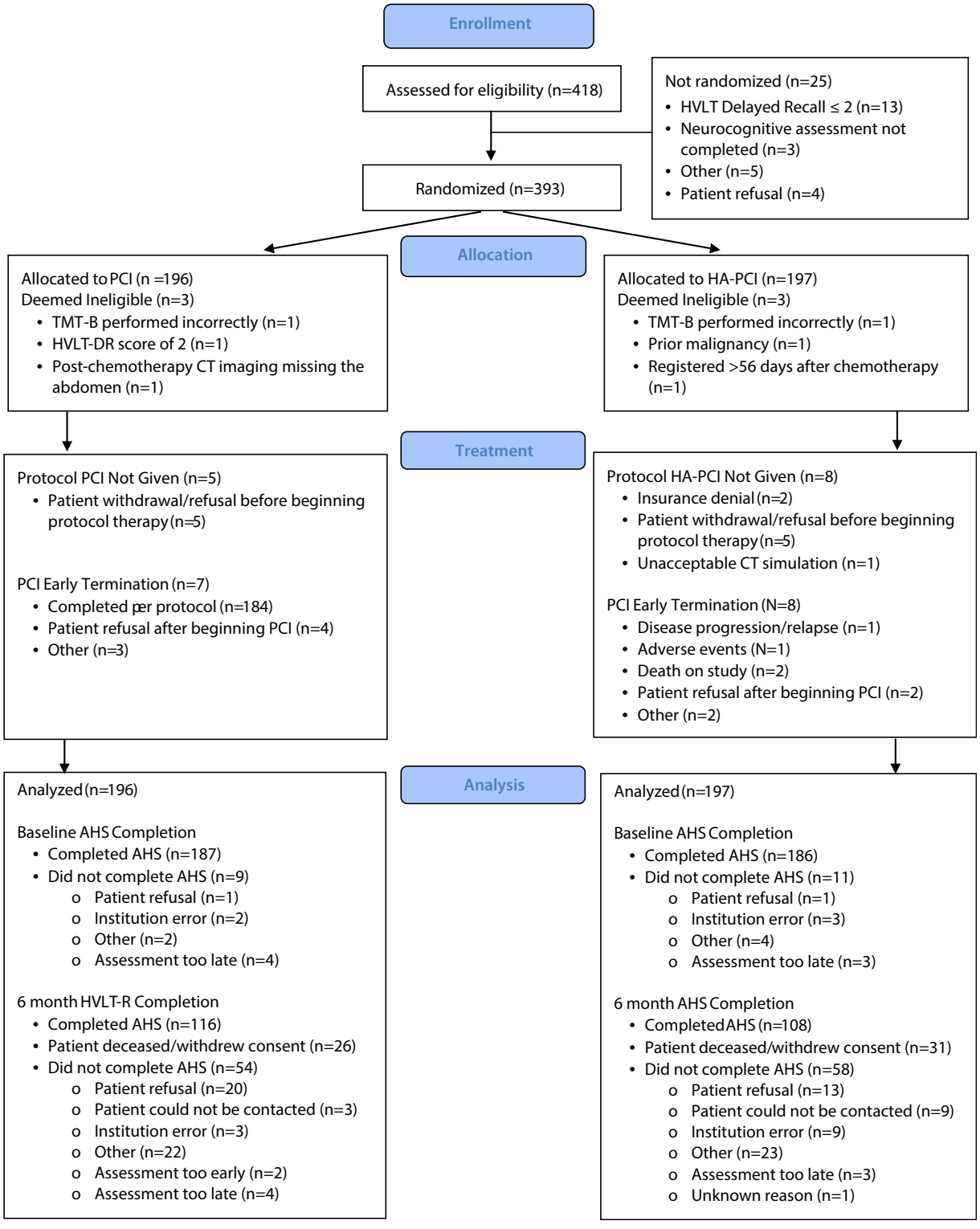

Fig. 1. CONSORT diagram.

pathways-related hopefulness at 6 months). There was no between arm difference (LS mean difference = −0.59;, 95% CI, −1.69-0.51; P = .29). The 6-month agency score was associated with age, stage of illness, and baseline agency score. Similarly, treatment arm was not significant (LS mean difference = 0.12,; 95% CI, −0.97 to 1.21; P = .82). Models using imputed data showed no significant associations for 6-month agency score while baseline pathway score, stage of illness, and depression were significantly associated with 6-month pathway score.

Table 1 Patient and tumor characteristics for all randomized patients

Patient or tumor characteristic	PCI alone (n = 196)	HA-PCI (n = 197)	Total (n = 393)
Age (y)			
Median (range)	64 (34-84)	65 (42-65)	64 (34-85)
<60	61 (31.1%)	45 (22.8%)	106 (27.0%)
≥60	135 (68.9%)	152 (77.2%)	287 (73.0%)
Sex			
Male	69 (35.2%)	83 (42.1%)	152 (38.7%)
Female	127 (64.8%)	114 (57.9%)	241 (61.3%)
Race			
White	175 (89.3%)	180 (91.4%)	355 (90.3%)
All others	21 (10.7%)	17 (8.6%)	38 (9.7%)
Ethnicity			
Hispanic or Latino	4 (2.0%)	1 (0.5%)	5 (1.3%)
Not Hispanic or Latino	185 (94.4%)	190 (96.4%)	375 (95.4%)
Unknown	7 (3.6%)	6 (3.0%)	13 (3.3%)
Zubrod performance status			
0	79 (40.3%)	83 (42.1%)	162 (41.2%)
1	100 (51.0%)	105 (53.3%)	205 (52.2%)
2	17 (8.7%)	9 (4.6%)	26 (6.6%)
Memantine use			
Planned concurrent memantine use*	100 (51.0%)	95 (48.2%)	195 (49.6%)
Actual concurrent memantine use	87 (44.4%)	97 (49.2%)	184 (46.8%)
Extent of disease*			
Limited	142 (72.4%)	133 (67.5%)	275 (70.0%)
Extensive	54 (27.6%)	64 (32.5%)	118 (30.0%)
Education level			
≤High school, unknown	113 (57.7%)	101 (51.3%)	214 (54.5%)
>High school	83 (42.3%)	96 (48.7%)	179 (45.5%)
Smoking history†			
Never smoked	5 (2.6%)	5 (2.5%)	10 (2.5%)
Former smoker	62 (31.6%)	61 (31.0%)	123 (31.3%)
Current smoker	106 (54.1%)	110 (55.8%)	216 (55.0%)
Unknown	23 (11.7%)	21 (10.7%)	44 (11.2%)
Years smoked (current/former smokers)	(n = 168)	(n = 166)	(n = 334)
Median (range)	41 (15-66)	41 (1-70)	41 (1-70)
Pack years‡	(n = 167)	(n = 167)	(n = 334)
Median (range)	40 (0-169.6)	40 (0-140)	40 (0-169.6)
Religion during childhood			
Protestant, Catholic, Jewish, Mormon/Latter Day Saints, Muslim/Islam, other	146 (74.5%)	146 (74.1%)	292 (74.3%)
None, prefer not to answer, unknown	50 (25.5%)	51 (25.9%)	101 (25.7%)

Abbreviation: HA-PCI = hippocampal avoidance-prophylactic cranial irradiation.
* Stratification factor.
† Smoking information self-reported by patient; years smoked and average cigarettes per day not reported by all people who reported at least some smoking. As a result, years smoked and pack years are missing for some patients.
‡ Never smokers are considered as having 0 pack years.

Six-month change in AHS Agency score was positively related to change in QLQ-C30 score ($\rho = 0.27$; $P < .0001$; Table 3). Likewise, 6-month change in AHS Pathways score was positively related to change in QLQ-C30 score ($\rho = 0.16$; $P = .022$). In other words, higher hope seems to be coupled with increased quality of life, although the correlation is weak.

Agency and pathway scores were also added to the complete case and imputed longitudinal models for NCF. The scores were not significantly correlated with any NCF score.

Discussion

Hopefulness is a key component of person-centered care[17]; therefore, oncologists have implemented techniques to enhance hope.[10,18] The randomized design of NRG-CC003 coupled with the commitment of NRG researchers to prospectively collect information about hope with validated tools, afforded several unique analyses. Within the primary analysis of NRG-CC003, it was determined that prophylactic cranial radiation therapy (PCI) significantly diminished intracranial relapse and provided survival benefit, for either limited or extensive stage SCLC patients. HA reduced cognitive dysfunction in non-SCLC patients receiving whole brain radiation therapy and CC-003 further demonstrated that HA-WBRT was safe as a PCI strategy, without

Table 2 Pretreatment characteristics by Adult Hope Scale (AHS) completion at baseline

	A. Baseline			B. 6 months		
	Did not complete AHS (n = 20)	Completed AHS (n = 373)	*P*value (chi-square or Fisher's exact test)	Did not complete AHS (n = 169)	Completed AHS (n = 224)	*P*- value (chi-square or Fisher's exact test)
Age (y)						
Median	64.5	64		65	63.5	
Min-Max	54-78	34-85		38-85	34-85	
<60	6 (30.0%)	100 (26.8%)	.75	43 (25.4%)	63 (28.1%)	.55
≥60	14 (70.0%)	273 (73.2%)		126 (74.6%)	161 (71.9%)	
Sex			.41			.45
Male	6 (30.0%)	146 (39.1%)		69 (40.8%)	83 (37.1%)	
Female	14 (70.0%)	227 (60.9%)		100 (59.2%)	141 (62.9%)	
Race						
American Indian or Alaska Native	0 (0.0%)	1 (0.3%)		1 (0.6%)	0 (0.0%)	
Asian	0 (0.0%)	3 (0.8%)		3 (1.8%)	0 (0.0%)	
Black or African American	2 (10.0%)	23 (6.2%)		11 (6.5%)	14 (6.3%)	
White	18 (90.0%)	337 (90.3%)		150 (88.8%)	205 (91.5%)	
>1 race	0 (0.0%)	1 (0.3%)		0 (0.0%)	1 (0.4%)	
Unknown	0 (0.0%)	8 (2.1%)		4 (2.4%)	4 (1.8%)	
White	18 (90.0%)	337 (90.3%)	1.00	150 (88.8%)	205 (91.5%)	.36
All others	2 (10.0%)	36 (9.7%)		19 (11.2%)	19 (8.5%)	
Ethnicity			.60			.17
Hispanic or Latino	0 (0.0%)	5 (1.3%)		4 (2.4%)	1 (0.4%)	
Not Hispanic or Latino	20 (100.0%)	355 (95.2%)		158 (93.5%)	217 (96.9%)	
Unknown	0 (0.0%)	13 (3.5%)		7 (4.1%)	6 (2.7%)	
Zubrod performance status			.82			.12
0	8 (40.0%)	154 (41.3%)		70 (41.4%)	92 (41.1%)	
1	10 (50.0%)	195 (52.3%)		83 (49.1%)	122 (54.5%)	
2	2 (10.0%)	24 (6.4%)		16 (9.5%)	10 (4.5%)	
Planned concurrent memantine use						
No	10 (50.0%)	188 (50.4%)		89 (52.7%)	109 (48.7%)	
Yes	10 (50.0%)	185 (49.6%)		80 (47.3%)	115 (51.3%)	
Actual concurrent memantine use			.12			
No	14 (70.0%)	195 (52.3%)		91 (53.8%)	118 (52.7%)	
Yes	6 (30.0%)	178 (47.7%)		78 (46.2%)	106 (47.3%)	
Extent of disease			.62			.066
Limited	13 (65.0%)	262 (70.2%)		110 (65.1%)	165 (73.7%)	
Extensive	7 (35.0%)	111 (29.8%)		59 (34.9%)	59 (26.3%)	
Education level						
Grade school	0 (0.0%)	11 (2.9%)		6 (3.6%)	5 (2.2%)	

(*Continued*)

Table 2 (*Continued*)

	A. Baseline			B. 6 months		
	Did not complete AHS (n = 20)	**Completed AHS (n = 373)**	***P*value (chi-square or Fisher's exact test)**	**Did not complete AHS (n = 169)**	**Completed AHS (n = 224)**	***P*- value (chi-square or Fisher's exact test)**
≤High school	1 (5.0%)	46 (12.3%)		23 (13.6%)	24 (10.7%)	
High school graduate/ GED	7 (35.0%)	145 (38.9%)		62 (36.7%)	90 (40.2%)	
Some college/Associate's degree	6 (30.0%)	104 (27.9%)		49 (29.0%)	61 (27.2%)	
Bachelor's degree	3 (15.0%)	43 (11.5%)		17 (10.1%)	29 (12.9%)	
Advanced degree	1 (5.0%)	22 (5.9%)		8 (4.7%)	15 (6.7%)	
Unknown	2 (10.0%)	2 (0.5%)		4 (2.4%)	0 (0.0%)	
≤ High school, unknown	10 (50.0%)	204 (54.7%)	.68	95 (56.2%)	119 (53.1%)	.54
>High School	10 (50.0%)	169 (45.3%)		74 (43.8%)	105 (46.9%)	
Hand preference			.24			.59
Ambidexterity	0 (0.0%)	3 (0.8%)		1 (0.6%)	2 (0.9%)	
Left	3 (20.0%)	29 (7.9%)		16 (10.1%)	16 (7.2%)	
Right	12 (80.0%)	334 (91.3%)		142 (89.3%)	204 (91.9%)	
Smoking history			.56			.79
Never smoked	0 (0.0%)	10 (2.7%)		5 (3.0%)	5 (2.2%)	
Former smoker, ≤10 pack y	2 (10.0%)	22 (5.9%)		11 (6.5%)	13 (5.8%)	
Former smoker, >10 pack y	7 (35.0%)	92 (24.7%)		39 (23.1%)	60 (26.8%)	
Current smoker	8 (40.0%)	208 (55.8%)		92 (54.4%)	124 (55.4%)	
Unknown	3 (15.0%)	41 (11.0%)		22 (13.0%)	22 (9.8%)	
Religion during childhood						
Protestant	3 (15.0%)	94 (25.2%)		40 (23.7%)	57 (25.4%)	
Catholic	4 (20.0%)	106 (28.4%)		48 (28.4%)	62 (27.7%)	
Jewish	0 (0.0%)	5 (1.3%)		0 (0.0%)	5 (2.2%)	
Mormon/Latter Day Saints	1 (5.0%)	3 (0.8%)		3 (1.8%)	1 (0.4%)	
Muslim/Islam	0 (0.0%)	1 (0.3%)		0 (0.0%)	1 (0.4%)	
None	0 (0.0%)	30 (8.0%)		9 (5.3%)	21 (9.4%)	
Other	3 (15.0%)	72 (19.3%)		34 (20.1%)	41 (18.3%)	
Prefer not to answer	2 (10.0%)	19 (5.1%)		10 (5.9%)	11 (4.9%)	
Unknown	7 (35.0%)	43 (11.5%)		25 (14.8%)	25 (11.2%)	
Protestant, Catholic, Jewish, Mormon/Latter Day Saints, Muslim/Islam, other	11 (55.0%)	281 (75.3%)	.043	125 (74.0%)	167 (74.6%)	.89
None, prefer not to answer, unknown	9 (45.0%)	92 (24.7%)		44 (26.0%)	57 (25.4%)	

Abbreviations: AHS = Adult Hope Scale; GED = General Educational Development Test.

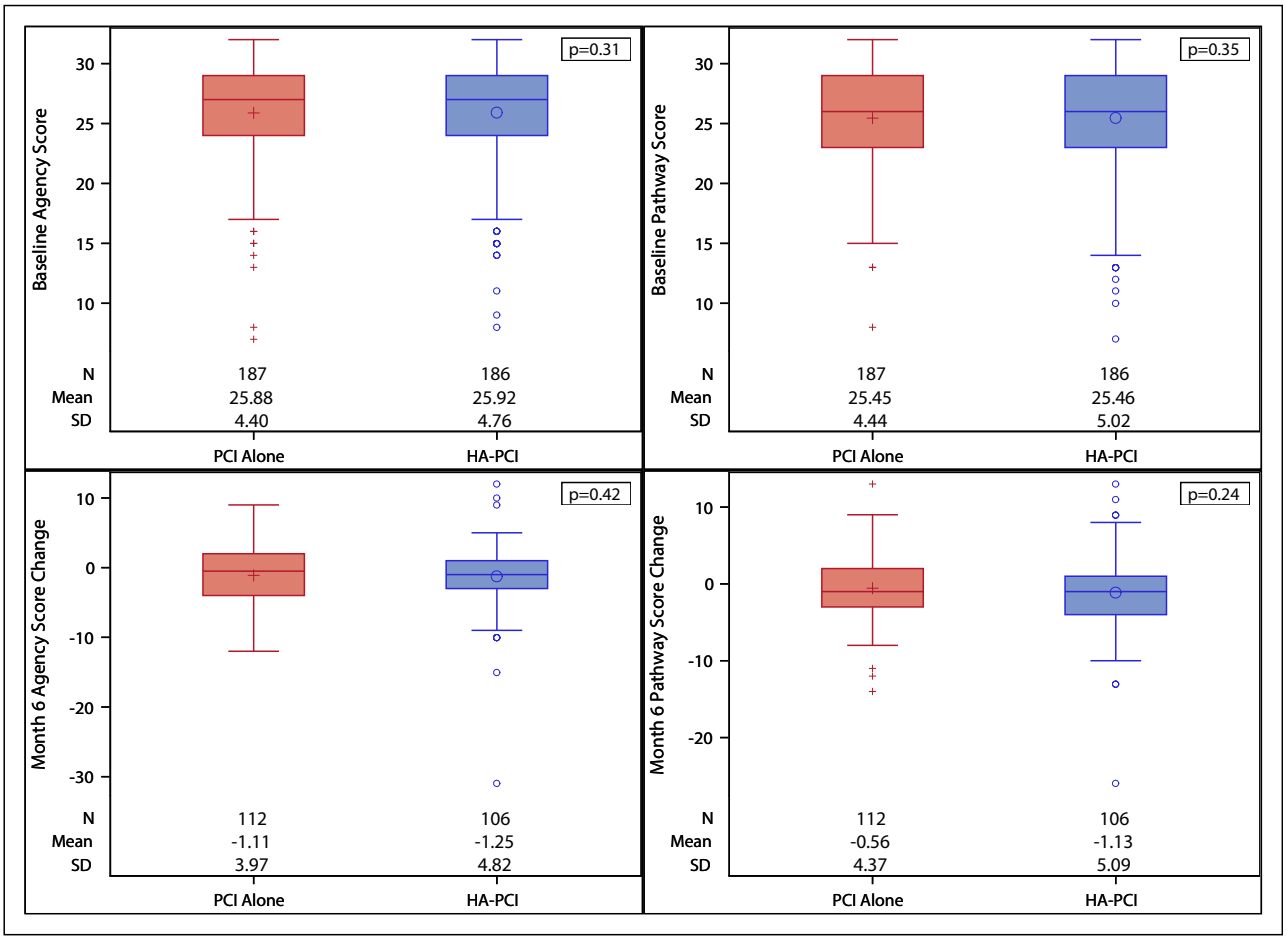

Fig. 2. Whisker plot showing "pathways score" and "agency score" within the Adult Hope Scale (AHS) at baseline and at 6 months as a function of treatment arm (PCI alone or PCI with hippocampal avoidance). *Abbreviation:* PCI = prophylactic cranial irradiation.

increasing intracranial relapse or negatively impacting overall survival. More importantly, an overall benefit in preventing neurocognitive failure (adjusted HR = 0.77; $P = .03$) was observed.

Since this was NRG Oncology's first study of hope, a decision was made to use the most validated metric; the AHS.[6] Participants completed the AHS questionnaire with levels of adherence resembling completion of traditional instruments measuring patient-reported outcomes (eg, EORTC-QLQ30). Therefore, it seems reasonable to conclude that the study of hope does not impose inordinately greater burden on patients compared to other assessment tools, and that it should be feasible to continue to interrogate this patient-reported outcome measure in future trials.

Although this analysis reflects the first time that NRG investigators have studied hopefulness, it is already evident that the NRG-CC003 database represents a valuable resource that can be mined to corroborate theories proposed by scholars in the social sciences. For instance, in NRG-CC003, patients who classified themselves as religious were more likely to complete the AHS in comparison to those who did not self-classify as religious. This proclivity may be a function of overlapping features between hope and faith.[19] Religious people also tended to be more hopeful, particularly with regard to the "pathways" (as opposed to the "agency") component of hopefulness. Snyder et al[20] have theorized that "pathways thinking" is more developed among members of faith-based communities since religious people typically engage in rituals—such as prayer—that are predicated on beliefs as well as aspirations, which can then be translated into community service. Several investigators have disentangled religiousness from spirituality[21] and it will be intriguing to determine whether people who regard themselves as spiritual—albeit irreligious—are also found to manifest relatively high pathways-related hopefulness which can be harnessed for constructive clinical practices (eg, adherence to medical regimens) or prosocial behaviors (ie, practices which cultivate kindness, empathy, gratitude, and altruism).[22]

The most intrinsic question posed in this study relates to the role of the hippocampus as a central source for hope. Since Snyder's theory posits that hope is a cognitive construct, it stands to reason that the CNS oversees the ability of humans to hope. Most investigators theorize that the seat

Table 3 Correlation between 6-mo change in AHS subscale scores and 6-mo change in EORTC QLQ-C30 global health status (n = 213)

	Subscale of AHS	QLQ-C30
AHS Agency subscale score		
Sample size	(n = 213)	(n = 213)
Mean	−1.20	−1.13
Standard deviation	4.42	21.08
Min-Max	−31.0 to 12.00	−66.7 to 66.67
Pearson correlation coefficient	0.2659	
P value	<.0001	
AHS Pathway subscale score		
Sample size	(n = 213)	(n = 213)
Mean	−0.89	−1.13
Standard deviation	4.76	21.08
Min-Max	−26.0 to 13.00	−66.7 to 66.67
Pearson correlation coefficient	0.1573	
P value	.022	

Abbreviation: AHS = Adult Hope Scale.

of hopefulness lies in the hippocampus.[9,10,23,24] Although hope implies an emphasis on the future and the hippocampus is known to be the repository of memory, the hippocampus has been regarded as the lead candidate for this locus because recollecting past experiences of achievement in the setting of early life adversity, often propels individuals to believe that they can replicate past success when confronting new challenges. Within this analysis, we did not identify a difference in hope (pathways nor agency) between the 2 arms, which differed in terms of radiation dose to the hippocampus (higher or lower dose), and this can imply either that (1) the hippocampus does not mediate hope or (2) the dose levels studied within the context of this protocol do not produce a differential impact on the putative hope center in the hippocampus.

A more detailed discussion of this observation is warranted. First, did we use the correct tool? The AHS is the instrument most frequently used to measure hopefulness, but may not be the ideal tool to probe the impact of hippocampal protection on maintenance of hope because the AHS primarily assesses "trait" hope, which is likely to be relatively constant over time. Other validated scales; however, have become available for the measurement of "state" hope which tends to change over time.[7,8] If additional studies can be mounted, it would be prudent to include measures of "state" hope. Second, the premise of our hypothesis subsumed an expectation that the regimen prescribed (10 fractions of 2.5 Gy) would diminish hippocampal function, particularly as related to the role of that structure with respect to hopefulness.[25] Unfortunately, little is known about tolerance levels of the hippocampus as a putative center for hope. It could be possible that the dose delivered was inadequate to diminish hippocampal-hope function and that the hippocampus is heartier than presumed, which would thus expose a fundamental flaw in our methodology. Third, given the complexity of neural circuitry, it is likely that hope is mediated through multiple loci, and the hippocampus might be only one station along an intricate central pathway for hopefulness. For example, Preston and Eichenbaum[26] have suggested that the medial pre-frontal cortex might exercise executive control over the hippocampus which provides safeguards in the event of hippocampal damage.

To our knowledge, this is the first prospective randomized study that shows an association between hopefulness (pathways-related hopefulness as well as agentic hope measured with a validated tool) and QOL among patients with cancer. Previous reports that asserted such a relationship neither used validated tools for hopefulness nor followed patients prospectively.[11] This offers encouragement because it implies that if we could intervene to augment hope, then we might be able to influence the quality of life of patients. Several experiences imply that hope can be improved among patients with cancer[27] via brief in-person workshops that have recently been shown to be transferrable to online platforms.[28] The interconnection of hope and quality of life may have even broader ramifications given the prognostic value of QOL vis-à-vis long-term survival among patients with non-SCLC treated on NRG protocols.[29] We plan to probe this correlation in ensuing analyses of the NRG-CC003 database.

Lately, considerable attention has been devoted to establishing a relationship between hopefulness and oncologic outcomes. In a secondary analysis of PROJECT ENABLE—a large database comprising patients with advanced cancer—an association was observed between patients with high hope levels (defined with a retrospectively-simulated hope index) and improved survival.[30] Those authors cautioned that the ad hoc nature of their analysis precluded causal inference. Recently, Lutgendorf et al[31] identified a biological signature of hope which was characterized by lesser levels of inflammatory cytokines (eg, lower IL-6 levels) and more normalized diurnal cortisol among women with ovarian cancer.[32] They posited that a salutary cascade may be operative, in which patients with high levels of hope have lower levels of beta-adrenergic signaling as well as lower levels of inflammation. In such a milieu, sympathetic nervous system activation would be dampened, which might translate into an environment less conducive to tumor progression. There is also emerging evidence that exposure to chronic stress is associated with increased risk of metastasis and poor survival in cancer patients, perhaps—as implied by rodent models—because chronic stress exposure engenders a glucocorticoid-mediated increase in the formation of neutrophil-extracellular traps (NETs) and that these NETs become critical drivers in the establishment of a stress-induced, metastasis-promoting microenvironment.[33] It is appealing to ponder the opportunities of hope-enhancement

interventions with respect to the classic oncologic endpoints of tumor control and survival. In subsequent work, we plan to systematically evaluate the possible linkage between hope and biochemical markers in NRG-CC003 and then examine the relationship between these parameters and not only survival but also intracranial tumor control. If intriguing associations are identified, NRG Oncology will consider incorporating baseline levels of hope as a stratification parameter in the design of ensuing trials.

Although several shortcomings of the present report have been discussed above, additional limitations should be considered. First, the demographics of the population studied are skewed toward a predominance of older Caucasians, thus limiting the generalizability of the findings. NRG Oncology has made commitments to incorporate methods that improve demographic diversification in future trials.[34] Second, the study of hopefulness constituted an exploratory objective, and hence, the trial might not have been sufficiently powered to answer the questions posed herein. Third, it is conceivable that the patients who used memantine benefited from the neuroprotective effect of this agent[35] which may have overshadowed the neuroprotective impact of HA on the hippocampus with respect to hope. Thus, NRG investigators plan to carry out a subanalysis of the impact of HA on hope, which is restricted to the cohort of patients who opted *not* to receive memantine. Finally, since NRG Oncology has been traditionally focused on questions that revolve around clinical and biological axes, it is possible that subtleties that are more familiar to behavioral scientists were overlooked. NCTN groups are now soliciting the expertise of additional colleagues (eg, psychometricians, anthropologists, and behavioral economists) to enable scholarly investigation of the interface between the virtues that have been explored in the social sciences and classical oncological endpoints.[36]

In summary, it is feasible to study the hopefulness of patients in the context of prospective trials conducted within the NCTN. The hippocampus could not be implicated as a critical structure in a central pathway that coordinates hopefulness, at least within the radiation dose levels evaluated in this trial; however, it is not clear that our data categorically refute the "hope-hippocampal hypothesis." For the first time, a validated tool prospectively established a relationship between hope and quality of life among patients with cancer. Given previous NRG studies correlating QOL with oncologic endpoints (eg, local control and survival), modeling will be carried out to determine if hope mediates, results from, or is associated with these endpoints. Meanwhile, as NRG Oncology delves into hopefulness research,[37] actionable data will be sought to help oncologists and patients to explore and exploit the benefits of hope.

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