Factors Affecting Use of PORT, Induction Chemotherapy, and Surgery to Improve Outcomes in NSCLC

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Patients with stage III non–small cell lung cancer (NSCLC) are a heterogeneous group at high risk for local and distant relapse. It is generally agreed that optimal treatment selection occurs in a multidisciplinary team setting after optimal staging. Adjuvant chemotherapy is now considered the standard of care for patients with resectable disease; the NSCLC Collaborative Group meta-analysis concluded that adjuvant chemotherapy improved survival in locally advanced NSCLC irrespective of whether it was performed after surgery alone or after surgery plus radiation therapy (RT) [NSCLC Meta-analyses Collaborative Group. *Lancet.* 2010]. The role of neoadjuvant or adjuvant RT, however, remains controversial. A landmark meta-analysis of 9 randomized trials with >2000 patients concluded that postoperative RT (PORT) was detrimental in patients with early-stage, completely resected NSCLC but that its role in patients with N2 disease was unclear [PORT Meta-analysis Trialists Group. *Cochrane Database Syst Rev.* 2003].

Cécile Le Péchoux, MD, Institut Gustave-Roussy, Villejuif, France, reviewed the evidence concerning the role of neoadjuvant or adjuvant RT in improving outcomes for patients with stage III disease. She noted that patient selection and treatment have changed considerably since the publication of the PORT meta-analysis. In addition, neoadjuvant or adjuvant chemotherapy has become the standard of care; surgical and RT techniques have improved; and positron emission tomography scanning is being used to refine patient selection.

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Prof Le Péchoux summarized the results of 4 large randomized trials of neoadjuvant RT and 2 of PORT in patients with stage III NSCLC, none of which showed a survival benefit (Table 1). In the most recently completed trial—SAKK 16/00 [Pless M et al. *Ann Oncol.* 2014; NCT00030771]—RT increased rates of response, complete resection, and pathologic complete response but failed to improve local control, event-free survival, or overall survival. In a 2005 update of the PORT meta-analysis, there was an 18% relative increase in the risk of death for PORT when compared with surgery alone [Burdett S, Stewart L. *Lung Cancer.* 2005]. A 2013 update using new statistical methodology found that the effect of PORT varied by stage and nodal status [Burdett et al. *Lung Cancer.* 2013], but Prof Le Péchoux stated that this analysis was underpowered.

Although findings from meta-analyses do not support a role for RT after complete resection, excess toxicity, poor local control, and the use of older techniques may have contributed to excess mortality, she said. Population-based studies have found superior 5-year survival in completely resected N2 patients who received PORT when compared with patients who received surgery alone or surgery plus chemotherapy [Mikell JL et al. *J Thorac Oncol.* 2015; Robinson CG et al. *J Clin Oncol.* 2015], but these studies cannot be considered robust evidence in favor of PORT, she said.

Both preoperative RT and PORT, however, have been shown to reduce local recurrence rates [Pless et al. *Ann Oncol.* 2014; Le Péchoux C. *Oncologist.* 2011]. Technical advances may enhance the ability of RT to improve local relapse-free survival, disease-free survival, and possibly overall survival. New evidence to reassess the role of PORT using modern radiation techniques may emerge from the international randomized LUNG ART trial [NCT00410683], Prof Le Péchoux said. In this ongoing phase 3 study, an expected enrollment of 700 patients with completely resected N2 NSCLC will be randomized to receive conformal mediastinal PORT or no PORT. Patients may also receive neoadjuvant or adjuvant chemotherapy. The trial's primary end point is disease-free survival.

Paul De Leyn, MD, PhD, University Hospitals Leuven, Leuven, Belgium, offered a surgeon's perspective on improving long-term outcomes for patients with stage III disease. Definitive

Table 1. RCTs of Neoadjuvant or Adjuvant RT in Patients With Stage III NSCLC

Study	Intervention	No. of Patients, Stage/TNM Status	Outcome
	Neoadjuvant RT		
Lung Intergroup 0139 [Albain KS et al. *Lancet.* 2009]	CRT followed by surgery vs CRT alone	429, IIIA (N2)	5-y survival: CRT + surgery, 27%; CRT alone, 20%; *P* = .10
German Lung Cancer Cooperative Group [Thomas M et al. *Lancet Oncol.* 2008]	IND-Ctx followed by CRT and surgery vs IND-Ctx alone followed by surgery	558, III (A + B)	5-y OS in patients undergoing tumor resection: Ctx + CRT + surgery, 45%; Ctx + surgery, 42%; *P* = .82
SAKK 16/00 [Pless M et al. *Ann Oncol.* 2014]	CRT followed by surgery vs Ctx alone followed by surgery	232, IIIA/N2	Median OS: CRT, 37.1 mo (95% CI, 22.6 to 50); Ctx, 26.1 mo (95% CI, 26.1 to 52.1); *P* = .938
ESPATUE [Eberhardt et al. *J Clin Oncol*. 2014]	IND-Ctx + CRT followed by surgery (arm B) vs IND-Ctx + CRT followed by CRT (arm A)	246, resectable stage IIIA (N2), selected stage IIIB	5-y survival: arm B, 44.2%; arm A, 40.6%; log-rank *P* = .31
	Adjuvant RT in postoperative setting		
ECOG [Keller SM et al. *N Engl J Med.* 2000]	RT alone vs CRT	488, resected stage II (T2N1M0) or stage IIIa (T1-2N2M0 or T3N1-2M0)	Median OS: RT alone, 39 mo; CRT, 38 mo; log-rank *P* = .56
ANITA [Douillard JY et al. *Lancet Oncol.* 2006]	Adjuvant Ctx vs observation; PORT optional per each center's policy	840, IB–IIIA	5-y OS with Ctx improved by 8.6%; adjusted risk for death was significantly reduced for Ctx vs observation; *P* = .017

CRT, chemoradiation therapy; Ctx, chemotherapy; IND-Ctx, induction chemotherapy; NSCLC, non–small cell lung cancer; OS, overall survival; PORT, postoperative radiation therapy; RCT, randomized clinical trial; RT, radiation therapy; TNM, tumor, node, and metastasis.

upfront stratification of tumors—as resectable, potentially resectable with an increased risk of incomplete resection, or unresectable—is crucial, he said. According to Prof De Leyn, good survival rates and acceptable morbidity and mortality have been achieved with induction chemotherapy or chemoradiotherapy in selected patients with potentially resectable tumors with an increased risk of incomplete resection.

Prof De Leyn reviewed the evidence from several studies involving patients with potentially resectable N2 disease and one study of patients with unresectable disease, all of whom underwent surgery following induction chemotherapy or chemoradiation therapy (CRT; Table 2). In the German Lung Cancer Cooperative Group study [Thomas M et al. *Lancet Oncol.* 2008], preoperative CRT increased postsurgical mortality compared with preoperative chemotherapy, primarily due to increased rates of empyema and bronchial insufficiency. The evidence does not support a role for induction CRT for N2 disease, Prof De Leyn said. For Pancoast tumors, however, induction CRT is the standard of care. For stage III tumors deemed unresectable at baseline assessment, the EORTC 8947 trial [van Meerbeeck JP et al. *J Natl Cancer Inst.* 2007] demonstrated that induction chemotherapy will not render an unresectable tumor resectable, Prof De Leyn said. He recommended that patients whose tumors are deemed unresectable should receive immediate CRT.

Both types of surgery and hospital surgical volume have been shown to influence outcomes. In a systematic review and meta-analysis of 27 studies published between 1990 and 2010, right pneumonectomy following neoadjuvant therapy was associated with significantly higher 30-day (*P* = .02) and 90-day (*P* = .03) mortality

Table 2. Studies of Potentially Resectable or Baseline Unresectable Stage III (N2) NSCLC

Study	Study Design, Intervention	No. of Patients, Stage/TNM Status	Outcome
		Potentially resectable	
Betticher DC et al. *Br J Cancer.* 2006; Betticher DC et al. *J Clin Oncol.* 2003	Phase 2 RCT, IND-Ctx followed by surgery	90, IIIA (pN2)	Perioperative mortality, 3%; median OS, 35 mo; 3-y relapse-free survival, 36%
Decaluwé H et al. *Eur J Cardiothorac Surg*. 2009	Prospective consecutive surgical database, 2000 to 2006; IND-Ctx followed by surgery in responders and stable disease	92, IIIA (N2)	Complete resection rate, 68%; in-hospital mortality, 2.3%; 5-y OS, 33%
Lung Intergroup 0139 [Albain KS et al. *Lancet.* 2009]	RCT; IND-CRT followed by surgery vs CRT alone	429, IIIA (pN2)	Complete resection rate 88%; disease progression at 5 y: CRT + surgery, 22%; CRT alone, 11%
German Lung Cancer Cooperative Group [Thomas M et al. *Lancet Oncol.* 2008]	RCT; IND-Ctx followed by CRT and surgery vs IND-CT alone followed by surgery	558, III (A + B)	5-y OS survival in patients undergoing tumor resection: Ctx + CRT + surgery, 45%; Ctx + surgery, 42%; $P = .82$; postsurgical mortality: CRT, 9.2%; IND-CT alone, 4.5%
SWOG 9416/Intergroup 0160 [Rusch VW et al. *J Thorac Oncol.* 2007; Rusch VW et al. *J Thorac Cardiovasc Surg*. 2001]	RCT; IND-CRT followed by surgery in responders and stable disease	110, III cT3-T4N0, mediastinoscopy negative (Pancoast tumors)	Complete resection rate, 92%; 5-y OS, 44%; 5-y OS in completely resected patients, 54%
De Leyn P et al. *J Thorac Oncol*. 2009	Prospective consecutive surgical database, 2002 to 2008; IND-CRT followed by surgery in responders and stable disease	32, III cT3-T4	5-y survival, resected patients (n = 25): 77%
		Baseline unresectable	
EORTC 8947 [van Meerbeeck JP et al. *J Natl Cancer Inst*. 2007]	RCT; IND-Ctx, responders randomized to RT or surgery ± PORT	579, IIIA-N2	5-y OS: resection 15.7% vs RT 14% (HR, 1.06; 95% CI, 0.84 to 1.35)

CRT, chemoradiation therapy; IND-Ctx, induction chemotherapy; NSCLC, non–small cell lung cancer; OS, overall survival; PORT, postoperative radiation therapy; RCT, randomized clinical trial; RT, radiation therapy; TNM, tumor, node, and metastasis.

compared with left pneumonectomy; 90-day mortality for all pneumonectomies was also higher than 30-day mortality [Kim et al. *J Thorac Cardiovasc Surg*. 2012]. Prof De Leyn noted that these findings highlight the need for careful patient selection for pneumonectomy and reporting of 90-day mortality.

In regard to surgical volume, Bach and colleagues reported in 2001 that 44% of patients who had surgery at the highest volume centers survived 5 years post-surgery, compared with 33% of patients treated at the lowest volume centers ($P < .001$). A 2013 analysis of data on > 134 000 patients with NSCLC diagnosed in England between 2004 and 2008 found that high procedure volume was strongly associated with improved survival, a higher resection rate, and a higher percentage of resections in patients with higher levels of comorbidity [Lüchtenborg M et al. *J Clin Oncol*. 2013].

In conclusion, evidence reviewed in this session showed that unanswered questions still surround the role of PORT in the treatment of patients with stage III NSCLC, that the role of induction CRT is dependent on tumor resectability, and that type of surgery and hospital surgical volume are important factors in surgical outcomes.