Postoperative radiotherapy versus no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART, IFCT 0503): an open-label, randomised, phase 3 trial

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Summary

Background In patients with non-small-cell lung cancer (NSCLC), the use of postoperative radiotherapy (PORT) has been controversial since 1998, because of one meta-analysis showing a deleterious effect on survival in patients with pN0 and pN1, but with an unclear effect in patients with pN2 NSCLC. Because many changes have occurred in the management of patients with NSCLC, the role of three-dimensional (3D) conformal PORT warrants further investigation in patients with stage IIIAN2 NSCLC. The aim of this study was to establish whether PORT should be part of their standard treatment.

Methods Lung ART is an open-label, randomised, phase 3, superiority trial comparing mediastinal PORT to no PORT in patients with NSCLC with complete resection, nodal exploration, and cytologically or histologically proven N2 involvement. Previous neoadjuvant or adjuvant chemotherapy was allowed. Patients aged 18 years or older, with an WHO performance status of 0–2, were recruited from 64 hospitals and cancer centres in five countries (France, UK, Germany, Switzerland, and Belgium). Patients were randomly assigned (1:1) to either the PORT or no PORT (control) groups via a web randomisation system, and minimisation factors were the institution, administration of chemotherapy, number of mediastinal lymph node stations involved, histology, and use of pre-treatment PET scan. Patients received PORT at a dose of 54 Gy in 27 or 30 daily fractions, on five consecutive days a week. Three dimensional conformal radiotherapy was mandatory, and intensity-modulated radiotherapy was permitted in centres with expertise. The primary endpoint was disease-free survival, analysed by intention to treat at 3 years; patients from the PORT group who did not receive radiotherapy and patients from the control group with no follow-up were excluded from the safety analyses. This trial is now closed. This trial is registered with ClinicalTrials.gov number, NCT00410683.

Findings Between Aug 7, 2007, and July 17, 2018, 501 patients, predominantly staged with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET (456 [91%]; 232 (92%) in the PORT group and 224 (90%) in the control group), were enrolled and randomly assigned to receive PORT (252 patients) or no PORT (249 patients). At the cutoff date of May 31, 2019, median follow-up was 4·8 years (IQR 2·9–7·0). 3-year disease-free survival was 47% (95% CI 40–54) with PORT versus 44% (37–51) without PORT, and the median disease-free survival was 30·5 months (95% CI 24–49) in the PORT group and 22·8 months (17–37) in the control group (hazard ratio 0·86; 95% CI 0·68–1·08; p=0·18). The most common grade 3–4 adverse events were pneumonitis (13 [5%] of 241 patients in the PORT group *vs* one [<1%] of 246 in the control group), lymphopenia (nine [4%] *vs* 0), and fatigue (six [3%] *vs* one [<1%]). Late-grade 3–4 cardiopulmonary toxicity was reported in 26 patients (11%) in the PORT group versus 12 (5%) in the control group. Two patients died from pneumonitis, partly related to radiotherapy and infection, and one patient died due to chemotherapy toxicity (sepsis) that was deemed to be treatment-related, all of whom were in the PORT group.

Interpretation Lung ART evaluated 3D conformal PORT after complete resection in patients who predominantly had been staged using (^{18}F-FDG PET-CT and received neoadjuvant or adjuvant chemotherapy. 3-year disease-free survival was higher than expected in both groups, but PORT was not associated with an increased disease-free survival compared with no PORT. Conformal PORT cannot be recommended as the standard of care in patients with stage IIIAN2 NSCLC.

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Introduction

Lung cancer is the leading cause of cancer incidence and mortality, with more than 2 million new lung cancers and 1·8 million deaths every year.[1] Surgery is the treatment of choice for suitable patients with stage I–IIIA non-small-cell lung cancer (NSCLC), but fewer than 30% of patients are eligible for this treatment option.[2] Even after the complete resection of operable NSCLC, patients are at a high risk of both distant and local recurrence. Consequently, adjuvant chemotherapy and radiotherapy have been evaluated in randomised trials to examine if they improve outcomes.[3–6] Postoperative adjuvant or neoadjuvant platinum-based chemotherapy was associated with an absolute survival benefit at 5 years post-randomisation of 5% and has therefore become the standard of care in patients with completely resected stage II–IIIA NSCLC.[5,6] More recently, EGFR tyrosine-kinase inhibitors have been evaluated as adjuvant treatment for patients with EGFR addictive mutations, with a disease-free survival benefit specifically in patients with N2 NSCLC.[7] Nonetheless, more than two-thirds of patients with operable stage III NSCLC present a

Research in context

Evidence before this study

Even among patients who have a complete resection of operable non-small-cell lung cancer (NSCLC), the risk of both distant and local recurrences is high. Adjuvant or neoadjuvant platinum-based chemotherapy has been part of the standard of care in patients with completely resected stage II to IIIA NSCLC with a survival benefit at 5 years of 5%, but with little effect on loco-regional control, especially in patients with stage IIIAN2 disease. A meta-analysis published in 1998 concluded that postoperative radiotherapy (PORT) was unsuitable for patients with pN0 and pN1 NSCLC, because it could be deleterious with regards to survival. In most of the included trials, suboptimal radiotherapy techniques by today's standards were used. Until June, 2021, no randomised phase 3 study evaluating modern PORT had been fully published, therefore the role of PORT in patients with completely resected N2 NSCLC was still controversial and debated for each individual patient by multi-disciplinary boards based on the evaluation of risks of loco-regional relapse.

We did a literature search on PubMed from date of publication of the meta-analysis in July 25, 1998, to June 15, 2021, using the terms from the Cochrane Database of Systematic Reviews applied in the review of PORT for NSCLC to search for clinical trials evaluating PORT in resected NSCLC published in English and French. The search terms used were: "lung cancer", "lung carcinoma", "NSCLC", "non-small cell", or "non small cell", and "surgery", "thoracic surgery", "lobectomy", or "surgical procedures", and "radiotherapy", "adjuvant radiotherapy", "PORT", or "post operative radiotherapy". We also identified review manuscripts or literature-based reported meta-analyses as well as meeting abstracts on lung cancer from several of the most important international conferences (American Society of Clinical Oncology, European Society of Medical Oncology, European Lung Cancer Conference, and World Conference on Lung Cancer) to find randomised studies, not included in the 1998 meta-analysis, evaluating PORT or adjuvant concomitant or sequential chemoradiotherapy after optimal resection. We identified two phase 2 randomised trials that were underpowered, one randomised single-centre phase 3 trial published in June, 2021, PORT-C, and a multi-institution phase 3 trial that was stopped because of poor accrual. Several large database studies, many retrospective studies, and one unplanned subgroup analysis from a randomised trial were identified, all that suggested that PORT could improve overall survival with acceptable cardiopulmonary toxicity. The question of the use of PORT in case of mediastinal involvement is valid, and has been unanswered for over 20 years since the publication of the meta-analysis. But two phase 3 randomised trials, PORT-C and the present trial, bring more insight to the debate surrounding PORT. The ongoing phase 3 JCOG1916, J-PORT study comparing postoperative radiotherapy to observation after adjuvant chemotherapy in patients with pathological N2 stage III NSCLC, initiated in January, 2021, might bring further insight.

Added value of this study

To the best of our knowledge, Lung ART, comparing postoperative radiotherapy with no postoperative radiotherapy in patients with completely resected NSCLC and proven mediastinal N2 involvement, is the first randomised study with an evaluation of both the quality of resection and three-dimensional (3D) conformal radiotherapy recorded after treatment to optimise the interpretation of the results. Although the 3-year disease-free survival was higher than expected in both groups (44% in the control group and 47% in the PORT group), the trial did not meet its primary objective of significantly improving disease-free survival with PORT.

Implications of all the available evidence

Lung ART provides robust evidence that 3D conformal PORT cannot generally be recommended as part of the standard of care in patients with resected stage IIIAN2 NSCLC. Because mediastinal relapse was substantially reduced by radiotherapy, other analyses are warranted to identify the patients for whom PORT could be used. Even if there was no deleterious effect of PORT in terms of overall survival, more toxicities were observed in the PORT group than the control group, especially cardiopulmonary toxicity, that need to be further explored. Whether intensity-modulated radiotherapy, which is an advanced form of 3D conformal radiotherapy, could reduce cardiopulmonary toxicities in the postoperative setting is a topic that could be explored in the future.

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recurrence, regardless of the use of neoadjuvant or adjuvant systemic treatment, and 20–40% of patients will present with loco-regional relapse.[8]

Postoperative radiotherapy (PORT) has been evaluated in several studies performed in the 1980–90s,[3,4,8] using radiotherapy techniques that would be suboptimal by current standards.[8] In the 2000s, three-dimensional (3D) conformal radiotherapy became the standard of care, allowing the radiation beams to match the shape of the tumour and subsequently reducing the exposure of normal tissues to radiation. In 1998, a meta-analysis on PORT clearly concluded that there was no place for PORT in patients with pN0 and pN1 NSCLC because it could be deleterious with regards to survival.[3] However, there was still potential for its use in patients with mediastinal nodal involvement. Since then, in addition to an improvement in radiotherapy techniques, there have been substantial improvements in the selection of patients with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT scan and brain imaging, and also in clinical management relating to thoracic surgery or intensive care, or both.[8,9] Furthermore, there is evidence that 3D conformal radiotherapy planning and delivery could improve the outcome of PORT through a decrease in the risk of death from radiotherapy-induced heart disease.[8,10–12] However, in the past two decades, the role of PORT in patients with completely resected N2 NSCLC in the era of 3D conformal radiotherapy is still controversial, and debated for each individual patient by multi-disciplinary boards on the basis of the evaluation of the risk of loco-regional relapse.[13,14] The Lung Adjuvant Radiotherapy Trial (Lung ART) was designed as a phase 3, randomised, superiority trial with the aim to provide robust evidence on the role of PORT in routine settings in patients with completely resected stage IIIAN2 NSCLC.

Methods

Study design and participants

Lung ART is an open-label, randomised, phase 3 study conducted in 64 hospitals and cancer centres in five countries in Europe (France, UK, Germany, Switzerland, and Belgium; appendix pp 109–110). Eligible patients were aged 18 years or older, with histological evidence of NSCLC, complete resection by lobectomy, bi-lobectomy, or pneumonectomy, and mediastinal lymph node exploration. Patients had to have pathologically or cytologically documented N2 mediastinal nodal involvement at the time of surgery if no preoperative chemotherapy was delivered or if there was mediastinal downstaging before preoperative chemotherapy. Chemotherapy was allowed (preoperative or postoperative adjuvant chemotherapy, or both), but not concomitantly during radiotherapy. Patients were required to have a WHO performance status of 0–2 to be fit enough to receive curative radiotherapy after surgery, and to have an adequate pulmonary function with a postoperative forced expiratory volume in 1 s after surgery of more than 1 L, or more than 35% of the theoretical value of each individual patient. Patients with a history of previous chest radiotherapy, synchronous contra-lateral lung cancer, past or current history of neoplasm, and recent (<6 months) severe cardiac or pulmonary disease were excluded (full list of inclusion and non-inclusion criteria is available in appendix pp 111–112). Participants gave written, informed consent and the study was done according to the Declaration of Helsinki and Good Clinical Practice Guidelines.

A French national ethics committee granted the initial approval for the study on June 22, 2006. The protocol was also approved by an institutional review board or research ethics committee in each country. The study protocol and statistical analysis plan are available (appendix).

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) to one of the two treatment groups (either receiving PORT *vs* not receiving PORT after surgery [control group]) via a web randomisation system (TENAlea, version 2.2; TransEuropean Network for Clinical Trial Services, Amsterdam, Netherlands). Randomisation was done in some centres by fax. The allocation method was minimisation based on institution, administration of chemotherapy (preoperative alone *vs* post-operative *vs* none), number of mediastinal lymph node stations involved (0 *vs* 1 *vs* 2 or more), histology (squamous cell carcinoma *vs* others), and the use of pre-treatment ^{18}F-FDG PET-CT (yes *vs* no). The patients' doctors enrolled the participants, and were further involved in treating and following up the patients. The trial was open label.

Procedures

Screening and random assignment occurred after the patients had undergone surgery or after they received adjuvant chemotherapy if applicable. Only patients who underwent a radiological evaluation to rule out metastatic disease, including thoracic and abdominal CT scans and brain imaging (brain CT scan or MRI) were eligible for participation in Lung ART. Whole body ^{18}F-FDG PET-CT was strongly recommended, but not mandatory. Staging was done using the Union for International Cancer Control and American Joint Committee on Cancer classification system, version 7.[15] Patients in the PORT group received PORT at a dose of 54 Gy in 27 fractions of 2·0 Gy or 30 fractions of 1·8 Gy, on five consecutive days a week for 5·5 weeks. Detailed timelines were defined in the protocol to ensure an appropriate randomisation procedure and, when applicable, PORT would be initiated after surgery, as per protocol.

The use of 3D conformal radiotherapy was mandatory, and intensity-modulated radiotherapy (IMRT) was permitted in centres with expertise. The target volume was treated through use of a suitable radiotherapy technique that resulted in the least amount of surrounding organs being at risk. According to the protocol recommendations, at least 95% of the planning target

volume (PTV) should receive 95% of the prescribed dose, and no more than 10% of the PTV should receive more than 107% of the prescription dose. The target volume comprised the resected clinical tumour volume (rCTV), corresponding to the lymph nodes involved according to the pathological report of the lymph node exploration. In the case of preoperative chemotherapy, the initially involved lymph node stations were included in the rCTV, even in the case of downstaging. The bronchial stump, the ipsilateral hilar node region, and the probable extension to the mediastinal pleura adjacent to the completely resected tumour bed were also included in the rCTV. The mediastinal CTV included the rCTV plus a margin of 1 cm to account for the microscopic extension of nodal disease. Because of the frequent involvement of subcarinal (LN7) and ipsilateral paratracheal nodes (LN4) reported previously,[16] these stations were systematically included in the CTV. To obtain the final PTV, an additional margin of at least 0·5 cm (lateral, anterior, and posterior) and 1 cm (superior and inferior) to the CTV was recommended. Dose constraints were used for the lungs, heart, and spinal cord (appendix p 113). A programme of surgical and radiotherapy quality assurance was used.[17,18] Refined definitions of complete resection incorporating quality standards of tumour resection and lymph node exploration were implemented in our analysis, based on the International Association for the Study of Lung Cancer definition of complete resection.[19] After a retrospective, careful review by the advisory surgical quality assurance committee of all available surgical and pathological reports, nodal explorations were analysed and qualified either as a sampling, selective dissection, or complete dissection. Complete resections were reclassified into a R0 resection, an uncertain resection (because of incomplete nodal staging, involved N2 nodes removed in the fragments, or the highest N2 station being positive), or R1 resection (because of nodal extracapsular extension). All available radiotherapy plans were analysed by the advisory radiotherapy quality assurance committee, taking into consideration the protocol recommendations and the involved stations to evaluate whether the mediastinal target coverage was adequate, inadequate, or non-evaluable. Quality assurance of local treatments and their possible effect on outcome and toxicity will be assessed in future and published elsewhere.

Patients were evaluated 3 and 6 months after randomisation, then subsequently every 6 months for the first 3 years and once per year afterwards. Investigations included a physical evaluation, reporting of adverse events, and a CT scan of the thorax; and a chest CT scan was required in the follow-up (other possible investigations were not specified because they were optional). To detect possible cardiac or pulmonary toxicity, patients had to undergo yearly lung function tests (forced expiratory volume in 1 s and diffusing capacity for carbon monoxide) and a cardiac ultrasound until disease progression. Adverse events (assessed using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) were reported 3 months after random assignment, then every 6 months for 3 years, and then once per year until the end of the study. All patients were followed up until 8 years after the date of last patient inclusion.

Outcomes

The primary endpoint was investigator-assessed disease-free survival, analysed at all times, defined as time from random assignment to local or distant recurrence, including mediastinal relapse, brain metastases, or other metastases, or death from any cause, whichever occurred first. The secondary endpoints were overall survival (defined as the time from random assignment to the time of death from any cause), adverse events (classified as early if occurring within the first 3 months after random assignment, and late if occurring after 3 months), local control and patterns of recurrence, secondary cancers, and prognostic and predictive factors of treatment effect on disease-free survival and overall survival. An ancillary health–economic analysis (which included French centres only) and exploratory translational objectives regarding efficacy and toxicity were also prespecified outcomes. Analysis of local control will be refined in future dedicated analyses accounting for patterns of failure with a competing events approach. Health–economic and translational analyses will be reported in future studies. Predictive and prognostic factors for overall survival were not assessed in this study because data for overall survival were not mature. Further analyses of safety data, including an exploration of prognostic and predictive factors and correlations with radiotherapy data will be reported elsewhere.

Statistical analysis

Considering a 3-year disease-free survival rate of 30% in the control group (ie, patients who were not treated with PORT),[5] 430 events were required to be able to detect a 10% absolute improvement in disease-free survival in the PORT group (ie, 40% at 3 years) in comparison by a log-rank test with a power of 80% and a bilateral 5% level of significance. 700 patients were therefore needed. An interim analysis for both efficacy and futility was planned and implemented after the occurrence of 215 events, based on a Haybittle–Peto boundary ($p<0·001$ for statistical significance).[20] On Dec 12, 2016, because of the slow recruitment caused by competitive trials evaluating adjuvant immunotherapy, and after agreement by the independent data monitoring committee and regulatory authorities, the protocol was amended to lower the targeted accrual to 500 patients (292 events), corresponding to a hypothesised 12% difference in 3-year disease-free survival (associated hazard ratio [HR] 0·72). Disease-free survival was estimated using the Kaplan-Meier method (Greenwood CIs) and compared between the two groups using a Cox regression analysis model

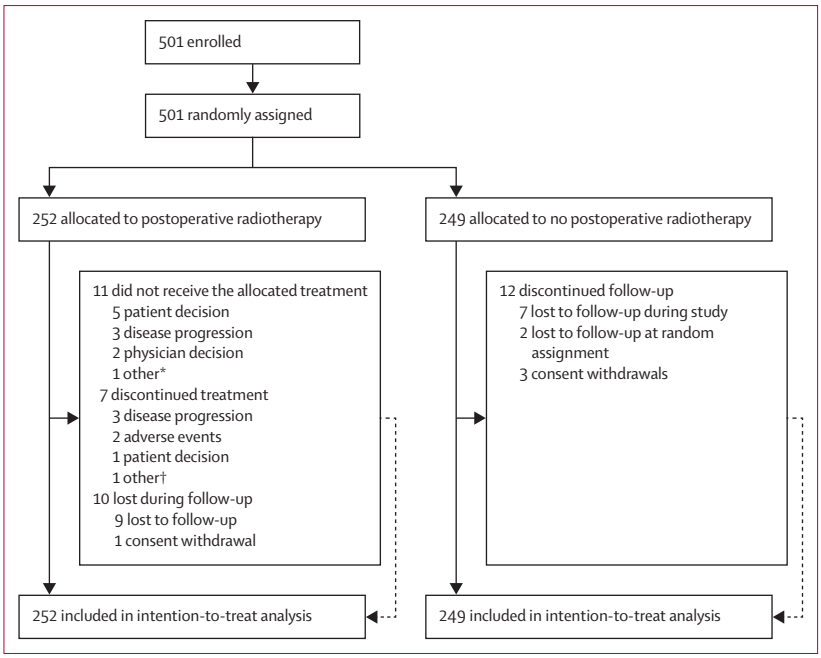

Figure 1: **Trial profile**
*Pulmonary infection. †Infectious pneumonitis.

adjusted on the stratification factors used for random assignment (Wald CIs and p values). The proportional hazards assumption was assessed through visual inspection. All efficacy analyses were performed in the intention-to-treat population, including all randomly assigned patients. Overall survival estimates and predefined predictive and prognostic factors for disease-free survival were assessed using the same methods used to assess disease-free survival. Considered factors included stratification factors, variables related to tumour location, nodal involvement, nodal exploration, quality of radiotherapy, and quality of surgery, and were selected in a multivariable model using backward selection with a 5% threshold for statistical significance. Median follow-up was calculated using the Schemper method.[21] Patients from the PORT group who did not receive radiotherapy and patients from the control group with no follow-up were excluded from the safety analyses. All reported toxicities were accounted for and analysed considering the highest reported grade. Adverse events were analysed as a whole, and considered early and late reports separately. Occurrence of a second cancer is described by group, along with type of cancer.

Analyses were performed with SAS (version 9.4). This study was registered with the ClinicalTrials.gov, NCT00410683.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Aug 7, 2007, and July 17, 2018, 501 patients were enrolled and randomly assigned after the completion of surgery or adjuvant chemotherapy: 252 (50%) in the PORT group and 249 (50%) in the control group (figure 1). They were enrolled by 64 hospitals and cancer centres in five different countries in Europe. The centres enrolled between one and 49 patients (median 13; IQR 7–16); the 21 largest centres (which each enrolled ten or more patients) recruited a total of 343 patients (69%). The Intergroupe Francophone de Cancérologie Thoracique in France recruited 427 patients (85%) from Aug 7, 2007; the National Cancer Research Networks in the UK recruited 50 patients (10%) from June, 2012; Germany recruited 15 patients (3%) from October, 2013; the Swiss Group for Clinical Cancer Research included eight patients (2%) from October, 2014; and one patient was recruited from Belgium.

Clinical and treatment characteristics are shown in tables 1 and 2. The median age at randomisation was 61 years (IQR 55–67). Most patients were fit: only six (1%) patients had a performance status of 2 at random assignment (two [1%] in the PORT group and four [2%] in the control group). 46 (9%) patients were never smokers (20 [8%] of 251 patients in the PORT group and 26 [11%] of 247 patients in the control group), most patients (398 [79%]) were former smokers (205 [82%] in the PORT group and 193 [78%] in the control group), and 54 (11%) were current smokers (26 [11%] in the PORT group and 28 [11%] in the control group). Most patients (456 [91%]) were staged with a PET-CT scan (224 [90%] in the control group and 232 [92%] in the PORT group), and the median interval between PET-CT scan and first treatment (surgery or chemotherapy) was 36 days (IQR 22–50).

The median interval between surgery and random assignment was 4·2 months (IQR 3·3–4·8) and the median time from adjuvant chemotherapy to PORT was 36 days (29–46), therefore the median interval between random assignment and PORT was 19 days (14–22). One of the inclusion criteria was complete surgical resection, and all patients except two (one in the control group and one in the PORT group) had no tumour involvement of the resection margins or no positive cytology of pleural or pericardial effusion, or both. Therefore, using a basic examination of resection margins to define complete resection,[19] 491 of 493 patients with full reports available were R0 (249 in the PORT group and 242 in the control group). To evaluate the effect of locoregional treatment on outcome, after a review of the surgical and pathological reports (all anonymised) in accordance with International Association for the Study of Lung Cancer,[19] 139 (28%) of 493 patients had R0 resection, 203 (41%) patients had an uncertain resection, and 149 (30%) patients had an R1 resection (table 2).

Most patients received either preoperative or postoperative chemotherapy, or both (480 [96%]), but few patients were treated exclusively with preoperative

	PORT group (n=252)	Control group (n=249)
Sex		
Men	167 (66%)	165 (66%)
Women	85 (34%)	84 (34%)
Age, median	61 (55–67)	61 (55–67)
Smoking status		
Current	26/251 (10%)	28/247 (11%)
Former	205/251 (82%)	193/247 (78%)
Never	20/251 (8%)	26/247 (11%)
Missing information	1	2
Performance status (WHO)		
0	121 (48%)	123 (49%)
1	129 (51%)	122 (49%)
2	2 (1%)	4 (2%)
N2 status before any treatment		
N0 nodal involvement (N2 unforeseen)	59/240 (25%)	70/239 (29%)
N1 (N2 unforeseen)	43/240 (18%)	29/239 (12%)
Single station N2	83/240 (35%)	80/239 (34%)
Multiple station N2	55/240 (23%)	60/239 (25%)
Missing information	12	10
Histology		
Squamous cell carcinoma	57 (23%)	51 (21%)
Adenocarcinoma	177 (70%)	189 (76%)
Large cell carcinoma	7 (3%)	5 (2%)
Mixed	8 (3%)	2 (1%)
Other*	3 (1%)	2 (1%)
Methods of adjuvant chemotherapy treatment		
No chemotherapy	10 (4%)	11 (4%)
Preoperative chemotherapy	36 (14%)	31 (12%)
Postoperative chemotherapy	189 (75%)	195 (78%)
Preoperative and postoperative chemotherapy	17 (7%)	12 (5%)
Pretreatment PET scan	232 (92%)	224 (90%)

Data are shown as median (IQR) or n (%). Percentages are calculated using non-missing values. PORT=postoperative radiotherapy. *Specific information on type was not collected.

Table 1: **Baseline characteristics**

	PORT group (n=252)	Control group (n=249)
Number of mediastinal node stations involved		
None	9 (4%)	6 (2%)
One station involved	169 (67%)	160 (64%)
Two or more stations involved	74 (29%)	83 (33%)
Nodal extracapsular extension		
Yes	59 (23%)	63 (25%)
No	98 (39%)	113 (45%)
Unspecified	95 (38%)	73 (29%)
Type of surgery		
Bilobectomy	19 (8%)	17/247 (7%)
Lobectomy	197 (78%)	201/247 (81%)
Pneumonectomy	31 (12%)	24/247 (10%)
Sublobar resection	5 (2%)	5/247 (2%)
Missing information	0	2
Quality of resection before surgical committee review intervention*		
R0	249/250	242/243
R2	1/250 (<1%)	1/243 (<1%)
Quality of resection according to surgical committee review*		
R (uncertain)	101/250 (40%)	102/243 (42%)
R0	74/250 (30%)	65/243 (27%)
R1 (nodal extracapsular extension)	74/250 (30%)	75/243 (31%)
R2	1/250	1/243
Missing information	2	6
Thoracic irradiation	241 (96%)	..
Early termination of radiotherapy†	7/241 (3%)	..
Total received dose (in Gy)†		
≤50	7/241 (3%)	..
51–57	231/241 (96%)	..
>57	3 (1%)	..
Main radiotherapy variables†		
Lung V20	23% (17–27)	..
Mean lung dose (Gy)	13 (10–15)	..
Mean heart dose (Gy)	13 (8–19)	..
Heart V35	15% (8–24)	..
PORT technique†		
Three-dimensional conformal radiotherapy	201/226 (89%)	..
Intensity-modulated radiotherapy	25/226 (11%)	..
Missing information	15	..

Data are median (IQR) or n (%). Percentages are calculated using non-missing values. Heart V35=percentage of the normal heart receiving at least 35 Gy. Lung V20=percentage of the normal lung receiving at least 20 Gy. PORT=postoperative radiotherapy. *Two patients in the PORT group and six patients in the control group did not have a surgical report or anatomopathological files, or both, available in the included centres and were thus not reviewed by the surgical committee. †11 patients did not receive radiotherapy.

Table 2: **Surgery and radiotherapy characteristics**

chemotherapy (67 [13%]; table 1). All patients given chemotherapy had platinum-based doublets. Among the 252 patients in the PORT group, 11 (4%) did not receive radiotherapy (figure 1). 241 (96%) patients received radiotherapy, and excluding the 15 patients with missing information, 201 (89%) had 3D conformal radiotherapy and 25 (11%) had IMRT (table 2). 230 patients (95%) received the prescribed dose of 54 Gy, eight (3%) patients received a lower dose (range 21–52), and three (1%) patients received a higher dose (range 56–70). The median heart dose was 13 Gy (IQR 8–19), median lung dose 13 Gy (10–15), and median percentage of the normal lung receiving at least 20 Gy was 23% (17–27; table 2, appendix p 126). All values were within the dose constraints specified in the protocol.

At the data analysis cutoff on May 31, 2019, the median follow-up was 4·8 years (IQR 2·9–7·0) for both groups, and 18 (4%) patients (nine in the control group and

	PORT group (n=252)	Control group (n=249)
All disease-free survival events	144	152
Relapses and metastases	123 (85%)	144 (95%)
Mediastinal relapse	36 (25%)	70 (46%)
Brain metastasis	34 (24%)	27 (18%)
Extracranial metastasis	71 (49%)	71 (47%)
Death	21 (15%)	8 (5%)
Causes of death		
Cardiopulmonary	11 (8%)	0
Non-cancer related	0	1 (1%)
PORT toxicity	2 (1%)	0
Progression	1 (1%)	0
Second primary cancer	4 (3%)	2 (1%)
Vascular	0	1 (1%)
Unknown	3 (2%)	4 (3%)

Data are n (%), regarding the number of patients with event. Patients can have several different events at the same time. PORT=postoperative radiotherapy.

Table 3: **Disease-free survival events**

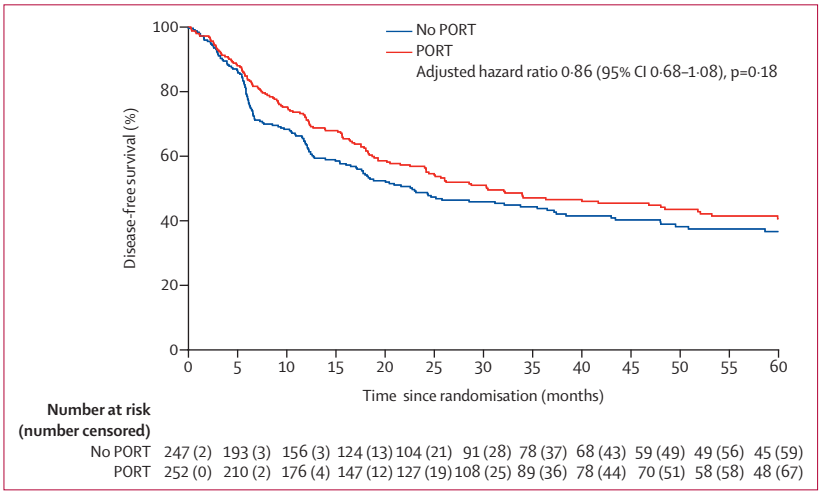

Figure 2: **Kaplan-Meier survival estimates for disease-free survival**
PORT=postoperative radiotherapy.

nine in the PORT group) were lost to follow-up. At the time of analysis, among the 501 allocated patients, 296 patients (59%) had a recurrence or died: 144 (57%) of the 252 in the PORT group and 152 (61%) of the 249 in the control group (table 3). 3-year disease-free survival was 47% (95% CI 40–54) in the PORT group and 44% (37–51) in the control group. The adjusted disease-free survival hazard ratio was 0·86 (95% CI 0·68–1·08; p=0·18; figure 2) and has to be interpreted in a context of slight non-proportionality of risks. The median disease-free survival was 30·5 months (95% CI 24·0–48·5) in PORT group and 22·8 months (17·0–36·5) in the control group. 267 patients had a relapse (one or more) as first event; of the 296 patients with disease-free survival events, 106 (36%) had mediastinal relapse (36 [25%] of 144 patients in the PORT group and 70 [46%] of 152 patients in the control group), 61 (21%) had brain failure (34 [24%] in the PORT group and 27 [18%] in the control group), and 142 (48%) had extracranial metastatic failure (71 [49% in the PORT group and 71 [47%] in the control group; table 3). 29 patients (10%) had death as the first event (21 [15%] in the PORT group and eight [5%] in the control group). The hazard ratio associated with PORT with respect to disease-free survival was consistent across all predefined subgroups according to stratification factors (appendix p 114).

201 patients died: 102 (42%) in the control group and 99 (41%) in the PORT group (table 4). Most patients died of recurrence: 87 (85%) in the control group and 68 (69%) in the PORT group. Two (2%) patents in the control group and 16 (16%) in the PORT group died due to cardiopulmonary disease. One (1%) in the control group and five (5%) in the PORT group died because of a second primary cancer. Three patients died of causes related to chemotherapy toxicity (one patient because of sepsis) or radiotherapy toxicity (two patients died from pneumonitis, partly related to radiotherapy and infection—both less than 3 months after randomisation), all in the PORT group. 19 additional patients died from pulmonary infection, vascular, other, or unknown causes: 12 (12%) in the control group and seven (7%) in the PORT group. 3-year overall survival was 69% (95% CI 61–75) in the control group and 67% (59–73) in the PORT group (appendix page 115). Early analysis of overall survival data show a similar occurrence of deaths in both treatment groups (adjusted HR 0·97; 95% CI 0·73–1·28). Further analyses will be performed with future follow-ups. 27 (11%) patients in the PORT group and 17 (7%) patients in the control group had second primary cancers (appendix p 124).

An analysis of the prognostic factors for disease-free survival is presented in the appendix (p 125).

Most patients (398 [82%]) had at least one early toxicity: 215 (89%) of 241 in the PORT group and 183 (74%) of 246 in the control group (table 4). Most of these early toxicity events were grade 1 or 2. Early grade 3–4 adverse events were reported in 28 patients (12%) in the PORT group and 19 patients (8%) in the control group (table 4). 341 patients (70%) described at least one late toxicity (188 [78%] in the PORT group and 153 [62%] in the control group), mostly grade 1 and 2. 26 (11%) of 241 were described in the PORT group and 12 (5%) of 246 in the control group had late grade 3–4 cardiopulmonary toxicities (where some participants had both cardiac and pulmonary events). The most common grade 3–4 adverse events were pneumonitis (13 [6%] patients in the PORT group *vs* one [<1%] in the control group), lymphopenia (nine [4%] *vs* 0), and fatigue (six [3%] *vs* one [<1%]; appendix pp 116–123).

Discussion

To our knowledge, Lung ART is the first, European, randomised, phase 3 study evaluating the role of

3D conformal PORT after a (considered) complete resection of stage IIIAN2 NSCLC, showing no decrease in the risk of death or progression for PORT. Notably, 91% of the patients were staged with PET-CT scan and 96% received neoadjuvant or adjuvant chemotherapy. 3-year disease-free survival (44% in the control group and 47% in the PORT group) was higher than initially hypothesised in both groups. In terms of the types of disease-free survival events, mediastinal relapse was lower in the PORT group (46% in control group *vs* 25% in the PORT group), but death was higher (5% in the control group *vs* 15% in the PORT group) with an excess of deaths related to cardiopulmonary diseases as reported by local investigators. Differences between the patterns of failure in the two groups, and in particular the increased early occurrence of mediastinal relapses in the control group, could potentially explain the Kaplan-Meier survival curves, with evidence for the non-proportionality of risks. These patterns will be further investigated in future analyses. A higher proportion of late toxicities was observed in the PORT group than in the control group, especially cardiopulmonary, which will require more detailed analyses.

The use of PORT in routine treatment settings for NSCLC had been challenged by the 1998 PORT meta-analysis.[3] Specifically, in patients with N2 NSCLC, PORT did not improve survival but did have an effect on local control, with a 24% reduction in the overall risk of local recurrence compared with surgery alone. Therefore, further studies were warranted that used more modern radiotherapy and surgical techniques, as well as contemporary chemotherapy as emphasised by reviews of the literature and guidelines.[8,9,13,14] Another meta-analysis compared the effect of PORT on local recurrence and survival in patients treated on linear accelerators or older cobalt machines.[22,23] No significant difference in overall survival was reported according to the type of radiotherapy machine used (relative risk 0·85 [95% CI 0·59–1·22]; p=0·38). Furthermore, the rate of local recurrences was decreased with PORT independent of the type of machine used.[22] It should be noted that the meta-analysis did not specifically address the question of use of two-dimensional (2D) versus 3D conformal radiotherapy.[22] However, in most of the studies included, patients were treated with 2D radiotherapy, which is no longer used in contemporary radiotherapy practice. Large database studies in North America have shown that 3D conformal radiotherapy seems to be independently associated with a survival advantage in patients with stage III NSCLC.[10–12,24] It should be highlighted that in the Lung ART study, all patients had conformal radiotherapy, customised according to the results of nodal exploration: 89% with a 3D technique and 11% with IMRT. In addition, 91% of patients were staged using ^{18}F-FDG PET-CT. The use of modern staging and radiotherapy techniques contributed to better patient selection and improved the accuracy of PORT. However, we also reported an increased number of non-cancer related deaths and cardiopulmonary adverse events in the PORT group compared with the control group. This is in line with the accumulating evidence on the effect of thoracic radiotherapy on cardiac toxicity and the role of IMRT, image-guided radiotherapy, and more sophisticated heart constraints[24–26] in reducing the cardiac and pulmonary toxicity risk. When accrual started in the Lung ART study, there was little evidence supporting the routine use of lung IMRT. The Lung ART trial management group decided that IMRT would be authorised only in centres with accredited IMRT expertise in thoracic tumours. Because of the long period of recruitment (2007–2018), the rate of IMRT was rather low. IMRT has now become a standard radiotherapy technique in many countries given its better dose conformity and scope for avoidance of the surrounding healthy tissues, such the heart and lung.[24,25] Further analysis of the quality of surgery and radiotherapy will be of needed for

	PORT group (n=241)	Control group (n=246)
Deaths*	99 (41%)	102 (42%)
Progression of recurrence	68 (69%)	87 (85%)
Chemotherapy toxicity	1 (1%)	..
Radiotherapy toxicity	2 (2%)	..
Cardiopulmonary disease	16 (16%)	2 (2%)
Second primary cancer	5 (5%)	1 (1%)
Pulmonary infection	1 (1%)	..
Vascular	1 (1%)	1 (1%)
Other†	..	3 (3%)
Unknown	5 (5%)	8 (8%)
Adverse event, any grade‡	222 (92%)	200 (81%)
Early adverse events	215 (89%)	183 (74%)
Late adverse events	188 (78%)	153 (62%)
Adverse events, grade 3–5	60 (25%)	37 (15%)
Adverse events, grade 3 or 4	57 (24%)	37 (15%)
Early adverse events	28 (12%)	19 (8%)
Late adverse events§	36 (15%)	22 (9%)
Total late cardiac events	10 (4%)	5 (2%)
Cardiac ischaemia or infarction	3 (1%)	..
Total late thoracic events	28 (12%)	9 (4%)
Dyspnoea (thoracic)	7 (3%)	5 (2%)
Pneumonitis (thoracic)	9 (4%)	..

Data are n (%). Presented numbers are the numbers of patients with at least one event. *Percentages calculated from the total number of deaths. †The other causes of death here were one suicide, one myeloma chemotherapy toxicity, and one chronic endstage renal disease. ‡Percentages calculated from the total number of patients. §The most reported adverse events categories (more than 3%) and terms (more than two events) are shown.

Table 4: **Safety profile**

exploring which groups of patients might benefit most from PORT with lower risks of toxicity.

The beneficial effect of PORT in terms of loco-regional control, as suggested by the results of the PORT meta-analysis,[3] is confirmed in Lung ART with a reduction of approximately 50% in the risk of mediastinal relapse using PORT compared with the control group. This finding is clinically relevant because mediastinal relapse can lead to troublesome symptoms and poor quality of life. PORT appeared to have a stronger effect on mediastinal control in our study than in the meta-analysis, probably because of the improved radiotherapy and surgery used.[3] There has been much controversy on the prognostic value of several common clinical factors in patients with NSCLC with resected N2 disease, and their relative importance varies across studies. The number of mediastinal nodes involved is one of the most consensual and significant prognostic factors and this was confirmed by our analysis.[27]

In resected NSCLC with N2 disease, the role of extracapsular extension has been poorly studied.[28] In head and neck squamous cell cancer, extracapsular extension is highly prognostic for local recurrence, but it is not for breast cancer. After careful review of all pathological reports of patients included in Lung ART, we noticed that the presence or absence of extracapsular extension was inconsistently reported by pathologists: this information was missing in 33% of reports. The presence of extracapsular extension in mediastinal nodes contributed to changing the status of the surgical resection from R0 to uncertain or R1, applying the International Association for the Study of Lung Cancer definition of complete resection.[19] To the best of our knowledge, neither the number of mediastinal nodes involved, their location, nor the status of extracapsular extension has ever been studied prospectively in a randomised study evaluating adjuvant treatment. Because there was an insufficient description of nodal extracapsular extension and whether such nodes were removed separately or not, it was decided that patients with nodal extracapsular extension would be considered R1. In our first explorative analysis, confirmed R0 resection was a prognostic factor and the effect of the status of surgical resection as well as of extracapsular extension on local failure and outcome will be reported in detail in the future.

When we started the study, there was no randomised study evaluating the role of PORT in patients with proven mediastinal nodal involvement who had received neoadjuvant or adjuvant chemotherapy, or both. Among the studies published since the start of Lung ART on PORT, the ANITA trial should be specifically highlighted because it was conducted in the era of adjuvant chemotherapy. This randomised phase 3 trial evaluated adjuvant chemotherapy in 840 patients with resected NSCLC, of which 232 patients also received PORT.[29] In an unplanned subgroup analysis of patients with N2 disease, PORT was associated with improved survival in both the chemotherapy group (median survival, 23·8 months without PORT and 47·4 months with PORT) and in the observation group (median survival, 12·7 months without PORT and 22·7 months with PORT).[29] The authors thereby advocated that further evaluation of PORT in completely resected pN2 NSCLC should be performed in randomised trials. In the past 10 years there have been few randomised trials comparing adjuvant chemotherapy to concomitant or sequential chemoradiotherapy: two phase 2 randomised studies showed no advantage in overall survival with the trimodality strategy (surgery and concomitant chemoradiotherapy) over surgery and adjuvant chemotherapy.[30,31] Both studies were underpowered. It should be outlined that, in the first study, patients had no PET-CT scan before treatment, and mediastinal node exploration might have been suboptimal because 60% of patients had nodal sampling.[30] In the second study, only patients with unsuspected N2 disease were included, and they all had a PET-CT scan before surgery.[31] In 2021, a phase 3 study comparing surgery plus chemotherapy versus surgery plus chemotherapy and PORT in 364 patients with completely resected pIIIA N2 NSCLC has been published. PORT did not significantly improve disease-free survival or overall survival, although it did significantly improve local relapse-free survival.[32]

Our trial has some limitations. Disease-free survival events have been reported based on investigator assessment. An independent centralised review could have been included but its input would be limited because eligible patients had no detectable disease at random assignment, because this study is a real life situation with recurrence being observed clinically or on imaging; in such a study evaluating adjuvant treatment, we deal with recurrence and not disease progression. Because of slow accrual, the total number of patients was reduced from 700 to 500 patients, but the statistical hypothesis was readjusted. Because the trial ran over 10 years, there is some heterogeneity regarding the techniques of PORT delivery. When we started the trial, 3D conformal radiotherapy was considered the safest and most appropriate technique for patients with lung cancer compared with IMRT, which was seldom used because of concerns regarding safe delivery and the low amount of evidence with lung cancer compared with head and neck and prostate cancer. In the past 5 years, IMRT has become more widely available for thoracic cancers such as lung and breast cancer.

In summary, until now, the administration of PORT in patients with mediastinal nodal involvement relied mostly on data from non-randomised studies. Several large database studies, as well as one unplanned subgroup analysis from a randomised trial, suggested that PORT given after adjuvant chemotherapy could improve overall survival,[10–12,29] assuming that 3D conformal radiotherapy would be associated with less cardiopulmonary toxicity.[10,24] Lung ART provides robust evidence that 3D conformal PORT cannot generally be recommended as the standard

of care in patients with resected stage IIIAN2 NSCLC. Incorporation of newer systemic treatments, such as immune checkpoint inhibitors or targeted therapy in patients with oncogene-addicted NSCLC, alongside neoadjuvant or adjuvant, or both treatments is underway. Whether the use of IMRT or, in the future, intensity modulated proton therapy in the postoperative setting, combined sequentially with immunotherapy, might contribute to improving the outcome of patients at a high risk of relapse should be evaluated. We hope that ongoing analyses will allow for refining the profile of optimal candidates for PORT. Analysis of circulating tumour DNA could also enable the identification of patients at a high risk of disease recurrence on the basis of the detection of post-surgical minimal (or molecular) residual disease.

Contributors

CLP and AD conceptualised the study after discussions within Intergroupe Francophone de Cancerologie Thoracique and the European Organisation for Research and Treatment of Cancer Lung Group and Radiation Oncology Group. CLP, AD, AB, and EB-M curated the data. AB and AD did the formal analysis. CLP, AD, CF-F, and OR acquired the funding. CLP, NP, FB, DL, DA, BL, UN, PB, ED, AP, KP, FT, GZ, JM, EP, ALar, ALav, DA-L, MD, CF-F, MQH, and OR did the investigation. JGE, PAT, and OM participated as co-investigators (thoracic surgeons). AD and AB produced the methods and did the project administration. CLP and AD supervised the study. CLP, AB, and AD validated and visualised the study, and wrote the original draft. CLP, NP, FB, DL, DA, BL, UN, PB, ED, AP, KP, FT, GZ, JM, EP, ALar, ALav, DA-L, MD, CF-F, MQH, OR, EB-M, AD, JGE, PAT, OM, and AB reviewed and edited the study. CLP, EB-M, and AB accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CLP reports grants to the institution from Amgen, AstraZeneca, Eli Lilly, Medscape, and Nanobiotix; grants to the institution for participation in advisory boards for Roche; and grants to the institution for speaker fees from PriMEOncology, all outside the submitted work. NP reports grants from Pfizer and Varian, all outside the submitted work. FB reports personal fees from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer-Ingelheim, Eli Lilly Oncology, Roche, Novartis, Merck, Merck Sharp & Dohme, Pierre Fabre, Pfizer, and Takeda, outside the submitted work. UN reports consulting fees, honoraria, and participation in advisory boards for AstraZeneca. PB reports honoraria from AstraZeneca, Bristol-Myers Squibb, and Merck; support for meetings and travel from Merck Sharp & Dohme; and participation in advisory boards for Merck. ED reports personal financial interests from Astra-Zeneca, Ipsen, Merck Sharp & Dohme, Novartis, and Roche, all outside the submitted work. GZ reports personal fees from AstraZeneca, BMS, Boehringer, and MSD; and non-financial support and funding for international meeting attendance from Abbvie, AstraZeneca, MSD, Pfizer, Roche, and Takeda, all outside the submitted work. EP reports personal financial interests from AstraZeneca, Bristol-Myers Squibb, Roche, and Takeda; and non-financial support from AstraZeneca, Bristol-Myers Squibb, and Merck Sharp & Dohme, all outside the submitted work. ALav reports travel and accommodation grants from Bristol-Myers Squibb; and a consulting role for AstraZeneca, all outside the submitted work. CF-F reports grants from AstraZeneca and Elekta, all outside the submitted work. PAT reports financial support for teaching lectures and advisory boards from AstraZeneca and Ethicon Endosurgery, all outside the submitted work. OM reports financial support for participation in advisory boards AstraZeneca and MSD, all outside the submitted work. AB reports consultancy fees from Roche. All other authors declare no competing interests.

Data sharing

The clinical study report is available upon request, after approval by the study principal investigator (corresponding author). Deidentified individual participant data from this clinical trial, as well as a data dictionary, can be requested by filling out the data request form for Gustave Roussy clinical trials at https://redcap.gustaveroussy.fr/redcap/surveys/?s=DYDTLPE4AM. The process is similar for every trial sponsored by Gustave Roussy. The trial steering committee and the sponsor will review the requests on a case-by-case basis. In the case of approval, a specific agreement between the sponsor and the researcher might be required for a data transfer.

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