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Short Communication

Association of different fractionation schedules for prophylactic cranial irradiation with toxicity and brain metastases-free survival in stage III non-small cell lung cancer: A pooled analysis of individual patient data from three randomized trials

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A B S T R A C T

We assessed the impact of different PCI fractionation schedules (30 Gy in 10 versus 15 fractions) on brain metastases-free survival (BMFS) and toxicity in stage III NSCLC. Our results suggest that 30 Gy in 10 fractions is associated with increased toxicity, while no conclusive evidence of improving BMFS was seen with this schedule.

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Approximately 30% of patients with stage III non-small cell lung cancer (NSCLC) develop brain metastases (BM) [1]. Prophylactic cranial irradiation (PCI) has been shown to effectively reduce the BM incidence [2–10]. Results of a recently published individual patient data meta-analysis showed that the progression-free survival, BM-free survival (BMFS) and the time to BM were significantly improved by PCI. However, the same study also showed that PCI was associated with an increased risk of toxicity, specifically late memory impairment and fatigue [11].

In the RTOG 0212 trial, the authors reported that limited-disease small cell lung cancer (SCLC) patients treated with a higher PCI dose (36 Gy) had a higher risk of developing neurocognitive decline (p = 0.03) compared to a lower dose (25 Gy) [12]. However, a trial by Le Pechoux et al. (25 Gy in 10 fractions versus 36 Gy in 18 daily or 24 two daily fractions) and a pooled analysis of RTOG 0212 (25 Gy in 10 fractions versus 36 Gy in 18 daily or 24 two daily fractions) and RTOG 0214 (30 Gy in 15 fractions) did not demonstrate a statistically significant difference in risk of toxicity between different PCI doses [13,14].

Toxicity is currently an important argument for clinicians not to treat stage III NSCLC patients with PCI. It is therefore important to explore whether the dose and fractionation of PCI affects the risk of toxicity and/or the effectiveness in terms of BM reduction. The aim of this study was therefore to explore the impact of different PCI fractionation schedules (30 Gy in 10 versus 15 fractions) on BM occurrence and risk of toxicity in patients with stage III NSCLC using individual patient data of three randomized controlled trials (RCTs).
Methods

Individual patient data of RCTs

The search strategy and selection criteria reported in a previously published individual patient data meta-analysis [11] were used to select eligible trials. Individual patient data of three RCTs (RTOG 0214 [6,7,15], Guangzhou 2005 [9] and NVALT-11 [10]) in which the impact of PCI in patients with stage III NSCLC was assessed, were analysed. Although the SWOG 8300 trial [5,16] met the search strategy and selection criteria, it did not report BMFS and toxicity data and was therefore excluded. In the three included trials, stage III NSCLC patients were randomized between PCI and observation after standard treatment with curative intent (mainly combinations of radiotherapy, chemotherapy and/or surgery). The total delivered PCI dose was 30 Gy in 15 fractions in the RTOG 0214 trial [6,7,15], 30 Gy in 10 fractions in the Guangzhou 2005 trial [9], and either 36 Gy in 18 fractions, or 30 Gy in 10 or 12 fractions in the NVALT-11 trial [10]. For the hospitals that used PCI fractionation schedules other than 30 Gy in either 10 or 15 fractions, patients of both arms were excluded from the analyses.

Outcomes

Time to BM and BMFS were used to assess the impact of different PCI fractionation schedules on BM occurrence. Time to BM was defined as the time from randomization until the first occurrence of BM. BMFS was defined as the time from randomization until the first occurrence of BM or death from any cause. Toxicity was based on adverse events pre-specified in the individual patient data meta-analysis protocol (Supplementary Appendix), and included alopecia, erythema, pharyngitis, xerostomia, and/or hyperpigmentation of scalp, pruritus of external auditory canals, nausea, vomiting, headache, lethargy/fatigue, somnolence, concentration dysfunction, memory dysfunction, radiation necrosis, accelerated atherosclerosis, ataxia and radiation-induced neoplasm. Per patient, the worst occurred pre-specified adverse event grade was categorized to no toxicity, low grade toxicity (grade 1 or 2) and high grade toxicity (grade ≥ 3).

Statistical analyses

Time to BM, BMFS, and toxicity were compared between a total PCI dose of 30 Gy given in either 10 fractions of 3 Gy or 15 fractions of 2 Gy. Time to BM was estimated using the Fine-Gray competing risk model, with death of any cause as competing event. For the analysis of BMFS, the log-rank observed minus expected number of events and its variance were used to calculate individual and overall pooled hazard ratios (HRs) and 95% confidence intervals (95% CIs) with a fixed effects model. Inter-trial heterogeneity was studied using the $\chi^2$ heterogeneity test and the $I^2$ test [17]. A multivariate Cox regression model, including age, sex, performance status, histology, tumour stage and prior surgery, was used to potentially correct for differences in prognostic factors. Multilevel mixed effects logistic regression, including age, sex, performance status and histology were used as covariates, was used to calculate odds ratios and 95% confidence intervals for toxicity, comparing 10 fractions of PCI with 15 fractions.

Results

BM incidence and BMFS

Of the 670 patients in the three trials, 580 patients were included in the analyses, with a median follow-up of 107 months (95% CI [97–111]). Trial and patient characteristics of each trial are summarized in Table 1. In total, 90 patients (45 patients in each arm) from 10 Dutch hospitals who received different fractionation schedules (mainly 30 Gy in 12 fractions) in the NVALT-11 trial were excluded from the analyses (Table 1).

The $\chi^2$ and $I^2$ tests in the BMFS analysis indicated no inter-trial heterogeneity ($\chi^2 = 1.06, I^2 = 0.00, p = 0.59$). For both fractionation schedules, the competing risk analysis showed that the BM incidence was significantly reduced by PCI compared to observation (10 fractions: HR 0.22, 95% CI [0.12–0.42], 15 fractions: HR 0.50, 95% CI [0.30–0.85]). No statistically significant interaction was found for BMFS between PCI given in 10 fractions and 15 fractions (10 fractions: HR 0.71, 95% CI [0.53–0.95], 15 fractions: HR 0.85, 95% CI [0.68–1.08], p-interaction = 0.34) (Fig. 1). The multivariate Cox regression model for BMFS, including age, sex, performance status, histology, tumour stage and prior surgery, resulted in slightly lower HR’s (10 fractions: HR 0.65, 95% CI [0.37–1.15], 15 fractions: HR 0.80, 95% CI [0.62–1.02]).

Toxicity

For the toxicity analyses adjusted for age, sex, performance status and histology, only the PCI arm from each trial was included (due to data availability). The risk of any grade toxicity was statistically significantly lower for patients who received PCI in 15 fractions compared to 10 fractions (OR 0.41, 95% CI [0.24–0.68], p = 0.001, number of events: 149/284). In addition, the risk of high grade (≥3) toxicity was also statistically significantly lower for patients who received PCI in 15 fractions (OR 0.19, 95% CI [0.05–0.69], p = 0.012, number of events: 15/284).

Table 1

Overview of patient and trial characteristics.

|                      | RTOG0214 | Guangzhou2005 | NVALT-11 |
|----------------------|----------|----------------|----------|
|                      | PCI      | Observation    | PCI      | Observation    | PCI      | Observation    |
| Total number of patients | 163      | 177            | 81       | 75             | 86       | 88            |
| Total excluded patients* | 0        | 0              | 0        | 0              | 45       | 45            |
| 30 Gy in 10 fractions | 0        | NA             | 81       | NA             | 41       | NA            |
| 30 Gy in 15 fractions | 163      | NA             | 0        | NA             | 0        | NA            |
| Follow-up time in months (95% CI) | 119.9 (109.1–125.2) | 64.0 (58.1–86.5) | 51.4 (44.8–58.4) |
| >60 years (%) | 60%       | 47%            | 35%      | 44%            | 68%      | 47%            |
| Male (%)              | 63%       | 62%            | 72%      | 71%            | 68%      | 58%            |
| PS 0 (%)              | 47%       | 59%            | 36%      | 37%            | 33%      | 30%            |
| PS 1 (%)              | 47%       | 39%            | 62%      | 62%            | 62%      | 68%            |
| PS ≥ 2 (%)            | 6%        | 2%             | 2%       | 2%             | 5%       | 2%             |
| Squamous disease (%)  | 31%       | 34%            | 25%      | 27%            | 43%      | 33%            |
| Proportion any toxicity | 71/163  | NA             | 49/81    | NA             | 29/41    | NA            |
| Proportion grade ≥ 3 toxicity | 5/163    | NA             | 3/81     | NA             | 7/41     | NA            |

*Patients of both the PCI and observation arm from hospitals applying fractionation schedules other than 30 Gy in 10 or 15 fractions were excluded from the analyses.
The aim of this study was to explore the impact of different PCI fractionation schedules (30 Gy in 10 versus 15 fractions) on BM occurrence and risk of toxicity in stage III NSCLC. Despite that the HR for both BM incidence and BMFS was slightly lower for PCI administered using 10 fractions compared with 15 fractions respectively, the interaction between the different fractionation schedules (tested for BMFS) was not statistically significant. The risk of any grade and high grade toxicity was significantly lower for the 15 fractions schedule compared to the 10 fractions schedule.

Our findings are in line with the results of the most recent individual RCTs in which PCI was assessed for NSCLC. Guangzhou 2005 [9] (30 Gy in 10 fractions), RTOG 0214 [6,7,15] (30 Gy in 15 fractions) and NVALT-11 [10] (mainly 30 Gy in 10 and 12 fractions) all showed statistically significant reductions in the BM incidence by PCI. The largest effect was observed in Guangzhou 2005 [9] (30.5% reduction after 3 years), followed by NVALT-11 [10] (20.2% reduction after 2 years) and RTOG 0214 [6,7,15] (13.4% reduction after 2 years). Results of the RTOG 0212 trial [12] suggested an increased risk of neurotoxicity for SCLC patients who received 18 fractions (OR 8.00, 95% CI [1.29–49.50], \( p = 0.03 \)) and 24 fractions (OR 4.37, 95% CI [0.81–23.60], \( p = 0.09 \)) of PCI compared to 10 fractions. However, the arms with higher number of fractions (18 and 24 fractions) also received a higher total dose of 36 Gy compared to a total dose of 25 Gy for the 10 fractions arm, and the results of this trial are therefore difficult to compare to the results of our current study. The finding that a decreased dose per fraction while delivering the same total dose was associated with less side effects is in line with previous studies and radiobiological models [18]. The similar tumour control between the fraction sizes may be explained by the relatively high \( a/b \) values of 8–10 Gy for NSCLC [19] and the probable shallow linear dose–effect relation for subclinical disease [20].

The main limitation of our study is related to the post-hoc exploratory character of the analyses. All analyses were performed post-hoc, and although the data of the trials included in our analyses were initially powered on the randomized comparison between PCI and observation, the toxicity analyses were based on an observational comparison between PCI arms including different fractionation schedules. Moreover, the burden of low grade (grade 1 or 2) toxicity may have been underestimated in our study. Although low grade concentration loss or memory dysfunction can be burdensome, high grade toxicity is expected to have the largest impact on the patients’ quality of life and was therefore the focus of our analysis. Also, toxicity time to event data were not available for the RTOG 0214 and Guangzhou 2005 trials and separate analyses for acute and late toxicities could therefore not be performed. In addition, patients that received 30 Gy of PCI in 15 fractions all originated from the RTOG2014 trial [6,7,15], whereas patients in the 30 Gy in 10 fractions arm originated from the NVALT-11 [10] and Guangzhou 2005 [9] trials and the observed results could therefore be driven by inter-trial differences rather than the received number of PCI fractions. Nevertheless, the \( \chi^2 \) and \( I^2 \) tests indicated, consistently with our previous analyses [11], no inter-trial heterogeneity regarding the PCI treatment effect on BMFS (\( \chi^2 = 1.06, I^2 = 0.00\% \), \( p = 0.59 \)). Next to that, the multivariate Cox regression model showed that correcting for differences in some prognostic factors did not substantially impact the result and thus, the impact of potential inter-trial differences is likely minor. Differences in follow-up time between the trials could potentially

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**Discussion**

The aim of this study was to explore the impact of different PCI fractionation schedules (30 Gy in 10 versus 15 fractions) on BM occurrence and risk of toxicity in stage III NSCLC. Despite that the HR for both BM incidence and BMFS was slightly lower for PCI administered using 10 fractions compared with 15 fractions respectively, the interaction between the different fractionation schedules (tested for BMFS) was not statistically significant. The risk of any grade and high grade toxicity was significantly lower for the 15 fractions schedule compared to the 10 fractions schedule.

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**Fig. 1.** Forest plot comparing brain metastases-free survival of patients who received PCI in 10 fractions of 3 Gy and 15 fractions of 2 Gy.

| No. Events / No. Entered | PCI | Observation | O-E | Variance | Hazard Ratio [95% CI] |
|--------------------------|-----|-------------|-----|----------|----------------------|
| **30 Gy in 10 fractions** |     |             |     |          |                      |
| NVALT-11                 | 23/41 | 33/43       | -5.9 | 13.9     | 0.65 [0.39;1.11]    |
| Guangzhou2005            | 64/81 | 65/75       | -9.6 | 31.5     | 0.74 [0.52;1.05]    |
| **Total**                | 87/122 | 98/118      | -15.5 | 45.4     | 0.71 [0.53;0.95]    |
| **30 Gy in 15 fractions**|     |             |     |          |                      |
| RTOG0214                 | 132/163 | 149/177     | -11.1 | 70.1     | 0.85 [0.68;1.08]    |
| **Total**                | 132/163 | 149/177     | -11.1 | 70.1     | 0.85 [0.68;1.08]    |

Test for heterogeneity: \( \chi^2 = 1.06 \), \( p = 0.5885 \), \( I^2 = 0.00\% \)

Test for interaction: \( \chi^2 = 0.92 \), \( p = 0.3376 \)
bias the toxicity analyses. However, all trials had a median follow-up of at least two years, in which the majority of adverse events was reported. Next to that, from the NVALT-11 trial [10], data were only included from the subset of hospitals who intended to treat patients in the PCI arm with 30 Gy in 10 fractions of 3 Gy. As a consequence, 90 patients (52% of the NVALT-11 trial population) of this study were excluded from our analyses, limiting the power of our analyses.

In conclusion, the results of our post-hoc exploratory analyses suggest that 30 Gy of PCI given in 15 fractions is less toxic than 30 Gy in 10 fractions, while not statistically significantly different in terms of BMFS. This may guide the fractionation schedule of PCI for patients with stage III NSCLC in future studies.

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Disclosures

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Bram L.T. Ramaekers: Consulting or Advisory Role: Janssen (Inst).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.09.029.

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