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J. Belderbos, Md Phd[1], D. De Ruysscher[2], K. De Jaeger[3], F. Koppe[4], M. Lambrecht[5], Y. Lievens[6], E. Dieleman[7], J. Jaspers[8], J. Van Meerbeeck[9], J. Ubbels[10], M. Kwint[1], M. Kuenen[11], S. Deprez[12], M. De Ruiter[11], K. Sikorska[13], H. Van Tinteren[13], S. Schagen[11]

[1]The Netherlands Cancer Institute, Radiation Oncology, Amsterdam, The Netherlands; [2]Maastricht University Medical Center- School For Oncology and Developmental Biology Grow, Radiation Oncology, Maastricht, The Netherlands ; [3]Catharina Hospital, Radiation Oncology, Eindhoven, The Netherlands ; [4]Institute Verbeeten, Radiation Oncology, Tilburg, The Netherlands; [5]Uz Gasthuisberg, Radiation Oncology, Leuven, Belgium ; [6]Ghent University Hospital And Ghent University, Radiation Oncology, Gent, Belgium ; [7]Amsterdam Umc-Location Amc, Radiation Oncology, Amsterdam, The Netherlands ; [8]Erasmus Mc Cancer Institute- Erasmus Mc University Medical Center, Radiation Oncology, Rotterdam, The Netherlands ; [9]Antwerp University Hospital, Department Of Pulmonology and Thoracic Oncology, Antwerp, Belgium ; [10]University of Groningen-University Medical Center Groningen, Radiation Oncology, Groningen, The Netherlands ; [11]The Netherlands Cancer Institute, Division of Psychosocial Research and Epidemiology, Amsterdam, The Netherlands ; [12]University Hospitals Leuven- Kul, Imaging and Pathology, Leuven, Belgium ; [13]The Netherlands Cancer Institute, Department of Biometrics, Amsterdam, The Netherlands

Purpose or Objective

Neurocognitive decline after Prophylactic Cranial Irradiation (PCI) may be related to the dose in the hippocampus. This multicenter randomized phase III trial (NCT01780675) investigated hippocampus dependent memory functioning and safety after PCI with or without hippocampus sparing in Small Cell Lung Cancer (SCLC) using the Hopkins Verbal Learning Test-Revised (HVLT-R).

Material and Methods

Patients with limited or extensive stage SCLC who received PCI (25 Gy in 10 fractions) were randomized to standard PCI or hippocampus avoidance PCI (HA-PCI), using IMRT or VMAT. In the HA-PCI group the objective was to get the mean dose in the right and left hippocampus ≤ 8.5 Gy (biological dose ≤ 6.1 Gy for α/ß=2Gy) and $D_{1\%}$ hippocampus ≤ 10 Gy, D_{max} PTV < 28.75 Gy (115%) and $V_{115\%}$ PTV ≤ 1%. Neurocognitive functioning was assessed by a neuropsychological test battery at baseline, 4, 8, 12, 18 and 24 months after the irradiation. The primary endpoint was a decline in the HVLT-R total recall at 4 months, where a decline of 5 or more out of a possible 36 points was considered a failure. Secondary objectives were other cognitive outcomes/quality of life, radiological brain abnormalities on MRI (baseline, 4 and 12 months) and evaluation of the incidence and location of brain metastases following HA-PCI compared with standard PCI and overall survival (OS) using the Kaplan-Meier method.

Results

From April 2013 until March 2018 a total of 168 patients were randomized in 10 centers in the Netherlands and Belgium. The median follow-up time was 24.6 months. Median age was 64 years, 51% was female, and performance score at baseline was WHO 0-1 in 93%. The stage distribution was comparable in both arms (70% limited- and 30% extensive stage). All patients were treated using 25 Gy in 10 fractions. A total of 75% of all patients alive and treated had neurocognitive tests at 4 and this was 66% at 8 months. The HVLT-R total recall score was ≥ 5 points lower compared to baseline in 28% PCI and 29% HA-PCI at 4 months (P=0.99) and 34% PCI and 26% HA-PCI at 8 months (P=0.46). Compared to baseline, the average HVLT-R total recall score dropped 2 points for both arms at 4 months and 3 points in the PCI arm and 1 point in the HA-PCI arm at 8 months. Nineteen patients developed brain metastases of which 50% were multiple. No patient developed an isolated brain metastasis in the HA zone. The OS at 18 months was 54% in the PCI arm and 53% in the HA-PCI arm.

Conclusion

This randomized phase III trial investigating the neurocognitive decline at 4 and 8 months after treatment of HA-PCI compared to conventional PCI revealed a decline by ≥ 5 points at HVLT-R total recall score in 28% of the total group. However, no significant difference between the two arms was seen. The incidence of brain recurrences was not increased in the avoidance region.