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CLINICAL INVESTIGATION **Lung**

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

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Purpose: To study the impact of postoperative radiation therapy (PORT) on survival in the Adjuvant Navelbine International Trialist Association (ANITA) randomized study of adjuvant chemotherapy.
Methods and Materials: ANITA is a randomized trial of adjuvant cisplatin and vinorelbine chemotherapy vs. observation in completely resected non–small-cell lung carcinoma (NSCLC) Stages IB to IIIA. Use of PORT was recommended for pN+ disease but was not randomized or mandatory. Each center decided whether to use PORT before initiation of the study. We describe here the survival of patients with and without PORT within each treatment group of ANITA. No statistical comparison of survival was performed because this was an unplanned subgroup analysis.
Results: Overall, 232 of 840 patients received PORT (33.3% in the observation arm and 21.6% in the chemotherapy arm). In univariate analysis, PORT had a deleterious effect on the overall population survival. Patients with pN1 disease had an improved survival from PORT in the observation arm (median survival [MS] 25.9 vs. 50.2 months), whereas PORT had a detrimental effect in the chemotherapy group (MS 93.6 months and 46.6 months). In contrast, survival was improved in patients with pN2 disease who received PORT, both in the chemotherapy (MS 23.8 vs. 47.4 months) and observation arm (median 12.7 vs. 22.7 months).
Conclusion: This retrospective evaluation suggests a positive effect of PORT in pN2 disease and a negative effect on pN1 disease when patients received adjuvant chemotherapy. The results support further evaluation of PORT in prospectively randomized studies in completely resected pN2 NSCLC. **© 2008 Elsevier Inc.**

Adjuvant chemotherapy, Non–small-cell lung cancer, Postoperative radiation therapy.

INTRODUCTION

The role of postoperative radiation therapy (PORT) in patients with completely resected non–small-cell lung carcinoma (NSCLC) remains controversial. Although an improvement in local control, either by a decreased event rate or by prolonged time to event, has been described in several studies (1–4), the effect on survival has been contradictory or inconclusive.

The PORT meta-analysis published in 1998 included nine studies (2,128 patients) in which PORT was compared with surgery alone (5). The meta-analysis concluded that PORT produced a significant detrimental effect on survival: 21% increase in the relative risk of death and 2-year survival rates of 48% for PORT and 55% for the control group. The survival curves diverged approximately at 4 months from randomization. The detrimental effect of PORT was marked

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Conflict of interest: none.

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for patients with pN0 or pN1 disease whereas in patients with Stage III and pN2 survival was slightly better with PORT, but the effect was not statistically significant. Detailed information on causes of death was not presented; 15% of deaths with PORT vs. 9% in the control were coded as ''intercurrent,'' and respectively 4% and 2% were coded as treatment related. No effect on local control was observed either. The data have been interpreted (6) as potentially indicative of toxic effects of PORT.

Since the PORT meta-analysis, one more randomized trial was published (3), comparing PORT to observation in 155 patients with completely resected Stage IB to IIIA NSCLC. There was a significant decrease in rate of local failure with PORT but no difference in survival.

The use of PORT for patients with pN0, pN1 or pN2 disease declined after the publication of the 1998 meta-analysis (7). However, the studies in the meta-analysis may not be representative of the patients receiving therapy today, as there have been significant technologic improvements and optimization of the doses and fractionation regimens. Administration of systemic chemotherapy has also changed after the demonstration that adjuvant cisplatin-based combinations prolong survival (8–12).

Growing evidence suggest that PORT has a favorable effect on survival of patients with pN2 disease. A retrospective analysis of the Surveillance Epidemiology and End Results (SEERs) database including 5,600 patients showed a decrease in overall survival for patients with pN0 or pN1 disease, whereas the pN2 subgroup of patients had a significant survival benefit that was maximal at 3 years (13). No prospectively randomized trial using modern radiotherapy standards has been performed so far. The Adjuvant Navelbine International Trialist Association (ANITA) trial is a prospectively randomized, Phase III comparison of postoperative cisplatin and vinorelbine versus observation in completely resected NSCLC. Administration of PORT was left to the institution decision before initiating the study. The present report describes the survival data of patients receiving PORT in the ANITA trial, as a hypothesis generating data set for new Phase III studies in adjuvant therapy.

METHODS AND MATERIALS

Data source and study cohort

ANITA is an open, multicentric, randomized, and previously published trial (10) in which 840 patients with completely resected NSCLC were randomized 1:1 to receive postoperative chemotherapy with cisplatin and vinorelbine or observation. Administration of PORT was recommended for patients with pathologic node-positive (pN+) disease, but patients were not randomized to PORT and it was not mandatory. Each center decided before study initiation whether to follow the recommendation. The recommended regimen was 45 to 60 Gy over 5 weeks (2 Gy per fraction, five fractions per week) using a high-energy linear accelerator. Treatment with PORT was to be initiated 2 weeks after the end of chemotherapy or within 2 weeks after randomization in the observation group. Information on whether PORT was administered was collected on the case report form of the study. Because PORT was not among the endpoints of ANITA, it was not monitored, and information on dose and fractionation regimen were not collected.

Data analysis

The population was studied on an intent-to-treat basis in ANITA and included all randomized patients ($n = 840$). Overall survival was analyzed by Kaplan-Meier curves and life tables according to pathologic nodal status. No statistical comparison has been performed in view of the nonrandomized, nonmandatory nature of PORT administration. Only a descriptive analysis is presented. Overall survival was defined using the same criteria as in ANITA (*i.e.,* time elapsed from the date of randomization until last follow-up or until death from any cause). Patients alive at the cutoff date or lost to follow-up were censored at the date of last news. Data were analyzed using SAS software version 8.2 for Windows (SAS Institute, Cary, NC). Kaplan-Meier plots and life tables were used to describe survival in each subgroup. Patients who received PORT were identified. Their overall survival was evaluated within each treatment group of ANITA (observation; observation + PORT; chemotherapy; chemotherapy + PORT) and in subgroups according to nodal status (pN0, pN1, pN2).

Role of sponsoring organization

Patients in the ANITA study were registered and randomized by the Biometric Department of the Institut de Recherche Pierre Fabre (IRPF), which sponsored the study, participated in data collection and patient monitoring, and was responsible for the data analysis. A steering committee was created under the chair of the corresponding author/investigator, with full access to the data and responsibility for the decision to submit the results for publication.

RESULTS

The open-label Phase III study ANITA was performed in 101 centers in 14 countries and the results were previously published (10). A total of 840 patients were randomized to chemotherapy ($n = 407$) or observation ($n = 433$). There were 367 patients with pN0 disease, 243 with pN1, 224

Table 1. Patient subgroups receiving postoperative radiation therapy (PORT) in the ANITA trial, by nodal status

	Observation			Cisplatin + vinorelbine			
	pN0	pN1	pN2	pN0	pN1	pN2	Total
Total population	188	136	106	179	107	118	840*
PORT population	16	60	68	15	25	48	232
% PORT	8.5	44.1	64.5	8.4	23.3	40.6	27.6

Abbreviation: ANITA = Adjuvant Navelbine International Trialist Association.
* Six patients had missing pN status.

with pN2, and 6 with pN status unknown. Overall, 232 patients (27.6%) received PORT (Table 1), including 50% (116 patients) with pN2 and 36.6% (85 patients) with pN1. Although not recommended per protocol, 13.4% of patients with pN0 disease received PORT (31 cases). Significantly more patients in the observation arm (144 patients, 33.3%) received PORT as compared with the chemotherapy arm (88 patients, 21.6%) (p = 0.0002). Five countries (France, Spain, Italy, Poland, and the Czech Republic) contributed 83.2% of the patients randomized in ANITA and 84% of the patients treated with PORT. Administration of PORT according to nodal stage was similar among these countries (data not shown).

Table 2 presents the baseline characteristics of all randomized patients and of the patients receiving PORT. There were more patients with performance status (PS) ≤1 and less with PS 0 in the PORT group, otherwise the baseline characteristics were similar in the group receiving PORT as compared with the overall population.

Survival results

In an univariate analysis of the overall ANITA patient population, PORT showed a significant detrimental effect on survival (p = 0.003; hazard ratio 1.34; 95% confidence interval, 1.10–1.63), generating further analysis of PORT.

Patients with PORT had a median survival of 33.3 months in the observation group and 47.4 months in the chemotherapy group to be compared with 43.7 and 65.7 months in the overall ANITA population. Conversely, the 5-year survival rates in the PORT group were 33% for those in observation and 44.6% for those in the chemotherapy group, as compared with 43% and 51%, respectively. in the overall population. The detrimental effect of PORT on the overall population survival curves is shown in Fig. 1.

The 5-year survival rates in patients receiving PORT were related to pN stage (Table 3). In pN1 patients who received chemotherapy, PORT was associated with a shorter median survival as compared with chemotherapy alone (46.6 months vs. 93.6 months) and a worse 5-year survival (40% vs. 56.3%). In contrast in the observation group, PORT had a beneficial effect on survival (MS 50.2 months with PORT vs. 25.9 months without, and 5-year survival 42.6% vs. 31.4%) (Fig. 2).

In patients with pN2 disease (Fig. 3), chemotherapy and PORT provided a longer median survival than chemotherapy alone (47.4 months vs. 23.8 months) as well as better 5-year survival (47.4% vs. 34%). A similar effect was observed in the observation group (MS 22.7 months with PORT vs 12.7 months without; 5-year survival 21.3% vs. 16.6%).

In patients with pN0 disease, 5-year survival rates were lower in patients receiving PORT (Table 3); however the sample was too small (31 patients) to draw any inferences.

Histologic subtypes were similar in PORT and the overall population. Survival at 5 years showed no difference according to squamous or nonsquamous histologic findings (data not shown).

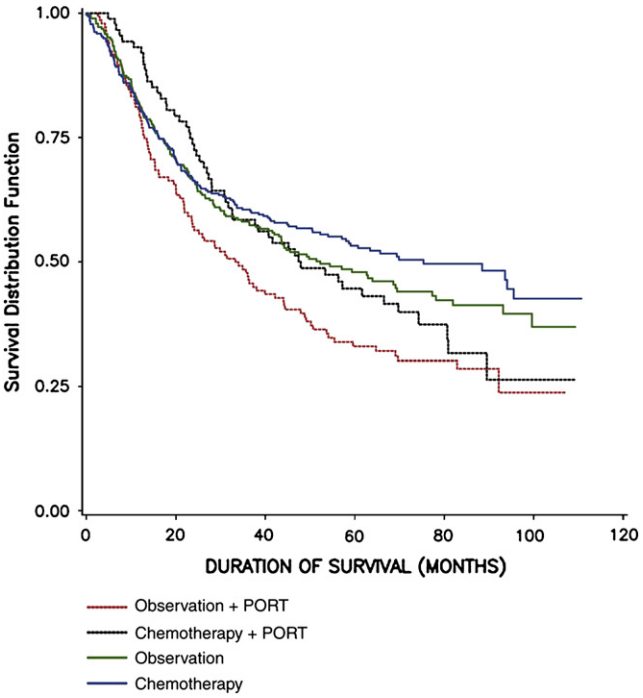

Fig. 1. Overall survival according to treatment received in the overall population in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

Table 2. Baseline characteristics of patients receiving postoperative radiation therapy (PORT) and of the overall population (%)

Covariate	Total patient group N = 840	Patients with PORT n = 232
Age (y), median	59	60
Age (y), range	18–75	(32–75)
WHO performance status		
0	50	43
1	45	56
2	3	1
Gender		
Male	86	86
Female	14	14
Histology		
Squamous cell carcinoma	58.7	54.3
Non–squamous-cell carcinoma	41.3	45.7
Surgery type		
Pneumonectomy	36.9	38.8
No pneumonectomy	63.1	61.2

Abbreviation: WHO = World Health Organization.

Table 3. ANITA trial results: Percentage of patients with 5-year survival, according to treatment received by nodal status

Treatment group	pN0	pN1	pN2
Observation (%)	62.3	31.4	16.6
Observation + PORT (%)	43.8	42.6	21.3
Chemotherapy* (%)	59.7	56.3	34.0
Chemotherapy* + PORT (%)	44.4	40.0	47.4

Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association.; PORT = postoperative radiation therapy.
* Chemotherapy consisted of vinorelbine + cisplatin.

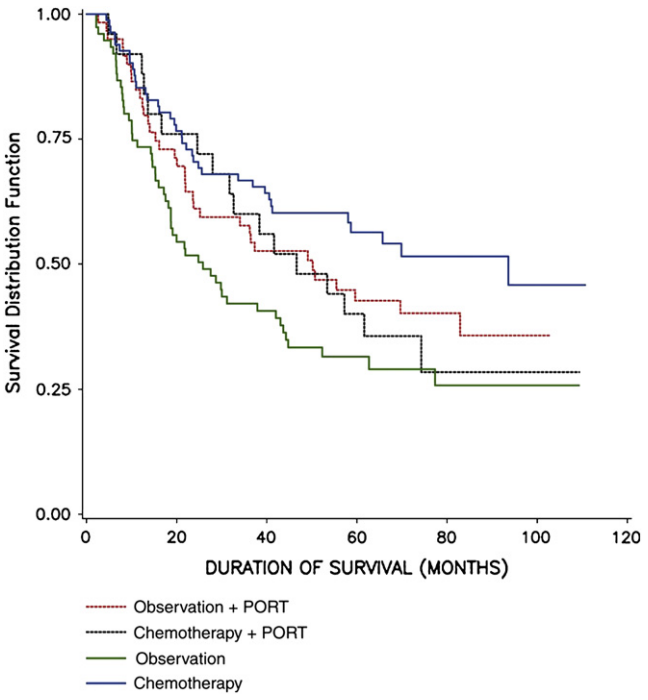

Fig. 2. Overall survival according to treatment received in the pN1 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

Type of surgery

The 5-year survival rate was lower in patients with pneumonectomy as compared with other types of surgery (mainly lobectomy and bilobectomy), both in the group of patients given PORT and in the group who did not receive PORT.

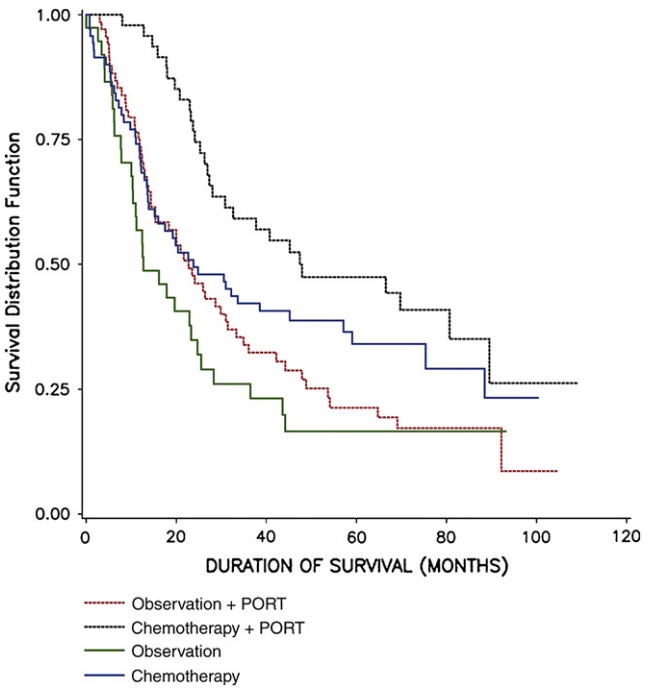

Fig. 3. Overall survival according to treatment received in the pN2 patients in the Adjuvant Navelbine International Trialist Association (ANITA) trial.

Causes of death

Deaths related to PORT could not be clearly evaluated, as PORT was not monitored per protocol. The death rate in the patient population who received PORT was 65% (pN0: 58%, pN1: 61%, pN2: 70%) and 50% in those without PORT (pN0: 41%, pN1: 56%, pN2: 70%). Patients with pN0 and pN1 disease had higher death rates with PORT than without. Among patients who died, the incidence of death resulting from progression was similar in all pN subgroups independently of administration of PORT (Table 4). Deaths for ''other'' reasons among the deceased population were reported in 20% in the PORT group as compared with 12% without PORT. Among the other reasons, the causes of death were mainly myocardial infarction, congestive heart failure, thromboembolism, and pulmonary failure, with an excess for acute myocardial infarction among patients given PORT (3% and 0.6%). When other and unknown reasons were considered together, the death rate was 18% with PORT and 11% without. There seems to be an excess of death in the PORT group as compared with the non-PORT group; this excess is essentially related to unknown and other reasons in regard to all pN stages.

Sites of relapse or progression

Distant metastasis were more frequent in patients receiving PORT for both the observation and the chemotherapy groups; this seemed to be more pronounced for patients with pN2 disease in the observation group. In contrast, PORT reduced the local relapse rate in both groups (Tables 5 and 6). More patients in the PORT group presented with brain (16.4% vs. 9.5%) or bone metastasis (10.8% vs. 5.9%).

DISCUSSION

We have described the survival data in the subgroups of patients who received PORT, as per the investigator choice, within the ANITA trial.

The subgroup of patients who received PORT had baseline characteristics similar to those of the overall population in terms of age and gender. There was a slight imbalance in World Health Organization (WHO) performance status, with more patients having PS 1 in the PORT group. Despite the recommendation that centers choosing to administer PORT should do so in all pN+ patients, a significantly higher proportion of patients received PORT in the observation group than in the chemotherapy group. Possible explanations include (*1*) investigator choice to favor PORT in patients without adjuvant chemotherapy; and (*2*) decision by treating physician or refusal by patients for the addition of PORT after adjuvant chemotherapy because of the duration of total adjuvant therapy, asthenia, or altered PS after chemotherapy, as discussed in the initial publication (10).

We found that patients who received PORT overall had a lower survival than the patients who did not receive PORT, in both the observation and the chemotherapy groups as compared with the overall survival in ANITA, as reflected in the univariate analysis,. There was an apparent relationship

Table 4. Cause of death, by postoperative radiation therapy (PORT) administration and pathologic node status

	PORT (n = 232)			No PORT (n = 602)			All cases N = 834*
	pN0	pN1	pN2	pN0	pN1	pN2	
Cause of death	n = 31	n = 85	n = 116	n = 336	n = 158	n = 108	834*
All deaths (%)	18 (100)	52 (100	82 (100)	139 (100)	89 (100)	76 (100)	456
Treatment related (%)	–	–	–	5 (3.6)	–	2 (2.6)	7
Disease progression (%)	12 (66.7)	37 (71.2)	64 (78.0)	97 (69.8)	71 (79.8)	60 (78.9)	341
Other reason (%)	6 (33.3)	11 (21.2)	13 (15.9)	21 (15.1)	11 (12.4)	5 (6.6)	67
Unknown cause	–	4 (7.7)	5 (6.1)	16 (11.5)	7 (7.9)	9 (11.8)	41

Abbreviation: NA = not assessed.
* Six case patients had unknown pathologic status.

between PORT effect and pathologic nodal status. In the pN2 subgroup, patients who received PORT had a strikingly longer survival, both in the chemotherapy group and in the control group. Among patients in the pN1 group, however, those receiving PORT in the chemotherapy group fared worse—as if PORT abrogated the benefit of adjuvant chemotherapy—whereas those in the observation group did slightly better. In the very small subset of patients with pN0 group who received PORT, survival was shorter, which was in line with results of previous studies and meta-analysis with the exception of the most recent Italian study (15). It that study, 98 patients randomly received 50.4 Gy with a classical fractionation and a high-energy linear accelerator. Locoregional relapse rates were significantly improved with adjuvant PORT. Distant relapses were not detailed but identical in numbers, and there was a trend toward better survival.

A potentially favorable effect of PORT in patients with pN2 disease is in agreement with results from other studies or meta-analysis suggesting that patients with pN2 disease are likely to benefit from PORT, whereas this is not the case for patients with pN1 disease in the same reports (1, 2, 14, 4). However a clear effect on survival has not been described so far.

The Lung Cancer Study Group 773 study found a significant reduction of local recurrence (1) for patients who received PORT (50 Gy; first site of relapse, 1% vs. 20%, $p < 0.001$; overall recurrence ($p = 0.188$), 37% vs. 47%; recurrence in pN2 29% vs. 57%, p = 0.03) but survival was not different. In a study by the Medical Research Council Lung Cancer Working Party (2) the local recurrence rate was 41% vs. 29%; the distant failure rate was not significantly different between groups in the pN1 but was much higher in the pN2 subsets (46% vs. 70%, $p = 0.03$), with a 3-year survival benefit in the radiotherapy group. This reduction of local relapses with PORT was also observed in the meta-analysis and in ANITA.

Adjuvant chemoradiotherapy consisting of four cycles of cisplatin + etoposide and concomitant radiotherapy (50.4 Gy) was compared with radiotherapy alone in 488 patients with Stages II and IIIA disease by the Eastern Cooperative Oncology Group (14). There were no differences in survival, overall relapse, and local relapse between the two groups. The authors concluded that sequential chemoradiotherapy might be more appropriate. This trial was actually comparing adjuvant PORT vs adjuvant chemoradiation, using an older drug combination, now known according to the LACE meta-analysis to provide no significant benefit in combination with cisplatin (8), including 41% of patients with Stage II disease, probably a majority with pN1. In another randomized study by Feng *et al.* (4), local recurrence was reduced significantly for patients with squamous cell carcinoma receiving PORT as compared with those with no postoperative treatment (35% vs. 16% in pN1 and pN2 disease), but no difference in OS was observed (43% with PORT vs. 40% in the control), probably because of a similar incidence (73%) of distant metastasis in both therapy groups.

In the older studies, radiotherapy-related morbidity and mortality has been one of the factors influencing outcomes of PORT. Improved equipment and modern dosimetry allow more selective delivery of radiation to the tumor lesion, and

Table 5. Sites of first relapse by stage with and without postoperative radiation therapy (PORT) in patients randomized to observation

	No PORT	No PORT, by pN stage			PORT	PORT, by pN stage		
	Total	pN0	pN1	pN2	Total	pN0	pN1	pN2
Total, n (%)	286* (100)	172 (100)	76 (100)	38 (100)	144 (100)	16 (100)	60 (100)	68 (100)
No relapse (%)	130 (45.5)	97 (56.4)	25 (32.9)	8 (21.1)	50 (34.7)	9 (56.3)	26 (43.3)	15 (22.1)
Locoregional (%)	58 (20.3)	31 (18.0)	16 (21.1)	11 (28.9)	17 (11.8)	–	7 (11.7)	10 (14.7)
Metastasis (%)	66 (23.1)	33 (19.2)	21 (27.6)	12 (31.6)	56 (38.9)	6 (37.5)	17 (28.3)	33 (48.5)
Locoregional+ metastasis (%)	17 (5.9)	6 (3.5)	6 (7.9)	5 (13.2)	12 (8.3)	1 (6.3)	6 (10.0)	5 (7.4)
Unknown site (%)	15 (5.2)	5 (2.9)	8 (10.5)	2 (5.3)	9 (6.3)	–	4 (6.7)	5 (7.4)

Data are absolute numbers with percentages in parentheses.
* Three patients were missing pN status.

Table 6. Sites of relapse with and without postoperative radiation therapy (PORT) in patients randomized to chemotherapy

	No PORT	No PORT by pN stage			PORT	PORT by pN stage		
Patient outcome	Total	pN0	pN1	pN2	Total	pN0	pN1	pN2
Total, *n* (%)	316* (100)	164 (100)	82 (100)	70 (100)	88 (100)	15 (100)	25 (100)	48 (100)
No relapse (%)	173 (54.7)	98 (59.8)	47 (57.3)	28 (40.0)	45 (51.1)	8 (53.3)	13 (52.0)	24 (50.0)
Locoregional (%)	41 (13.0)	17 (10.4)	11 (13.4)	13 (18.6)	8 (9.1)	3 (20)	2 (8.0)	3 (6.3)
Metastasis (%)	74 (23.4)	33 (20.1)	19 (23.2)	22 (31.4)	27 (30.7)	3 (20.0)	17 (28.0)	17 (35.4)
Locoregional and metastasis (%)	17 (5.4)	12 (7.3)	–	5 (7.1)	8 (9.1)	1 (6.7)	3 (12.0)	4 (8.3)
Unknown site (%)	11 (3.5)	4 (2.4)	5 (6.1)	2 (2.9)		–	–	–

Column percentages.
Percentage of total number of patients receiving PORT.
* Three patients were missing pN status.

an improved therapeutic ratio is expected. In the Eastern Cooperative Oncology Group trial (14) mentioned above, the rates of therapy-related mortality were low and were similar between the groups (1.2% for the group receiving radiotherapy alone vs. 1.6 for the other group receiving adjuvant chemoradiotherapy).

In the present evaluation, PORT-related mortality was not assessed per protocol. Overall the death rate was higher in the PORT population, mainly for reasons other than disease progression, which might include late toxic effects of PORT as suggested by the meta-analysis (5). In the recent Italian trial (15) for Stage I disease, adjuvant PORT was also associated with toxicity, but no detailed information was provided on non–cancer-related death.

Another important recent development has been the demonstration in several large studies of adjuvant chemotherapy or in meta-analysis that cisplatin-based chemotherapy is beneficial in fully resected Stages II to IIIA disease (8–12). The order of magnitude of the survival benefit varies among studies according to the drug combined with cisplatin and the disease stage. In the ANITA trial, there was overall no observable benefit in patients with Stage IB disease, a 12% improvement in Stage II, and 16% improvement in Stage IIIA at 5 years (10). The unplanned subgroup analysis of the effect of PORT showed that patients with pN2 disease benefited the most, with a 47.4% survival at 5 years with adjuvant chemotherapy plus PORT, compared with 34% survival in patients with adjuvant chemotherapy, 21.3% with adjuvant PORT, and 16.6% with surgery only. Therefore combined use of adjuvant chemotherapy plus PORT increases the chance of survival by a factor of almost 3 in patients with pN2 disease as compared with those treated with surgery alone.

In addition, for patients who are not deemed fit to receive adjuvant chemotherapy, PORT provides a survival benefit in patients with both pN1 and pN2 disease.

Based on the present descriptive data, a basis exists for the evaluation of the role of PORT in resected pN2 disease. The Lung Adjuvant Radiotherapy Trial (Lung ART) is a randomized study of PORT in patients with pN2 disease and complete resections. The trial findings will help in setting new standards of care for such patients, with more advanced radiation technology and evaluation of possible late toxic effects as well as radiation-related death, which are not presently assessable in the meta-analysis (5) and the ANITA trial (10).

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