Role of adjuvant radiotherapy in completely resected non-small-cell lung cancer

Cecile Le Péchoux [a,b,*], *Olaf Mercier* [b,c], *Deborah Belemsagha* [a], *Ryan Bouaita* [a], *Benjamin Besse* [b,d], *Elie Fadel* [b,c]

[a] *Gustave Roussy University Hospital, Radiation Oncology Department, Thoracic Oncology Unit, Villejuif, France*
[b] *Institut d' Oncologie Thoracique, Le Plessis-Robinson, France*
[c] *Centre Chirurgical Marie Lannelongue, Thoracic Surgery Department, Le Plessis-Robinson, France*
[d] *Gustave Roussy University Hospital, Medical Oncology Department, Thoracic Oncology Unit, Villejuif, France*

Most long-term survivors of non-small-cell lung cancer (NSCLC) are patients who have had a completely resected tumour. However, this is only achievable in about 30% of the patients. Even in this highly selected group of patients, there is still a high risk of both local and distant failure. Adjuvant treatments such as chemotherapy (CT) and radiotherapy (RT) have therefore been evaluated in order to improve their outcome. In patients with stage II and III, administration of adjuvant platinum-based chemotherapy is now considered the standard of care, based on level 1 evidence. The role of postoperative radiation therapy (PORT) remains controversial. In the PORT meta-analysis published in 1998, the conclusions were that if PORT was detrimental to patients with stage I and II completely resected NSCLC, the role of PORT in the treatment of tumours with N2 involvement was unclear and further research was warranted. Thus at present, after complete resection, adjuvant radiotherapy should not be administered in patients with early lung cancer. Recent retrospective and non-randomised studies, as well as subgroup analyses of recent randomised trials evaluating adjuvant chemotherapy, provide evidence of the possible benefit of PORT in patients with mediastinal nodal involvement. The role of PORT needs to be evaluated also for patients with proven N2 disease who undergo neoadjuvant chemotherapy followed by surgery. The risk of local recurrence for N2 patients varies between 20% and 60%. Based on currently available data, PORT should be discussed for fit patients with completely resected NSCLC with N2 nodal involvement, preferably after completion of adjuvant chemotherapy or after surgery if patients have had preoperative chemotherapy. There is a need for new randomised evidence to reassess PORT using modern three-dimensional conformal radiation technique, with attention to normal organ sparing, particularly lung and heart, to reduce the possible over-added toxicity. Quality assurance of radiotherapy as well as quality of surgery – and most particularly nodal exploration modality – should both be monitored. A new large multi-institutional randomised trial Lung ART evaluating PORT in this patient population is needed and is now under way.

1. Introduction

Most long-term survivors of non-small-cell lung cancer (NSCLC) are patients having had a complete surgical resection. However, this is only achievable in about 30% of the patients. Even in this highly selected group of patients, there is still a high risk of both local and distant failure. Adjuvant treatments such as chemotherapy (CT) and

* *Corresponding author:* Address: Gustave Roussy University Hospital, 114 Rue Edouard Vaillant, Villejuif 94800, France
E-mail address: cecile.lepechoux@gustaveroussy.fr (C.L. Péchoux).
1359-6349/$ - see front matter
http://dx.doi.org/10.1016/j.ejcsup.2013.07.022

radiotherapy (RT) have therefore been evaluated in order to improve their outcome. For years, the use of adjuvant CT and/or RT was a controversial issue, as neither seemed to have any impact on survival in individual trials that were often under-powered. However, the meta-analysis including trials comparing surgery alone to surgery + adjuvant CT published in 1995 showed a modest survival benefit of 5% in completely resected patients having received postoperative cisplatin-based adjuvant CT compared with patients without CT [1]. The beneficial effect of adjuvant CT was confirmed in large trials initiated after the meta-analysis. It varies between 4% and 15% at 5 years in favour of surgery plus adjuvant chemotherapy [2–8]. Furthermore, the meta-analysis published in 2010 including 8447 patients with updated data from the old trials, and data from all recent trials show an absolute increase in survival of 4% at 5 years (from 60% to 64%, $P < 0.0001$) [9]. Thus, most clinicians now consider adjuvant CT as standard treatment in patients with stages II and III completely resected lung cancer. Updated survival analysis of two individual trials has also been published with contrasting results as to the persistent long-term beneficial effect of adjuvant chemotherapy [10,11]. On the other hand, concerning adjuvant RT, an individual data-based meta-analysis evaluating the role of postoperative radiotherapy (PORT) after surgery for NSCLC was also undertaken in the 1990s: it showed that adjuvant RT could be deleterious in patients with early lung cancer (i.e. stages I and II) but that in more advanced lung cancer (i.e. stage IIIA) it should be better explored in new studies, especially in patients with mediastinal involvement [12]. At the current time, adjuvant treatment is focused on chemotherapy and the risk of distant metastases rather than on postoperative radiotherapy which may also have an impact on disease control. It seems, however, that 20–60% of patients may be at risk for loco-regional recurrence. In view of the high proportion of patients still suffering from local failure after a complete resection and adjuvant chemotherapy, a new interest in PORT has been generated, even though PORT remains a controversial issue. We have therefore reviewed the evidence regarding adjuvant radiotherapy in completely resected NSCLC in 2013. Assessing the patterns of failure after surgery and the possible PORT-related toxicity is helpful in evaluating the benefit/risk ratio of postoperative therapy. Even if the risk of local recurrence in early lung cancer is generally considered to be small in comparison with the risk of distant recurrence, the rates of local failure are highly variable in the literature, ranging from 6% to 45% in stage I and from 7% to 55% for stage II disease. There are various reasons for this: problem of definition, and local failures often not reported when they occur at the same time as distant metastases or after distant failure.

An additional difficulty in the decision to administer adjuvant treatment may be the new tumour-node-metastasis (TNM) classification [13,14]. Five-year rates of locoregional recurrence (LRR) for stages IA, IB, IIA, IIB and IIIA disease using TNM-6 were 16%, 26%, 43%, 35% and 40%, respectively. Using TNM-7, corresponding rates were 16%, 23%, 37%, 39% and 30%, respectively, and there about 10–15% 'stage shifters' [14,15].

2. Studies evaluating mediastinal postoperative radiotherapy

Several retrospective studies, contemporaneous to the studies included in the meta-analysis, have shown that the risk of local recurrence could be reduced by PORT (25–35%) in historical comparisons [16–22]. However, this finding was not corroborated by most randomised trials.

In this review article, we will focus on randomised trials and on the meta-analyses on PORT [12,23–29]. Several of the trials are old, conducted in the era before computed tomography (CT) scan and positron emission tomography (PET), with patients treated with cobalt 60 (Co60) or even orthovoltage therapy; this resulted in a higher risk of both morbidity and mortality [30,31]. Furthermore, irradiated volumes were often large, fractionations often superior to 2 Gy daily, all these factors contributing to a higher morbidity; other technical factors such as the absence of CT-based planning in most trials or the use of spinal cord blocks which potentially block mediastinal disease may explain several LRRs. As previously stated, the rates of local failures at 5 years vary according to stage, and in several studies patients at low risk for LRR were included, possibly obscuring a radiation-induced benefit in higher-risk patients.

3. Randomised trials of adjuvant radiotherapy in stage I resected NSCLC

Van Houtte et al. [23] conducted a randomised trial in 175 patients who had a complete resection and had no lymph-node involvement. The 5-year survival rate was 24% in the RT arm versus 43% in the control arm. PORT was significantly deleterious, especially after pneumonectomy (16% in the PORT arm versus 43% in the control arm). They concluded that TRT should not be recommended in N0 patients. A more recent Italian randomised trial compared PORT at the dose of 50.4 Gy to no PORT in 104 patients with pathological stage I disease [24]. The patients included in this study benefited from more modern radiotherapy: all patients had a CT-planned treatment, linear accelerators were used and treatment volumes – including the bronchial stump and ipsilateral hilum – were small. Radiotherapy significantly decreased the risk of local recurrence from 23% in the control group to 2.2% in the PORT group ($P = 0{,}002$) but there was no significant difference in terms of 5-year overall survival (67% in the PORT group and 58% in the control group). There was no over-added toxicity in the PORT group. However, it may be argued that patients with pathological stage I NSCLC have such a low risk of local recurrence, that routine PORT is generally not recommended except for patients with R1 or R2 resections.

4. Randomised trials of adjuvant radiotherapy in stages II and III resected NSCLC

The Lung Cancer Study Group conducted a randomised study including 230 patients with stage II and III squamous-cell carcinoma to evaluate postoperative PORT at the dose of 50 Gy [25]. PORT significantly decreased the risk of local recurrence:

1% versus 41% in the control arm ($P = 0.001$). But this effect did not translate into a demonstrable overall survival benefit (5-year survival rate around 40% in both arms), since most recurrences were outside the radiation field or were distant failures. However a subgroup analysis suggested that PORT could prolong disease-free interval in patients with N2 disease. The design of the Medical Research Council study was quite similar but also included patients with adenocarcinoma [26]. Patients with pathologically staged T1–2, N1–2 NSCLC were randomly assigned to receive either surgery alone or surgery and PORT at the dose of 40 Gy in 15 fractions. The results confirmed previous studies: there was no advantage for survival in the PORT group over the control arm, but in the N2 subgroup analysis there was a non-significant trend towards improved survival and local control. Thus, the authors concluded that there was no indication for PORT in N1 disease, but the question remained open for N2 patients. The largest trial evaluating PORT included 728 patients (221 with stage I, 180 with stage II and 327 with stage III disease) [27]. It demonstrated that PORT had a detrimental effect on survival: the 5-year survival rate was 43% for the control group and 30% for the RT group ($P = 0.002$). In terms of 5-year rate without local recurrence, there was a trend in favour of PORT among N2 patients. The excess mortality rate in the radiotherapy group was due to an increase in intercurrent deaths. In a Chinese randomised study of 366 completely resected patients with N1 or N2 nodal disease, PORT significantly reduced the rate of local relapses: the local failure rate was 12.7% versus 33.2% in the control group ($P = 0.01$), but this had no impact on survival [28].

In conclusion, before the meta-analysis was published, the role of PORT was unclear as the individual trials showed conflicting and inconclusive results. They did not have the statistical power to detect moderate survival differences. Thus the PORT meta-analysis group gathered individual data on 2128 patients from nine randomised trials [12]. Its results indicated that PORT had a significant detrimental effect on survival, with an absolute decrease of 7% at 2 years, reducing the overall survival from 55 to 48% ($P = 0.001$). Subset analyses suggested that PORT could be deleterious in terms of overall survival, predominantly among patients who had a complete resection and no mediastinal involvement (either pN0 or pN1). However, than authors could observe a 24% relative reduction in local recurrence rate (all stages together), so that the question of PORT in pN2 patients who have a high local recurrence rate remained valid and could warrant further research. This overview was updated in 2005 and included an additional trial by Trodella et al. in the analysis; it still showed PORT to be detrimental, with an 18% relative increase in the risk of death [32]. A very recent letter updating the results of the meta-analysis was published using different statistical methods, confirming that PORT should not be routinely used unless there is supporting evidence from new trials of modern PORT [33]. Unfortunately no phase III trial evaluating more modern PORT versus no PORT has been published since 1998. However, there have been studies on adjuvant chemotherapy as well as chemoradiotherapy. The already mentioned meta-analysis on the role of adjuvant chemotherapy in completely resected patients also comprised a second analysis based on 13 trials and 2660 patients, mostly stage III patients, and compared surgery plus radiotherapy versus surgery plus radiotherapy and chemotherapy [9]. It showed a significant improvement in survival of 4% at 5 years (from 29% to 33%). It should be outlined that a similar 4% absolute benefit was observed in the analysis of trials comparing surgery with surgery and chemotherapy that included mainly patients with stages I and II NSCLC. Thus the effect of chemotherapy was similar irrespective of which loco-regional treatment was used: surgery alone or surgery plus PORT. The authors concluded that, as this meta-analysis was not designed to study the effect of PORT, randomised trials were needed to assess modern radiotherapy as adjuvant treatment.

5. Studies on adjuvant chemoradiotherapy in stage II and III patients

Until 1998, PORT was considered the standard treatment by many clinicians in stage II and stage III patients; thus the Eastern Cooperative Group (ECOG) completed a prospective trial comparing PORT at the dose of 50.4 Gy in 1.80 Gy fractions with PORT and concomitant chemotherapy combining etoposide and cisplatin [34]. The 3-year survival rate was, respectively, 52% in the PORT arm and 50% in the combined treatment arm ($P = 0.56$). The loco-regional recurrence rate within the radiotherapy field was about 13% in both arms and was therefore smaller than the rates reported in the literature. A better standardised surgical treatment may explain these results in terms of local control, as well as the use of more modern radiotherapy using CT-scan-based planning. The protocol required a thorough mediastinal lymph-node dissection or sampling according to the American Thoracic Society lymph node definitions [35,36]. There was a significant difference ($P < 0.05$) between the recurrence rate of patients with mediastinal dissection (50%) and those with mediastinal sampling (60%) [37]. Thus the authors concluded that cisplatin and VP-16 administered concomitantly with PORT did not prolong survival or modify local failures compared to PORT alone. Other phase II trials have evaluated adjuvant concomitant chemoradiation in stage II and IIIA patients [38,39]. In the RTOG 9705 phase II trial, where 86 patients had concurrent paclitaxel/carboplatin and PORT at the dose of 50.4 Gy, the 3-year progression-free and overall survival rate was respectively 50% and 61%, and local failure was a component of first failure in 15% of patients [38]. In another phase II study that included 42 patients (40% of pN1 and 60% of pN2 patients) treated with a similar regimen, the 2- and 5-year Kaplan–Meier estimates of local regional control were 92% and 88%, whereas the 2- and 5-year overall survival rate was 72% and 44%, respectively [39]. Even if these results seemed better that those reported in the Intergroup trial, no randomised trial was undertaken, so that adjuvant concomitant chemoradiation after complete surgery cannot be considered as a standard treatment.

6. Postoperative radiotherapy (PORT): toxicity issues

The excess of toxicity (mostly cardiac and pulmonary) and non-cancer-related deaths observed after PORT in the meta-analysis trials can probably be explained by old radiation 2D techniques, excessive volumes of radiation, too large doses

and fraction sizes and no CT-scan-based planning. Unfortunately, the authors could not collect data on toxicity or causes of intercurrent deaths in the different studies. Late cardiac complications that are described after mediastinal radiotherapy are linked to the total dose, the fraction size, the irradiated volume, the technique of irradiation, as well as comorbidities (tobacco use, overweight) [40,41]. Pulmonary complications such as pneumonitis and lung fibrosis can also be observed, but they occur earlier; there are strong volume and fractionation effects [42]. In a recent prospective study of 291 patients, cardiopulmonary functions as well as quality of life were evaluated prospectively at baseline and at 2 years among 171 pN2 patients who had PORT and 120 pN1 patients who did not have PORT. The authors found no significant difference in terms of cardiopulmonary morbidity among patients alive at 2 years [43]. The administration of certain radiosensitising drugs such as gemcitabine may increase this risk. In the phase II trial RTOG 9705 evaluating adjuvant concomitant chemo-radiotherapy, a 6% crude incidence of late pulmonary toxicity and similarly a 5% rate of late cardiac toxicity of grade 3 or over were observed [38]. Miles et al. elaborated a mathematical model to describe the tumour stage- and field-size-dependent risks/benefits of postoperative radiotherapy and showed that RT-induced mortality was strongly dependent on field size [44]. In the largest published randomised trial, Dautzenberg could determine that the use of fraction sizes >2 Gy resulted in a high risk of late toxicity [27]. The risk of non-cancer-related death was, respectively, 7% in the control group, 16–18% among patients who had daily RT fractions $\leqslant$2 Gy and 26% among those who had higher doses per fraction. Several studies reported reduced toxicity and mortality with more modern PORT. A retrospective study focusing on toxicity issues showed that PORT could be administered safely if patients were treated with more modern treatment techniques, more limited volumes of irradiation, daily fraction sizes $\leqslant$2 Gy and total doses $\leqslant$54 Gy [45]. The 4-year actuarial rate of death from intercurrent disease (DID) for patients treated with PORT within the E3590 trial was 12.9%: not significantly different from the 10.1% expected rate of DID observed in a control population matched for age and gender and corrected for smoking status [46]. A Surveillance, Epidemiology and End Results (SEER) data-based study analysed deaths from heart disease in a group of 6148 pN1 or pN2 patients operated between 1983 and 1993 who were followed up until 2005 [47]. Amongst them, 58% had PORT. PORT delivery was associated with an increase in the hazard for heart disease. However, this increase was only significant in patients treated between 1988 and 1993. For the authors, this could reflect the impact of more modern radiotherapy techniques utilised in the second half of the 1990s on morbidity.

7. Should PORT be considered for patients with mediastinal involvement?

Lally et al. have reported on PORT in a population-based cohort of 7465 patients with stage II and III non-small-cell lung cancer who had surgery [48]. They selected from the SEER database patients treated between 1988 and 2002, out of which 47% received PORT. Patients who had PORT were presumably treated with more modern radiotherapy techniques than patients included in the meta-analysis. The 5-year survival rate was 20% in the no-PORT versus 27% in the PORT group ($P = 0.0036$). The authors concluded that PORT offered a significant survival benefit for patients with N2 nodal disease, but that there was a detrimental effect for patients with N0 or N1 nodal disease. However, as with any retrospective study using a large database, one should be cautious with the results. Another recently published trial by Douillard et al. also suggested the possible impact of PORT on survival in patients included in the adjuvant Navelbine International Trialist Association (ANITA) randomised trial [5,49]. In a subgroup analysis according to nodal status, survival was improved in patients with pN2 disease who received PORT, both in the chemotherapy (MS 23.8 versus 47.4 months) and observation arms (median 12.7 versus 22.7 months). The authors concluded that their retrospective evaluation suggested a positive effect of PORT administered after CT in pN2 disease, and that these results supported further evaluation of PORT in prospectively randomised studies. They also could show as in the meta-analysis that PORT seemed to be deleterious in pN1 patients. However, most studies do not specify the exact location of locoregional recurrence. In a large retrospective study of 406 patients with pN2 nodal involvement, the local recurrence rate among the 332 evaluated patients was 39.2% and most of these recurrences occurred in the mediastinum [50]. Some additional interesting issues concerning local control have been outlined by retrospective studies. Kelsey observed that left-sided tumours tended to recur in the contralateral mediastinum more frequently than right-sided tumours, and this could be explained by lymph node exploration techniques as left lymph-node exploration is considered more difficult than right-sided lymph-node exploration [37,51]. Sawyer et al. have tried to divide pN2 patients into three different subgroups according to their respective risk of failure: high-risk (in cases of multiple distant mediastinal nodes involved), intermediate-risk (in cases of involvement of inferior nodes or superior nodes with eventual invasion of hilar nodes). and low-risk (if there is no hilar node involvement) [22]. Several recent mono-institutional studies have evaluated PORT retrospectively in patients with pN2 involvement and they show positive results not only in terms of local recurrence but also in terms of survival [52–55]. Furthermore, most patients had no adjuvant chemotherapy, no staging according to today's standards and this delineates the importance of a new randomised study comparing PORT to no PORT in such a frequent cancer as NSCLC.

Another issue is whether patients with proven mediastinal involvement and who have neoadjuvant chemotherapy should have PORT after a complete resection. Many clinicians treat patients with clinical N2 involvement with preoperative chemotherapy. Several studies, as well as a meta-analysis based on literature, have indeed suggested a benefit in terms of survival in favour of preoperative chemotherapy [56–60]. Mediastinal down-staging has been shown to be an important prognostic factor [57,59]. However, the recurrence rate can be quite high as seen in the updated results of a phase II trial of neoadjuvant chemotherapy where at 5-year follow-up, 60% of patients had local relapse [61]. Another recently published

trial also showed a high incidence of local failure in stage IIIA N2 patients down-staged after neoadjuvant chemotherapy. The 5-year local-regional failure (LRF) rate was 31%, and most locoregional recurrences appeared in the mediastinal (92%) and hilar lymph nodes (23.7%), the risk being particularly high in case of N1 disease [62]. In another retrospective study, the 5-year actuarial local control rate was 82% among patients given PORT versus 35% who had no PORT. Thus even if PORT after neoadjuvant chemotherapy followed by surgery may reduce local recurrence as reported in small retrospective studies, this remains to be proven [63,64] Thereby the question of PORT is also valid among patients who have histologically proven N2 disease before preoperative chemotherapy, whatever their response is: persistent mediastinal involvement or mediastinal down-staging (from N2 histologically proven to pN0 or pN1). No randomised study has been published on this issue.

8. Importance of surgery and preoperative staging in the perspective of modern adjuvant radiotherapy

New data concerning PORT should take into consideration the quality of surgery and the progress made in terms of preoperative staging or re-staging after neoadjuvant chemotherapy. At present most patients considered for surgery are much better selected on the basis of a PET scan and brain imaging. PET–CT is highly sensitive and specific in detecting mediastinal nodal spread and extracranial metastases [65,66]. After induction chemotherapy for patients with N2 involvement, repeated FDG-PET may select surgical candidates among patients with mediastinal down-staging or persistent minor disease [67].

In the past years there has been an important collaborative effort of thoracic surgeons to define lymph-node exploration and complete resection. The European Society of Thoracic Surgeons (ESTS) has proposed guidelines for appropriate intraoperative and preoperative lymph-node staging [68,69]. The International Association for the Study of Lung Cancer (IASLC) staging committee has proposed a definition of complete resection [70]. All resection margins – including bronchial, venous and arterial stumps and peribronchial soft tissue – should be microscopically free of disease. Systematic nodal examination should comprise at least three intrapulmonary and hilar nodes and at least three nodes from the following mediastinal nodal stations according to the location of the primary tumour. There is no consensus about whether the highest mediastinal node that has been explored and removed should be negative. It is also unclear whether the extent of mediastinal exploration can affect long-term survival. Even if randomised trials have been performed comparing these two mediastinal approaches, there still is a debate between advocates of radical mediastinal node dissection who claim not only a potential prognostic benefit but a better tumour staging and treatment, and opponents of the radical approach because of higher morbidity and mortality and possibly a negative effect on survival because of impaired local immunity [71–73].

Considering resected patients, an exploratory analysis of the IASLC database studied survival after complete resection in relation to the extent of node involvement using the zonal concept [74,14]. Three groups were identified, with significant differences in terms of survival. Group 1 with single-zone N1 disease had a 5-year survival rate of 48%. Group 2 consisting of patients with multizone N1 and single-zone N2 disease had 5-year survival rates around 35%. Group 3 comprised patients with multizone N2 disease, and the 5-year survival rate did not exceed 20%. More recently, two large retrospective studies have tried to question whether the number of lymph nodes involved were of added prognostic significance compared with the pathological nodal stage (pN category) [75,76]. However, among the 2538 pathologically staged N1 and N2 cases in the IASLC database, such results were not observed [77]. The importance of mediastinal node involvement seems therefore the best and most consensual prognostic factor.

9. Implications for a new trial evaluating PORT

At present, based on level 1 evidence, patients who have had a complete resection of the primary tumour with mediastinal lymph-node dissection showing no mediastinal involvement (pN0 and pN1) should not have PORT. The issue of PORT is not as clear among patients with N2 mediastinal involvement. Indication of PORT is currently debated for each individual patient with mediastinal involvement. A new trial is needed addressing PORT in stage IIIA patients. Conformational radiotherapy should be mandatory so as to reduce toxicity and improve outcome [78–80]. The irradiation volume should take into account the data of thoracic CT scan and the eventual PET scan data before surgery, as well as the description of mediastinal exploration and histopathological results. A recent study has shown there are wide variations in target volume definition for PORT [81]. Based on previous studies, it seems reasonable to treat only involved lymph-node stations and uninvolved stations at high risk to better protect surrounding normal structures and consequently minimise treatment-related mortality [82–85]. An atlas of CT-based definition of thoracic lymph-node stations may be helpful [86].

In the ongoing study LungART, the irradiation volume includes the lymph-node stations involved according to the pathological report as well as lymph-node stations considered at high risk of involvement according to tumour location [87].

Among pN2 patients included in the PORT overview, the high rate of distant metastases diluted any real effect of local control on overall outcome. As the standard treatment for patients with mediastinal involvement has changed in the last 10 years from surgery plus adjuvant radiotherapy to surgery plus chemotherapy, and selection of surgical candidates has evolved with PET–CT as well as minimally invasive staging procedures, it is of utmost importance to evaluate whether modern adjuvant radiotherapy can improve survival in patients after complete resection and adjuvant chemotherapy. Lung ART is a randomised trial evaluating modern PORT in patients with mediastinal involvement. Patients may have chemotherapy in the neoadjuvant setting or adjuvant setting. It is an inter-group study involving the Intergroupe Franco-

phone de Cancerologie Thoracique (IFCT 0503), a United Kingdom group (UK 11/NW/0075) and the EORTC (EORTC 22055-08053) (NCT00410683). Another trial is ongoing in China comparing adjuvant chemotherapy followed by PORT to adjuvant chemotherapy alone (NCT00880971). Such studies could result into an optimisation of standard care in operable stage III patients.

Conflict of interest statement

The author has no conflict of interest regarding this article but is the coordinator of Lung ART which is a randomised trial evaluating post operative radiotherapy in stage III patients with mediastinal involvement.

REFERENCES

[1] Non Small Cell Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. Br Med J 1995;311:899–909.

[2] International Adjuvant Lung cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. New Engl J Med 2004;350:351–60.

[3] Strauss GM, Herndon 2nd JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043–51.

[4] Winton TL, Livingston R, Johnson D, et al. For the National Cancer Institute of Canada Clinical Trials Group and the National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators Vinorelbine plus cisplatin vs observation in resected non-small cell lung cancer Intergroup. New Engl J Med 2005;352:2589–97.

[5] Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719–27.

[6] Scagliotti GV, Fossati R, Torri V, et alfor the ALPI/EORTC Cooperative Group Investigators. Randomized study of adjuvant chemotherapy for completely resected stage I, II or IIIA non-small cell lung cancer. J Natl Cancer Inst 2003;95:1453–61.

[7] Waller D, Peake MD, Stephens RJ, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004;26:173–82.

[8] Pignon JP, Tribodet H, Scagliotti GV, et alfor the LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552–9.

[9] NSCLC Meta-analyses Collaborative Group. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267–77.

[10] Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010;28:35–42.

[11] Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010;28:29–34.

[12] PORT Meta-analysis Trialists Group. Post-operative radiotherapy in non-small cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet 1998;352:257–63.

[13] Goldstraw P. New staging system: how does it affect our practice? J Clin Oncol 2013;31:984–91.

[14] Goldstraw P. New staging system: how does it affect our practice? J Clin Oncol 2013;31:984–91.

[15] Pepek JM, Chino JP, Marks LB, et al. How well does the new lung cancer staging system predict for local/regional recurrence after surgery? A comparison of the TNM 6 and 7 systems. J Thorac Oncol 2011;6:757–61.

[16] Astudillo J, Conill C. Role of postoperative radiation therapy in stage IIIa non-small cell lung cancer. Ann Thorac Surg 1990;50:618–23.

[17] Green N, Kurohara SS, George FW. Postresection irradiation for primary lung cancer. Radiology 1975;116:405–7.

[18] Choi NC, Grillo HC, Gardiello M, et al. Basis for new strategies in postoperative radiotherapy of bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1980;6:31–5.

[19] Chung CK, Stryker JA, O'Neil M, et al. Evaluation of adjuvant postoperative radiotherapy for lung cancer. Int J Radiat Oncol Biol Phys 1982;8:1877–80.

[20] Patterson R, Russell MH. Clinical trials in malignant disease. IV Lung Cancer. Value of postoperative radiotherapy. Clin Radiol 1962;13:141–4.

[21] Kirsch M, Sloan H. Mediastinal metastases in bronchogenic carcinoma: influence of postoperative irradiation, cell types and location. Ann Thorac Surg 1982;33:459–63.

[22] Sawyer TE, Bonner JA, Gould PM, et al. Effectiveness of postoperative irradiation in stage IIIA non-small cell lung cancer according to regression tree analysis of recurrence risk. Ann Thorac Surg 1997;64:1402–8.

[23] Van Houtte P, Rocmans P, Smets P. Postoperative radiation therapy in lung cancer: a controlled trial after resection of curative design. Int J Radiat Oncol Biol Phys 1980;6:983–6.

[24] Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11–9.

[25] Lung Cancer Study Group. Effects of post-operative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. N Engl J Med 1986;315:1377–81.

[26] Stephens RJ, Girling DJ, Bleehen NM, et alfor the Medical Research Council Lung Cancer Working Party. The role of postoperative radiotherapy in nonsmall cell lung cancer: a multicentre randomised trial in patients with pathologically staged T1–T2, N1–N2, M0 disease. Br J Cancer 1996;74:632–9.

[27] Dautzenberg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Cancer 1999;86:265–73.

[28] Feng QF, Wang M, Wang LJ, et al. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 2000;47:925–9.

[29] Mayer R, Smolle-Juettner FM, Szolar D, et al. Postoperative radiotherapy in radically resected non-small cell lung cancer. Chest 1997;112:954–9.

[30] Philips P, Rocmans P, Vanderhoeft P, Van Houtte P. Post-operative radiotherapy after pneumonectomy: impact of

modern treatment facilities. Int J Radiat Oncol Biol Phys 1993;27:525–9.
[31] DiBiase SJ, Werner-Wasik M, Croce R, Sweet J, Curran Jr WJ. Standard off-cord lung oblique fields do not include the entire mediastinum: a computed tomography simulator study. Am J Clin Oncol 2000;23:249–52.
[32] Burdett S, Stewart LOn behalf of the PORT Meta-analysis Group. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. Lung Cancer 2005;47:81–3.
[33] Burdett S, Rydzewska L, Tierney JF, Fisher DJ. A closer look at the effects of postoperative radiotherapy by stage and nodal status: updated results of an individual participant data meta-analysis in non-small-cell lung cancer. Lung Cancer 2013;80:350–2.
[34] Keller SM, Adak S, Wagner H, et alFor the Eastern Cooperative Oncology Group. A randomised trial of post-operative adjuvant therapy in patients with completely resected stage II or IIIa non-small cell lung cancer. New Engl J Med 2000;343:1217–22.
[35] Mountain CF. A new international staging system for lung cancer. Chest 1986;89(4 Suppl):225S–33S.
[36] Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997;117:1710–7.
[37] Keller SM, Adak S, Wagner H, Johnson DHfor the Eastern Cooperative Oncology Group. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. Ann Thorac Surg 2000;70:358–65.
[38] Bradley JD, Paulus R, Graham MVfor the Radiation Therapy Oncology Group. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group – RTOG 9705. J Clin Oncol 2005;23:3480–7.
[39] Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. J Thorac Oncol 2007;2:287–92.
[40] Adams MJ, Hardenbergh PH, Constine LS, Lipshultz SE. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol 2003;45:55–75.
[41] Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010;76(3 Suppl):S77–85.
[42] Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76:S70–6.
[43] Kepka L, Bujko K, Orlowski TM, et al. Cardiopulmonary morbidity and quality of life in non-small cell lung cancer patients treated with or without postoperative radiotherapy. Radiother Oncol 2011;98:238–43.
[44] Miles EF, Kelsey CR, Kirkpatrick JP, Marks LB. Estimating the magnitude and field-size dependence of radiotherapy-induced mortality and tumor control after postoperative radiotherapy for non-small-cell lung cancer: calculations from clinical trials. Int J Radiat Oncol Biol Phys 2007;68:1047–52.
[45] Machtay M, Lee JH, Shrager JB, Kaiser LR, Glatstein E. Risk of death from intercurrent disease is not excessively increased by modern postoperative radiotherapy for high-risk resected non-small-cell lung carcinoma. J Clin Oncol 2001;19:3912–7.
[46] Wakelee HA, Stephenson P, Keller SM, et al. Post-operative radiotherapy (PORT) or chemoradiotherapy (CPORT) following resection of stages II and IIIA non-small cell lung cancer (NSCLC) does not increase the expected risk of death from intercurrent disease (DID) in Eastern Cooperative Oncology Group (ECOG) trial E3590. Lung Cancer 2005;48:389–97.
[47] Lally BE, Detterbeck FC, Geiger AM, et al. The Risk of death from heart disease in patients with non small cell lung cancer who receive postoperative radiotherapy. Analysis of the Surveillance, Epidemiology, and End Results database. Cancer 2007;110:911–7.
[48] Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non–small-cell lung cancer using the Surveillance, Epidemiology, and End Results database. J Clin Oncol 2006;24:2998–3006.
[49] Douillard JY, Rosell R, De Lena M, et al. Adjuvant Navelbine International Trialist Association. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695–701.
[50] Ichinose Y, Kato H, Koike T, et al. Overall survival and local recurrence of 406 completely resected stage IIIa-N2 non-small cell lung cancer patients: questionnaire survey of the Japan Clinical Oncology Group to plan for clinical trials. Lung Cancer 2001;34:29–36.
[51] Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006;65:1097–105.
[52] Matsuguma H, Nakahara R, Ishikawa Y, et al. Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: focusing on an effect of the number of mediastinal lymph node stations involved. Interact Cardiovasc Thorac Surg 2008;7:573–7.
[53] Scotti V, Meattini I, Saieva C. Et al Post-operative radiotherapy in N2 non-small cell lung cancer: a retrospective analysis of 175 patients. Radiother Oncol 2010;96:84–8.
[54] Moretti L, Yu DS, Chen H. Prognostic factors for resected non-small cell lung cancer with pN2 status: implications for use of postoperative radiotherapy. Oncologist 2009;14:1106–15.
[55] Dai H, Hui Z, Ji W, et al. Postoperative radiotherapy for resected pathological stage IIIA-N2 non-small cell lung cancer: a retrospective study of 221 cases from a single institution. Oncologist 2011;16:641–50.
[56] Martini N, Kris MG, Flehinger BJ, et al. Preoperative chemotherapy for stage IIIa (N2) lung cancer: the Sloan–Kettering experience with 136 patients. Ann Thorac Surg 1993;55:1365–73.
[57] André F, Grunenwald D, Pignon JP, et al. Survival of patients with resected N2 non-small cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 2001;16:2981–9.
[58] van Meerbeeck JP, Kramer GW, Van Schil PE, et alfor the European Organisation for Research and Treatment of Cancer-Lung Cancer Group. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442–50.
[59] Betticher DC. Hsu Schmitz SF, Tötsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. J Clin Oncol 2003;21:1752–9.
[60] Burdett S, Stewart LA, Rydzewska L. A systematic review and meta-analysis of the literature: chemotherapy and surgery versus surgery alone in non-small cell lung cancer. J Thorac Oncol 2006;1:611–21.

[61] Betticher DC, Hsu Schmitz S-F, Totsch M, et alfor the Swiss Group for Clinical Cancer Research (SAKK). Prognostic factors affecting long-term outcomes in patients with resected stage IIIA pN2 non-small-cell lung cancer: 5-year follow-up of a phase II study. Br J Cancer 2006;94:1099–106.
[62] Amini A, Lou F, Correa AM, et al. Predictors for locoregional recurrence for clinical stage III-N2 non-small cell lung cancer with nodal downstaging after induction chemotherapy and surgery. Ann Surg Oncol 2013;20:1934–40.
[63] Taylor NA, Liao ZX, Stevens C, et al. Postoperative radiotherapy increases locoregional control of patients with stage IIIA non-small-cell lung cancer treated with induction chemotherapy followed by surgery. Int J Radiat Oncol Biol Physics 2003;56:616–25.
[64] Amini A, Correa AM, Komaki R, et al. The role of consolidation therapy for stage III non-small cell lung cancer with persistent N2 disease after induction chemotherapy. Ann Thorac Surg 2012;94:914–20.
[65] Ung YC, Maziak DE, Vanderveen JA, et al. 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review. J Natl Cancer Inst 2007;99:1753–67.
[66] Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for Staging Non-small Cell Lung Cancer: Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2013;143(5 Suppl):e211S–50S.
[67] Dooms C, Verbeken E, Stroobants S, et al. Prognostic stratification of stage IIIA-N2 non-small-cell lung cancer after induction chemotherapy: a model based on the combination of morphometric-pathologic response in mediastinal nodes and primary tumor response on serial 18-fluoro-2-deoxy-glucose positron emission tomography. J Clin Oncol 2008;26:1128–34.
[68] Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006;30:787–92.
[69] De Leyn P, Lardinois D, Van Schil PE, et al. ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. Eur J Cardiothorac Surg 2007;32:1–8.
[70] Rami-Porta R, Wittekind CGoldstraw for the International Association for the Study of Lung Cancer (IASLC) staging committee. Complete resection of lung cancer surgery: proposed definition. Lung Cancer 2005;49:25–33.
[71] Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. Ann Surg 1998;227:138–44.
[72] Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. Lung Cancer 2002;36:1–6.
[73] Wright G, Manser RL, Byrnes G, Hart D, Campbell DA. Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. Thorax 2006;61:597–603.
[74] Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2009;4:568–77.
[75] Wei S, Asamura H, Kawachi R, Sakurai H, Watanabe S. Which is the better prognostic factor for resected non-small cell lung cancer: the number of metastatic lymph nodes or the currently used nodal stage classification? J Thorac Oncol 2011;6:310–8.
[76] Lee JG, Lee CY, Park IK, et al. Number of metastatic lymph nodes in resected non-small cell lung cancer predicts patient survival. Ann Thorac Surg 2008;85:211–5.
[77] Rusch VW, Giroux DJ. Nodal staging in lung cancer: lymph node location or number? J Thorac Oncol 2011;6:237–8.
[78] Armstrong J. Mc Gibney C. The impact of three-dimensional radiation on the treatment of non-small cell lung cancer. Radiother Oncol 2000;56:157–67.
[79] von Lieven H, Burkhardt E. Postoperative radiotherapy of NSCLC. Outcome after 3-D treatment planning. Strahlenther Onkol 2001;177:302–6.
[80] De Ruysscher D, Faivre-Finn C, Nestle U, et al. European Organisation for Research and Treatment of Cancer recommendations for planning and delivery of high-dose, high-precision radiotherapy for lung cancer. J Clin Oncol 2010;28:5301–10.
[81] Spoelstra FO, Senan S, Le Péchoux C, et alfor the Lung Adjuvant Radiotherapy Trial Investigators Group. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. Int J Radiat Oncol Biol Phys 2010;76:1106–13.
[82] Watanabe Y, Shimizu J, Tsubota M, Iwa T. Mediastinal spread of metastatic lymph nodes in bronchogenic carcinoma. Mediastinal nodal metastases in lung cancer. Chest 1990;97:1059–65.
[83] Kiricuta IC, Mueller G, Stiess J, Bohndorf W. The lymphatic pathways of non-small cell lung cancer and their implication in curative irradiation treatment. Lung Cancer 1994;11:74–82.
[84] Emami B, Kaiser L, Simpson S, et al. Postoperative radiation therapy in non-small cell lung cancer. Am J Clin Oncol 1997;20:441–8.
[85] Belderbos JS, Kepka L, Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2008;72:335–42.
[86] Chapet O, Kong FM, Quint LE, et al. CT-based definition of thoracic lymph node stations: an atlas from the University of Michigan. Int J Radiat Oncol Biol Phys 2005;63:170–8.
[87] Le Péchoux C, Dunant A, Pignon JP, et al. Need for a new trial to evaluate adjuvant postoperative radiotherapy in non-small-cell lung cancer patients with N2 mediastinal involvement. J Clin Oncol 2007;25:e10–1.