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Decline in Tested and Self-Reported Cognitive Functioning After Prophylactic Cranial Irradiation for Lung Cancer: Pooled Secondary Analysis of Radiation Therapy Oncology Group Randomized Trials 0212 and 0214

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Summary

Prior studies have demonstrated an association between prophylactic cranial irradiation 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

Purpose: To assess 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).

Methods and Materials: Radiation Therapy Oncology Group (RTOG) protocol 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, Hopkins Verbal Learning Test (HVLT)-Recall and -Delayed Recall and SRCF were assessed at baseline (after locoregional therapy but before PCI or observation) and at 6 and 12 months. Patients developing brain relapse before 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 HVLT decline.

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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.

Results: 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. 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, $P<.0001$) and 12 months (odds ratio 3.44, 95% confidence interval 1.84-6.44, $P<.0001$). Decline on HVLT-Recall at 6 and 12 months was also associated with PCI ($P=.002$ and $P=.002$, respectively) but was not closely correlated with decline in SRCF at the same time points ($P=.05$ and $P=.86$, respectively).
Conclusions: In lung cancer patients who do not develop brain relapse, PCI is associated with decline in HVLT-tested and self-reported cognitive functioning. Decline in HVLT and decline in SRCF are not closely correlated, suggesting that they may represent distinct elements of the cognitive spectrum.

Introduction

Recent clinical trials have demonstrated cognitive impairment as an adverse effect of cranial irradiation, on the basis of recall and delayed recall testing using the Hopkins Verbal Learning Test (HVLT). For instance, Radiation Therapy Oncology Group (RTOG) protocol 0214 was a phase 3 trial of prophylactic cranial irradiation (PCI) versus observation in patients with locally advanced non-small cell lung cancer (NSCLC) (1). Radiation Therapy Oncology Group 0214 tested HVLT as a secondary endpoint and observed greater decline in HVLT in the PCI cohort as compared with 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 (4) attempted to address this question in a phase 3 trial of PCI versus observation for extensive-disease small cell lung cancer (SCLC) and observed a 2-fold increase in the proportion of patients experiencing SRCF decline with PCI, although this result did not reach statistical significance. 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, because RTOG 0214 was not able to reach target accrual, and both trials reported significant noncompliance with QOL follow-up.

To overcome this limitation, we pooled neurocognitive and QOL data from RTOG 0214 with data from RTOG 0212, a phase 2 trial of high-dose versus standard-dose PCI for limited-stage SCLC. In addition to using HVLT for cognitive function testing, both RTOG trials used the same QOL instrument, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), in which self-reported cognitive functioning is specifically assessed as a 2-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 radiation therapy; Zubrod performance status of $\leq$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 $\leq$2 of any acute or subacute grade $\geq$3 toxicities from prior therapy. All patients signed an institutional review board-approved, study-specific consent form.

Radiation Therapy Oncology Group 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). Radiation Therapy Oncology Group 0214 randomized patients to PCI (30 Gy in 15 daily fractions) or observation (1) (Fig. 1). Both trials are registered with ClinicalTrials.gov, numbers NCT00057746 (RTOG 0212) and NCT00048997 (RTOG 0214).

QOL and HVLT assessments

In both studies, self-reported outcomes were captured prospectively using the EORTC QLQ-C30. The EORTC QLQ-C30 is a 30-item self-report questionnaire containing multiple QOL domains (scales) (6). For this analysis, global QOL as well as each symptom and functional scale, including SRCF, were analyzed separately. Specifically, SRCF is a 2-item functioning scale captured with questions pertaining to concentration and memory. As with other functional scales, higher scores indicate better functioning. The EORTC QLQ-C30 scores were converted to lie in a range between 0 and 100, according to the guidelines of EORTC (7). The 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 HVLT, a well-validated and reliable assessment of list-learning memory, including encoding, retrieval, and retention of new information over time (9). The HVLT 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 to 36 for HVLT-Recall (HVLT-R) and 0-12 for delayed recall (HVLT-DR).

In both studies, baseline HVLT and EORTC QLQ-C30 were completed after definitive locoregional therapy but before the initiation of PCI or observation. Serial follow-up HVLT and EORTC QLQ-C30 testing was performed at 6 and 12 months after