ORIGINAL ARTICLE

Prophylactic Cranial Irradiation in Extensive Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

We conducted a randomized trial of prophylactic cranial irradiation in patients with extensive small-cell lung cancer who had had a response to chemotherapy.

METHODS

Patients between the ages of 18 and 75 years with extensive small-cell lung cancer were randomly assigned to undergo prophylactic cranial irradiation (irradiation group) or receive no further therapy (control group). The primary end point was the time to symptomatic brain metastases. Computed tomography or magnetic resonance imaging of the brain was performed when any predefined key symptom suggestive of brain metastases was present.

RESULTS

The two groups (each with 143 patients) were well balanced regarding baseline characteristics. Patients in the irradiation group had a lower risk of symptomatic brain metastases (hazard ratio, 0.27; 95% confidence interval [CI], 0.16 to 0.44; P<0.001). The cumulative risk of brain metastases within 1 year was 14.6% in the irradiation group (95% CI, 8.3 to 20.9) and 40.4% in the control group (95% CI, 32.1 to 48.6). Irradiation was associated with an increase in median disease-free survival from 12.0 weeks to 14.7 weeks and in median overall survival from 5.4 months to 6.7 months after randomization. The 1-year survival rate was 27.1% (95% CI, 19.4 to 35.5) in the irradiation group and 13.3% (95% CI, 8.1 to 19.9) in the control group. Irradiation had side effects but did not have a clinically significant effect on global health status.

CONCLUSIONS

Prophylactic cranial irradiation reduces the incidence of symptomatic brain metastases and prolongs disease-free and overall survival. (ClinicalTrials.gov number, NCT00016211.)

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Small-cell lung cancer constitutes nearly 13% of all newly diagnosed lung cancers.[1] Most patients present with extensive disease, and without treatment, the median survival is 2 to 4 months. Chemotherapy has improved short-term survival, but long-term survival remains disappointing. The 2-year survival rate among patients with extensive small-cell lung cancer was 1.5% in 1973 and 4.6% in 2000.[1] Brain metastases are common in this disease. At diagnosis, at least 18% of patients have brain metastases,[2] and the incidence of such metastases increases considerably during the course of the disease, approaching 80% at 2 years.[3] The presence of brain metastases is an indication of a poor prognosis. Maintenance chemotherapy does not reduce the incidence of brain metastases,[4] and in previously untreated small-cell lung cancer, chemotherapy is less effective against small, asymptomatic brain metastases than against large, symptomatic brain or extracranial metastases,[5,6] suggesting, at least to some degree, the presence of an effective blood–brain barrier.

Among patients with a brain-only relapse, the rate of response to whole-brain irradiation is only 50%, and survival is relatively short.[7] The European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer Group evaluated the efficacy of chemotherapy in patients with a symptomatic brain relapse[8,9]; the results were poor, even with the administration of drugs that potentially did not have cross-resistance.[10] Combined chemotherapy and radiotherapy for symptomatic brain relapse improved the response rate and quality of life but had no effect on survival.[11] Overall, many patients with small-cell lung cancer have symptomatic brain metastases,[12] and most of these patients (59%) die with or from active metastases in the central nervous system.[13] A number of studies[14-16] and meta-analyses[17,18] have shown a reduced risk of symptomatic brain metastases and (in the meta-analyses) improved survival with prophylactic cranial irradiation. Such treatment can be neurotoxic, but the use of low-fraction dose schedules and the avoidance of concomitant chemotherapy have reduced the incidence of neurotoxic effects considerably. Even with moderate neurotoxicity, cranial irradiation is associated with improved quality-adjusted life expectancy.[19]

The role of prophylactic cranial irradiation in patients who do not have a complete response to chemotherapy is unclear. Patients with extensive small-cell lung cancer are unlikely to have a complete response and are at high risk for symptomatic brain metastases.[20,21] These factors — together with poor treatment results, ineffectiveness of surveillance for early detection of brain metastases on computed tomography (CT),[13] and the major effect of brain metastases on physical and psychological functioning of patients[12,13] — prompted the evaluation of prophylactic cranial irradiation in extensive small-cell lung cancer. We report on the results of a randomized trial of this treatment, initiated by the EORTC Radiation Oncology Group and Lung Cancer Group.

METHODS

STUDY DESIGN

We conducted a multicenter, phase 3, randomized trial aimed at showing a difference in outcome between patients who underwent prophylactic cranial irradiation (irradiation group) and those who received no further therapy (control group). Patients were eligible for the study if they had cytologically or histologically confirmed, extensive small-cell lung cancer, defined as disease beyond the hemithorax and supraclavicular nodes or pleural effusion containing tumor cells. All patients had to have had a response to systemic chemotherapy, as judged by the standard treatment policy of each participating center. No specific criteria for a treatment response were defined; any response, as judged by the local investigator, was acceptable. Eligible patients underwent randomization centrally at the EORTC Data Center with the use of a minimization technique for random assignments to study groups,[22] stratified according to institution and performance status.

INCLUSION CRITERIA

Criteria for inclusion in the study were an age of 18 to 75 years; a performance status of 0 to 2, according to the criteria of the World Health Organization (with a higher score indicating a poorer performance status); documented extensive small-cell lung cancer before the start of chemotherapy; a response after four to six cycles of initial chemotherapy; an interval of no more than 5 weeks between the last cycle of chemotherapy and randomization; no evidence of brain or leptomeningeal metastases; no previous radiotherapy to the head and neck area; no history of corticosteroid use; and no previous or other current cancer. Pa-

tients needed to be able to comply with the protocol and follow-up schedule and were required to provide written informed consent, according to provisions of the International Conference on Harmonisation, Guidelines for Good Clinical Practice, or national or local regulations. The ethics committee at each center reviewed and approved the protocol.

PROPHYLACTIC CRANIAL IRRADIATION

Radiation to the intracranial content (planning target volume) was administered with the use of two opposed lateral fields with a linear accelerator (4 to 18 MV) or cobalt unit. Each field was treated daily on a schedule of four to five fractions per week. The dose was specified to the midline. The following schedules for cranial irradiation could be used: 20 Gy in 5 or 8 fractions, 24 Gy in 12 fractions, 25 Gy in 10 fractions, or 30 Gy in 10 or 12 fractions. The biologically equivalent doses for these schedules range from 25 to 39 Gy. Each center had to select one of these schedules and had to adhere to it for all study patients. Radiotherapy had to start 4 to 6 weeks after chemotherapy.

STAGING AND FOLLOW-UP PROCEDURES

Brain imaging was not part of standard staging and follow-up procedures, unless symptoms suggestive of brain metastases were present. In addition, each center specified whether contrast-enhanced CT, magnetic resonance imaging (MRI), or both of the brain would be performed before chemotherapy, after chemotherapy, during follow-up, and at the time of extracranial recurrence in patients without symptoms of brain metastases. Each center had to adhere to this policy for all patients in both study groups. Treatment for subsequent extracranial progression was not part of the protocol and was left to each center's policy, but all patients with subsequent extracranial progression had to be followed until death for possible intracranial relapse. Treatment for intracranial relapse was also left to the discretion of the investigator.

Acute toxic effects were recorded during and after treatment in the irradiation group only. Patients in both groups were seen for follow-up 6 weeks and 3, 6, 9, and 12 months after randomization and thereafter every 6 months. Investigations at each visit included the taking of a medical history and performance of a physical evaluation, review of a checklist for key symptoms of brain metastases, the performance of contrast-enhanced CT or MRI of the brain in case of any suspicion of brain metastases, and patients' completion of surveys regarding quality of life, including the EORTC's core quality-of-life questionnaire (QLQ-C30) and an instrument specific for brain tumors (QLQ-BN20).

END POINTS AND SAMPLE SIZE

The primary end point was the development of symptomatic brain metastases. The primary objective of the study was to investigate whether cranial irradiation could reduce the incidence of symptomatic brain metastases as reflected by a hazard ratio of 0.44. The presence of such metastases in 52 patients was needed to detect this expected difference with a power of 80% at a two-sided significance level of 0.05. On the basis of an estimate that 40% of the patients would die or be lost to follow-up by year 3, it was determined that 287 patients were required for the study.

The following key symptoms suggestive of a diagnosis of brain metastases were specified: signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and focal neurologic symptoms. If any of these symptoms developed, CT or MRI of the brain was performed. Symptomatic brain metastasis was defined as the presence of at least one key symptom in combination with radiologic evidence (positive contrast-enhanced CT or MRI of the brain).

Secondary study end points were survival, quality of life, toxic effects, and treatment costs. The primary quality-of-life end points were global health status, hair loss, fatigue, role functioning, cognitive functioning, and emotional functioning as assessed with the EORTC's QLQ-C30. Cognitive functioning tests (including the Mini–Mental State Examination) and cost evaluations were performed in selected centers only, so the results are not reported here.

STATISTICAL ANALYSIS

Cumulative incidence curves were used to estimate the cumulative risk of symptomatic brain metastases over time, and Gray's tests were used to compare the study groups[23,24]; the hazard ratios and confidence intervals for time-to-event comparisons are also reported for illustration. Death without evidence of brain metastases was considered a competing risk in the analysis. Patients with dis-

ease that progressed outside the brain were followed for the occurrence of brain metastases, and a sensitivity analysis was performed in which such progression was considered as another competing risk. Overall and disease-free survival (i.e., the time to death and the time to disease progression, respectively) were estimated by the Kaplan–Meier method and compared by means of log-rank tests. For clinical end points, all reported P values are two-sided; a P value of less than 0.05 was considered to indicate statistical significance.

Scores on the quality-of-life survey range from 0 to 100. For function scales, higher values represent better function; for symptom scales, higher values indicate a greater severity of symptoms. Longitudinal data analysis with the use of linear mixed models was first performed to obtain an overall test comparing each selected quality-of-life scale between the two study groups. Only the assessments up to 9 months after randomization were included, since starting at year 1, too few quality-of-life data were available for statistical analysis. Clinical significance was defined as a 10-point difference; statistical significance was set at 0.01 to account for the six primary end points. The analysis of the other 20 scales was exploratory. The comparisons at each time point were considered only if the overall test was statistically significant at the 0.01 level. All analyses were performed strictly according to the intention-to-treat principle.

Table 1. Characteristics of the Patients.*

Variable	Prophylactic Cranial Irradiation (N=143)	Control (N=143)
Median age — yr (range)	62 (37–75)	63 (39–75)
Median time after diagnosis — mo	4.2	4.2
Sex — no. (%)		
Male	97 (67.8)	82 (57.3)
Female	46 (32.2)	61 (42.7)
WHO performance score — no. (%)†		
0	52 (36.4)	52 (36.4)
1	80 (55.9)	76 (53.1)
2	11 (7.7)	15 (10.5)
Persistent disease — no. (%)		
Primary	108 (75.5)	110 (76.9)
Distant	99 (69.2)	104 (72.7)

* There were no significant differences between patients in the irradiation group and those in the control group in any category.
† Higher scores on the World Health Organization (WHO) scale indicate poorer performance status.

RESULTS

PATIENTS

Between February 2001 and March 2006, we recruited 286 patients (143 in each group). At the time of analysis in October 2006, all but 31 patients had progressive disease or had died. Of the patients in the irradiation group, 10 did not receive treatment: 6 died before the start of treatment, 1 had disease progression before the start of treatment, and 3 declined treatment. One patient in the control group insisted on undergoing cranial irradiation.

The median interval between diagnosis and randomization was 4.2 months. There were no significant differences between the two groups with respect to the characteristics of the patients (Table 1). The fractionation schedules that were most commonly used in the irradiation group were 20 Gy given in 5 fractions (89 patients), 30 Gy given in 10 fractions (23 patients), 30 Gy given in 12 fractions (9 patients), and 25 Gy given in 10 fractions (7 patients). Other schedules were used infrequently (six patients). Treatment compliance was good; three patients had an interruption in therapy for logistical reasons, and one patient declined to undergo treatment. For one patient, treatment was stopped owing to disease progression after 16 of the planned 20 Gy had been given.

Symptomatic brain metastases were observed in 24 of the 143 patients in the irradiation group (16.8%) and in 59 of the 143 in the control group (41.3%). The cumulative incidence curves are shown in Figure 1 (P<0.001). The cumulative risks of symptomatic brain metastases at 6 and 12 months were 4.4% and 14.6%, respectively, in the irradiation group and 32.0% and 40.4% in the control group. The hazard ratio for the irradiation group (accounting only for the competing risk of death without symptomatic brain metastases) was 0.27 (95% confidence interval [CI], 0.16 to 0.44). Radiotherapy for symptomatic brain metastases was administered in 2 of 24 patients in the irradiation group (8.3%), as compared with 35 of 59 patients in the control group (59.3%).

At 1 year, the risk of extracranial progression did not differ significantly between the irradiation

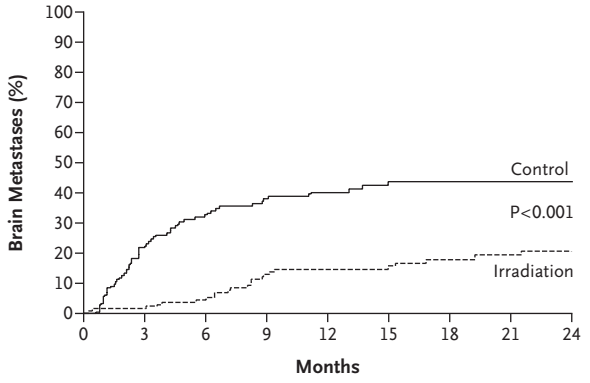

Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.

The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

group and the control group (88.8% and 92.8%, respectively). Treatment for extracranial progression (mostly consisting of chemotherapy, radiotherapy, or both) was given to 68.0% of patients in the irradiation group and 45.1% in the control group.

Survival without disease progression was significantly longer in the irradiation group than in the control group, with a median of 14.7 weeks versus 12.0 weeks (P=0.02) (Fig. 2). The hazard ratio was 0.76 (95% CI, 0.59 to 0.96) in favor of irradiation. At 6 months, the rate of survival without disease progression was 23.4% (95% CI, 16.6 to 30.9) in the irradiation group and 15.5% (95% CI, 10.1 to 22.0) in the control group.

Patients in the irradiation group also had significantly longer overall survival than those in the control group (P=0.003), with a median survival of 6.7 months, as compared with 5.4 months in the control group (Fig. 3). The hazard ratio for death in the irradiation group was 0.68 (95% CI, 0.52 to 0.88). The survival rate at 1 year was 27.1% (95% CI, 19.4 to 35.5) in the irradiation group and 13.3% (95% CI, 8.1 to 19.9) in the control group.

Among the 134 patients who underwent irradiation (including 1 in the original control group), acute reactions included headache (41 with grade 1 events, 12 with grade 2 events, and 5 with grade 3 events), nausea and vomiting (33 with grade 1 events and 15 with grade 2 events), fatigue or lethargy (6 with grade 1 events and 7 with grade 2 events), and skin reactions (3 with grade 1 events and 2 with grade 2 events). The worst late reactions (after 3 months) included mild headache or slight lethargy in 29 patients (21.6%), moderate headache or severe lethargy in 15 patients (11.2%), and severe headache or central nervous system dysfunction in 3 patients (2.2%). A clear distinction between late reactions and tumor progression could not always be made.

The rate of compliance with the quality-of-life assessment was 93.7% at baseline but decreased to 46.3% at 9 months. From baseline to month 9, there was no statistically or clinically significant difference in global health status between the study groups (P=0.10) (Table 2). Side effects in the irradiation group were hair loss and fatigue (P<0.001 for both comparisons with the control group). No significant difference was found between the study groups in role functioning (P=0.17), cognitive functioning (P=0.07), or emotional functioning (P=0.18). An exploratory analysis of the remaining quality-of-life scales showed differences of nearly 10 points (the cutoff for clinical significance) for appetite loss, nausea and vomiting, and leg weakness (Table 2).

DISCUSSION

A number of randomized trials have unequivocally shown that prophylactic cranial irradiation reduces the incidence of brain metastases in patients with limited small-cell lung cancer, with no increase in late toxic effects if such irradiation is not given concurrently with chemotherapy.[14-18] A meta-analysis revealed a survival benefit for patients with small-cell lung cancer treated with cranial irradiation,[17,18] with a 3-year survival rate of 20.7% among patients who underwent irradiation and 15.3% among those who did not.[17] The magnitude of this survival benefit is similar to that achieved with the use of thoracic radiotherapy in patients with limited small-cell lung cancer.[25] Guidelines for the treatment of small-cell lung cancer generally recommend that all patients who have a complete remission after chemotherapy undergo cranial irradiation. However, these guidelines also indicate that the role of cranial irradiation for most patients with extensive small-cell lung cancer is uncertain, particularly because the median survival is only 9 months,[26] and there are virtually no long-term survivors.[27] In view of the poor survival in

extensive small-cell lung cancer, enrollment in our study was limited to patients who had had a response to chemotherapy, and relatively short fractionation schedules were used. For the same reason, and to ensure that any favorable results could be easily applied to every practice outside the trial setting, patients with a response to chemotherapy were not subjected to brain imaging but were simply screened for predefined key symptoms of brain metastases.

Our study shows a clear advantage of cranial irradiation with respect to the incidence of symptomatic brain metastases (hazard ratio, 0.27). This reduction is greater than the hazard ratio of about 0.50 reported in previous trials, which mainly involved patients with limited small-cell lung cancer.[17,18] As expected, no effect of cranial irradiation on extracranial progression was seen, but cranial irradiation had a significantly positive effect on disease-free survival.

In our study, irradiation also had a significant effect on overall survival, with a hazard ratio for death of 0.68 and a prolongation of median survival by 6 weeks. At 1 year, survival in the irradiation group was 27.1%, as compared with 13.3% in the control group. This relative effect is greater than that observed in the meta-analysis by Aupérin et al., who reported a hazard ratio of 0.84.[17] Since previous studies mainly enrolled patients with limited small-cell lung cancer and determined survival from the time of diagnosis, not from the time of the initiation of irradiation (the criterion used in our study), the absolute survival rates in these studies were higher.[14-18]

The question of the optimal dose for cranial irradiation in limited small-cell lung cancer is unresolved. A dose–response relationship was reported for radiobiologically equivalent doses of up to 30 to 35 Gy (in 2-Gy fractions) but not for higher doses, provided that radiotherapy was started early after chemotherapy.[28] In the meta-analysis involving patients with mainly limited small-cell lung cancer, a trend toward a decreased rate of brain metastases after higher doses of radiotherapy was observed.[18] A randomized trial examining the dose–response relationship for cranial irradiation in patients with limited small-cell lung cancer has recently been completed (unpublished data). Since the median survival is only 9 months in extensive small-cell lung cancer,[26] irradiation schedules for patients undergoing this therapy should preferably be short. The majority of patients in our study (88 of 143) received only 20 Gy in five fractions, and an impressive reduction in the risk of brain metastases was still seen. The extracranial-progression rate of about 90% should be given priority for further investigations, since it is a more pressing concern than the dose–response relationship for prophylactic cranial irradiation in extensive small-cell lung cancer.

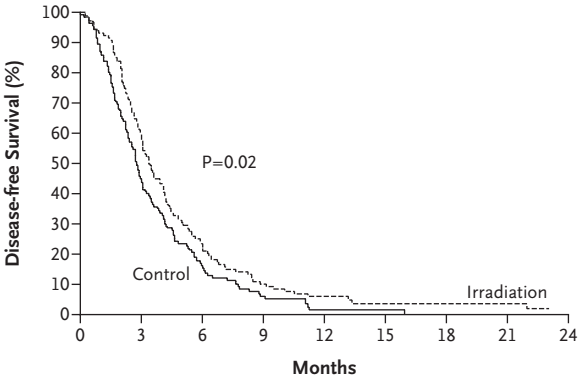

Figure 2. Disease-free Survival.

Patients in the irradiation group had a longer median period of disease-free survival (14.7 weeks) than did those in the control group (12.0 weeks) (P=0.02 by log-rank test; hazard ratio, 0.76; 95% CI, 0.59 to 0.96).

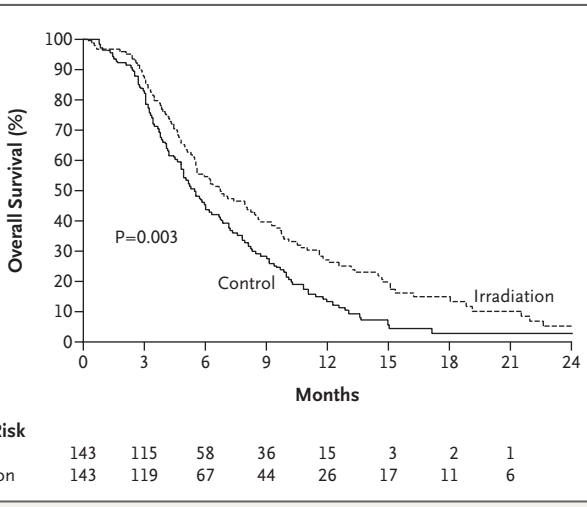

Figure 3. Overall Survival.

Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Table 2. Scores on Quality-of-Life Assessment.*

Quality-of-Life Score	Assessment Time	Prophylactic Cranial Irradiation	Control	P Value†
Primary end points				
Global health status	0–9 mo‡			0.10
Role functioning	0–9 mo‡			0.17
Cognitive functioning	0–9 mo‡			0.07
Emotional functioning	0–9 mo‡			0.18
Fatigue	6 wk	43.2±2.56	29.3±2.47	<0.001
	3 mo	53.6±3.03	38.5±3.24	<0.001
Hair loss	6 wk	36.5±3.96	11.7±3.73	<0.001
Exploratory results				
Appetite loss	6 wk	28.9±3.25	10.6±3.06	<0.001
	3 mo	43.9±3.87	14.8±4.18	<0.001
Nausea and vomiting	6 wk	15.0±1.73	5.3±1.64	<0.001
	3 mo	26.9±2.92	8.2±3.15	<0.001
Leg weakness	6 wk	25.2±2.71	11.8±2.48	<0.001
	3 mo	32.2±3.62	16.0±3.93	0.003

* Plus–minus values are means ±SD. The primary quality-of-life end points were assessed with two EORTC instruments: the core quality-of-life questionnaire (QLQ-C30) and an instrument specific for brain cancer (QLQ-BN20). Scores range from 0 to 100. For functional scales, higher scores represent a higher level of functioning; for symptom scales, higher scores represent a greater severity of symptoms.
† The comparisons at each time point were considered only if the overall test was significant at the 0.01 level.
‡ The differences between the two study groups were not significant in the overall analyses at any time point.

Maintenance chemotherapy has not been shown to improve survival in patients with extensive small-cell lung cancer, and despite such treatment, brain metastases developed in about 30% of patients.[4] Survival after relapse is generally poor, with a median of approximately 4 months.[29] A noteworthy finding in our study was that patients with extracranial progression who had also undergone cranial irradiation were more often treated for their progression than those in the control group (68.0% vs. 45.1%). Previous studies have reported that only 42% of the patients who underwent initial chemotherapy were suitable candidates for second-line chemotherapy at the time of disease progression,[30] with the remaining 58% suitable only for supportive care.[31]

Cranial irradiation was generally well tolerated, and side effects did not significantly influence patients' self-assessment of their global health status. However, a significant number of quality-of-life assessments were missing, owing to the rapid clinical deterioration of the patients. The relatively low frequency of quality-of-life assessments may not have allowed us to detect a benefit resulting from a prolonged remission time in the irradiation group.

Prophylactic cranial irradiation should be part of standard care for all patients with small-cell lung cancer who have a response to initial chemotherapy, and it should be part of the standard treatment in future studies involving these patients.

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APPENDIX

In addition to the authors, the following investigators and centers participated in this study: *National Cancer Institute, Cairo, Egypt* — R. Gafaar; *University Medical Center, St. Radboud, Nijmegen, the Netherlands* — J. Bussink; *Western Infirmary, Glasgow, United Kingdom* — A. Armour, N. Mohammed; *Universitair Ziekenhuis, Rotterdam, the Netherlands* — J. van Meerbeeck, P. Levendag, M. Van Mierlo; *Western General Hospital, Edinburgh* — A. Price; *Nottingham General–City Hospital, Nottingham, United Kingdom* — J. Christian, S. Morgan; *Southampton General Hospital, Southampton, United Kingdom* — C. Ottensmeier; *Dr. Bernard Verbeeten Instituut, Tilburg, the Netherlands* — P. Rodrigus, M. van de Pol; *Gdansk Medical University, Gdansk, Poland* — R. Dziadziuszko; *Radiotherapeutisch Instituut Friesland, Leeuwarden, the Netherlands* — W. Smit; *Radiotherapeutisch Instituut Stedendriehoek en Omstreken, Deventer, the Netherlands* — J. Immerzeel; *University Medical Center Groningen, the Netherlands* — A. van der Leest; *Velindre Hospital, Cardiff, United Kingdom* — F. Macbeth; *Newcastle General Hospital, Newcastle, United Kingdom* — P. Mulvenna; *Sophia Ziekenhuis, Zwolle, the Netherlands* — J. Stigt; *Universiteit Gent, Ghent, Belgium* — J. van Meerbeeck; *Academic Medical Center, Amsterdam* — L. Uitterhoeve; *Bristol Oncology Center, Bristol, United Kingdom* — S. Falk; *Centre Hospitalier Regional La Citadelle, Liege, Belgium* — L. Bosquee; *Algemeen Ziekenhuis Middelheim, Antwerp, Belgium* — C. Goor; *Bank of Cyprus Oncology Center, Nicosia, Cyprus* — D. Papamichael; *Clatterbridge Centre, Bebington, United Kingdom* — E. Marshall; *Marmara University Hospital, Istanbul, Turkey* — M. Abacioglu; *Royal Marsden Hospital, London* — M. O'Brien; *Universita Genova, Genoa, Italy* — T. Scolaro; *Dokuz Eylul University, Izmir, Turkey* — R. Cooper; *Mount Vernon Hospital, Northwood, United Kingdom* — N. Shah; *Nevill Hall Hospital, Abergavenny, United Kingdom* — J. Lester; *Princess Royal Hospital, Hull, United Kingdom* — M. Lind; *Raigmore Hospital, Inverness, United Kingdom* — D. Whillis; *Rambam Medical Center, Haifa, Israel* — T. Tzuk-Shina; *Santa Croce Hospital, Cuneo, Italy* — G. Numico; *University Medical Center Leiden, Leiden, the Netherlands* — L. Willems; and *University of Kaposvar, Kaposvar, Hungary* — K. Hideghety.

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