Role of Postoperative Radiotherapy in the Management for Resected NSCLC – Decision Criteria in Clinical Routine Pre- and Post-LungART

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Abstract

The role of postoperative radiation therapy (PORT) in stage III N2 nonsmall cell lung cancer patients remains controversial. PORT is still widely used among European thoracic radiation oncology experts with a clear decrease in its use for patients with completely resected pN+ NSCLC after the presentation of LungART trial results at ESMO 2020. The full publication of the LungART trial hopefully will shed additional light on the dilemma of the decision-making process for PORT in completely resected pN+ patients and identify the appropriate patients who might benefit from PORT.

Background: The role of postoperative radiation therapy (PORT) in stage III N2 NSCLC is controversial. We analyzed decision-making for PORT among European radiation oncology experts in lung cancer. **Methods:** Twenty-two experts were asked before and after presentation of the results of the LungART trial to describe their decision criteria for PORT

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in the management of pN+ NSCLC patients. Treatment strategies were subsequently converted into decision trees and analyzed. **Results:** Following decision criteria were identified: extracapsular nodal extension, incomplete lymph node resection, multistation lymph nodes, high nodal tumor load, poor response to induction chemotherapy, ineligibility to receive adjuvant chemotherapy, performance status, resection margin, lung function and cardiopulmonary comorbidities. The LungART results had impact on decision-making and reduced the number of recommendations for PORT. The only clear indication for PORT was a R1/2 resection. Six experts out of ten who initially recommended PORT for all R0 resected pN2 patients no longer used PORT routinely for these patients, while four still recommended PORT for all patients with pN2. Fourteen experts used PORT only for patients with risk factors, compared to eleven before the presentation of the LungART trial. Four experts stated that PORT was never recommended in R0 resected pN2 patients regardless of risk factors. **Conclusion:** After presentation of the LungART trial results at ESMO 2020, 82% of our experts still used PORT for stage III pN2 NSCLC patients with risk factors. The recommendation for PORT decreased, especially for patients without risk factors. Cardiopulmonary comorbidities became more relevant in the decision-making for PORT.

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Introduction

Nonsmall cell lung cancer (NSCLC) accounts for approximately 80%-85% of all lung cancer and one-third of patients with NSCLC have stage III disease at diagnosis.[1,2] Multimodal therapy is the standard of care for patients with locally advanced (LA) NSCLC (stage IIIA-C). Within stage III disease with N2 nodal involvement, there is considerable heterogeneity leading to different treatment options for individual scenarios.[3] For potentially resectable stage III NSCLC patients a surgically based multimodal approach can be offered.[4,5] The high rate of recurrences had led to the development of peri-operative treatment strategies to improve outcomes. Neoadjuvant or adjuvant chemotherapy is considered a standard treatment in patients with stage IB (>4 cm) to IIIA NSCLC.[6,7] However, even after complete resection and adjuvant chemotherapy, node-positive (pN+) patients still have a 20%-40% risk of locoregional relapse which is correlated with poor overall survival (OS).[8,9] Thus, postoperative radiation therapy (PORT) is often recommended to improve local tumor control in stage III pN+ NSCLC patients, yet the role of PORT has been historically controversial.

The largest trial evaluating PORT included 728 stage I-III patients and demonstrated that PORT had a detrimental effect on survival.[10] The PORT meta-analyses showed a deleterious effect of PORT in pathological stages I–III NSCLC, with an absolute detriment of 7% at 2 years after a complete resection due to the low risk of local recurrence in pN0-pN1 patients, high risk of distant relapse due to the lack of systemic treatment and relatively high toxicity of outdated radiotherapy techniques.[11-13] While this negative effect was observed for pN0 and pN1 patients, no definitive conclusion could be made for pN2. This negative result led to a change in clinical practice, with fewer patients treated with PORT even for pN2 disease. More recently retrospective databases and a prospective clinical trial with subgroup analysis with better patient selection and routinely performed (neo)adjuvant chemotherapy suggested PORT could improve outcome of completely resected stage III N2 patients.[14-18]

In this context of uncertainty, there was a clear need for a large randomized trial to assess the role of modern mediastinal PORT in adequately staged and surgically treated patients. The LungART trial presented at ESMO 2020 explored the role of mediastinal PORT in patients with completely resected NSCLC with histologically proven nodal involvement in the modern era of staging, surgery and radiotherapy.[19] More than 90% of the patients were staged preoperatively using PET/CT in this trial. Patients with positive margins, extracapsular mediastinal nodal extension breaching the surface of the pathological specimen or without systematic/complete mediastinal dissection were excluded. PORT showed no statistically significant difference in 3-year disease free survival (47.1% in the PORT arm and 43.8% in the control arm, $P = .16$). Overall survival (OS) at three years was 66.5% for patients in the PORT arm compared to 68.5% in the control arm. However, a decrease in the rate of mediastinal relapse from 46% to 25% at 3 years should be noted, hinting that some patients with high risk for relapse could benefit from PORT. This must be balanced against the risk of cardio-pulmonary toxicity leading to death, which was significantly higher compared to the control arm (16.2% vs. 2.0%). Generally more toxicities, especially, late cardiopulmonary toxicity grade 3-4 (10.8% vs. 4.9%, mostly cardiac rhythm disorders, pericarditis, pneumonitis, and dyspnea/respiratory failure) were reported in the PORT arm. The conclusion of the study was that PORT should not be considered a standard of care for completely resected stage IIIA N2 patients. However further analysis is needed to identify cohorts that could potentially benefit from PORT.

In the past, several clinicopathological factors were reported to be associated with different survival rates.[16,17,20-24] These suggest that treatments for IIIA N2 NSCLC should be individualized.

In clinical routine practice many criteria influence the decision-making process.[25] Thus, the aim of this work was to identify relevant criteria in the complex process of patient selection and decision-making for PORT in pN+ NSCLC patients and to identify to what degree the results of the LungART trial changed the decision-making process. We also evaluated whether there was a difference in the prescribed dose of PORT when applied by European experts.

Methods

We asked 22 European radiation oncologists who were identified by the European SocieTy for Radiotherapy and Oncology (ESTRO) and by the Advisory Committee on Radiation Oncology Practice (ACROP) as experts in the field of lung cancer to participate in this analysis. Each expert was asked the following question: «Please describe if and for which patients you would recommend adjuvant thoracic radiotherapy in pN+ NSCLC. If you use thoracic radiotherapy in this setting, please also describe your dose. Please describe any criteria used in your decision-making». Answers were allowed in any format (eg, free text, tables, diagrams or figures). No specific clinical scenarios, examples or decision criteria were proposed in order to avoid influencing responses. After the initial collection of all responses, treatment strategies were converted into decision trees and decision criteria were extracted.[26] To enable cross-comparison of algorithms, compatible criteria are a prerequisite. Similar decision criteria were fused into new comprehensive categories. Criteria such as extracapsular nodal extension (ENE), incomplete mediastinal lymphadenectomy, multistation/-level lymph node involvement, bulky pN2 disease, multiple lymph nodes (LN), invasion of lymphatic vessels, poor response to induction chemotherapy or ineligibility to receive adjuvant chemotherapy were summarized as risk factors.

Consensus and discrepancies were evaluated with the objective consensus methodology as previously described.[26-28] When 13 or more of the experts (>59%) recommended the same management option we defined it as a consensus.

We started this project in April 2020. We collected decision trees from all experts from April 2020 until August 2020, at which time a first consensus analysis was performed. After the presentation of the first results of the LungART trial in September at the ESMO 2020 we asked the experts whether the results had changed their daily decision making process. In such case, the individual decision trees of the expert were modified. The final decision trees were confirmed in May 2021.

Results

Twenty-two experts provided their decision-making and treatment strategies. The decision criteria used for pN+ NSCLC included (Table 1): ENE/capsular rupture, incomplete lymph node resection, multistation lymph nodes, high nodal tumor load (large/bulky nodes and/or multiple lymph nodes in one station) and poor response to induction chemotherapy. For all experts a good performance status and sufficient lung function were mandatory for PORT. Regardless of the lymph node status, a positive resection margin was an indication for adjuvant radiotherapy for all participating radiation oncologists.

After presentation of the LungART data, some of the experts (18%) explicitly mentioned that cardio-pulmonary comorbidities had more impact on the decision-making process compared to the pre-LungART era.

pN1 NSCLC

While no expert recommended PORT in pN1 patients without risk factors, 27% of the experts (7/22) recommend PORT for pN1 NSCLC patients with risk factors.

After LungART, three experts changed their decision-making for pN1 patients toward a more conservative strategy without PORT, so that only 4/22 experts would recommend PORT in pN1 NSCLC with risk factors. For the majority (83%) the most relevant risk factor in this setting was ENE. For one expert the invasion of lymphatic vessels and for another expert poor response to induction chemotherapy were also important in decision-making of PORT in pN1 NSCLC patients.

pN2 NSCLC - "pre-LungART" Results

Before the presentation of the LungART results, 95% of the experts recommended PORT in R0-resected pN2 NSCLC patients, 10 of them (45%) offered PORT for all pN2 NSCLC patients and 11 experts (50%) used risk factors for decision-making. For one expert PORT played no role for completely resected pN2 NSCLC patients regardless of risk factors. The most commonly used risk factor was the presence of ENE and/or capsular rupture of LNs (11/11 experts), followed by incomplete mediastinal lymphadenectomy (6/11 experts), multistation LNs (5/11 experts), high nodal tumor load (3/11 experts) and poor response to induction chemotherapy (3/11 experts). Involvement of a single pN2 LN station/level was a contraindication for PORT mentioned by five experts. If patients had complete pathological remission of initially involved mediastinal lymph nodes after induction treatment (ypN0), two experts explicitly mentioned that they did not offer adjuvant mediastinal irradiation in this setting.

pN2 NSCLC - "post-LungART" Results

We found that the ESMO presentation of the LungART results already had a substantial impact on decision-making and substantially reduced the number of recommendations for PORT in completely resected pN1-2 NSCLC patients (Figure 1, Table 2). After the first presentation of the LungART data six experts (of ten initially) no longer used PORT routinely for all pN2 patients. Fourteen experts used PORT for patients with risk factors and four still recommended PORT for all patients with pN2. Four experts stated that PORT played no role in case of R0 resected pN2 patients regardless of risk factors.

The individual risk factors used by the individual experts for decision-making also changed (Table 1).

After the LungART presentation, new risk factors were used for PORT: ENE or capsular rupture for three experts, incomplete lymph node resection for four experts, the ineligibility to receive adjuvant chemotherapy for two experts and high nodal tumor load for one expert. Cardiopulmonary comorbidities as a new decision criterion appeared in the decision-making for four experts.

The indication for PORT for R+ resected patients remained unchanged with all twenty-two experts recommending its use.

RT-Dose/Sequence

The recommended postoperative therapy sequence for completely resected pN+ patients in most centers was adjuvant chemotherapy followed by PORT. In one center PORT was delivered first followed by adjuvant chemotherapy.

The RT dose used by the experts (n = 21) for R0 resected pN+ NSCLC varied between 50 and 60 Gy with conventional fractiona-

Table 1 Decision Criteria by the Individual Experts (A-V) for PORT

Experts	Risk Factors							Card/pulm. Comorbidities	PS	Lung Function	R+
	ENE/Capsular Rupture	Incomplete LA	Multistation	High Nodal Tumor Load	L1	Ineligibility to Adjuvant ChT	Poor Response to Induction ChT				
A	x/o	o							x/o	x/o	x/o
B	x/o		x/o	x			x/o		x/o	x/o	x/o
C	x/o		x						x/o	x/o	x/o
D									x/o	x/o	x/o
E	x/o								x/o	x/o	x/o
F									x/o	x/o	x/o
G	o	x/o	x/o						x/o	x/o	x/o
H	o	o						o	x/o	x/o	x/o
I									x/o	x/o	x/o
J	x/o	x/o							x/o	x/o	x/o
K	x/o	x/o							x/o	x/o	x/o
L		o		o				o	x/o	x/o	x/o
M					x/o				x/o	x/o	x/o
N	o					o			x/o	x/o	x/o
O	x/o	x/o					x		x/o	x/o	x/o
P	x/o	x/o							x/o	x/o	x/o
Q		o				o		o	x/o	x/o	x/o
R	x/o	x/o	x/o				x		x/o	x/o	x/o
S								o	x/o	x/o	x/o
T	x			x					x/o	x/o	x/o
U	x		x	x					x/o	x/o	x/o
V									x/o	x/o	x/o

x – criteria pre-LungART, o – criteria post-LungART.
Abbreviations: ChT = chemotherapy; card/pulm = cardiopulmonary; ENE = extracapsular nodal extension; LA = lymph node resection; L1 = invasion of lymphatic vessels; PS = performance status; R+ = positive resection margin.

Figure 1 Consensus and discrepancies for PORT and the changes between pre- and post-LungART presentation. NSCLC = nonsmall cell lung cancer; pN = pathological nodal staging; PORT = postoperative radiotherapy; R+ = positive resection margin.

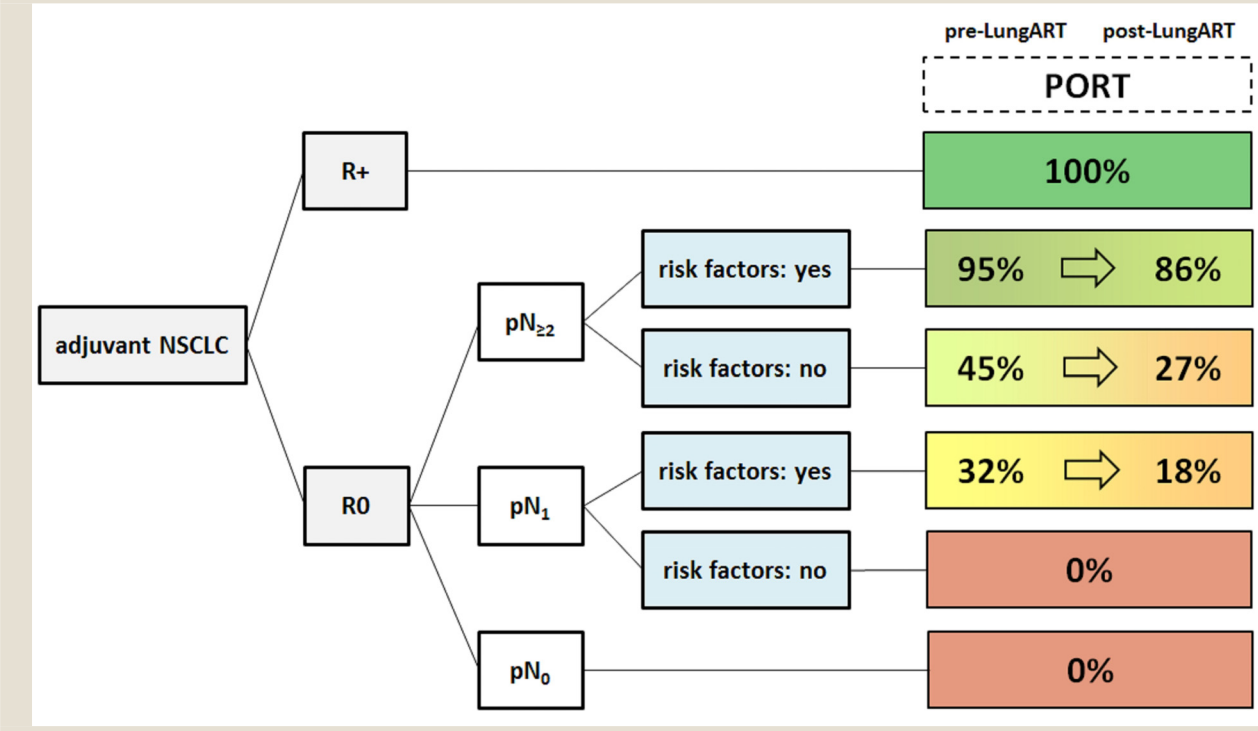

Table 2 Changes in Recommendations for PORT in Completely Resected pN2 NSCLC Patients Before and After the Presentation of the First Results of the LungART Trial

Indication for PORT in pN2 NSCLC	Pre-LungART (n = experts)	Post-LungART (n = experts)
For all patients regardless of risk factors	10	4
Only for patients with risk factors	11	14
Never recommended	1	4

tion. Nine experts (43%) offered 54 Gy, five centers preferred 50 Gy (24%), four experts recommended 56 Gy (19%) and two experts (10%) treated pN+ patients with 60 Gy with daily single doses of 2 Gy. One center generally used 24×2.42 Gy (58.1 Gy) for mediastinal nodes in stage III disease and 66 Gy in 24 fractions to the primary tumor. In three centers ENE or capsular rupture resulted in a dose escalation from 56 Gy to 60 Gy. R1 resected tumors were treated with 54-66 Gy. Most experts prescribed an RT dose of 60 Gy (11 experts) for R1 resected tumors, most of them prescribed the dose to the tumor bed and the mediastinal lymph nodes, while a few centers preferred a simultaneous integrated boost with 54 Gy to the mediastinum and a boost up to 60 Gy for the high risk (R1) region. Most experts (n = 18) preferred PORT after adjuvant chemotherapy for R1 resected tumors, two experts recommended PORT first followed by chemotherapy and two experts used concurrent radiochemotherapy for R1 resected stage III NSCLC. R2 resected NSCLC was treated analogous to primary radiotherapy of LA NSCLC with doses between 60 and 66 Gy and with (mostly concurrent) chemotherapy.

All experts preferred intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) over 3D-RT for adjuvant mediastinal radiotherapy. Fourteen experts always recommended VMAT, four preferred IMRT technique and four did not have a preference between IMRT and VMAT. One expert explicitly mentioned proton therapy as an option.

Discussion

In the current guidelines PORT is considered potentially beneficial for selected patients with proven pN2 disease, however, due to conflicting results in the literature, to the best of our knowledge, no relevant guideline recommends PORT routinely.[29,30] The aim of this work was to assess criteria in the complex process of patient

selection, especially to give insight into real life decision-making for PORT in pN+ NSCLC and how first results of the LungArt trial influenced decision-criteria among experts.

Stage III pN+ NSCLC patients are a very heterogeneous group with different clinicopathologic features including the number of N2 metastases, number of N2 stations involved, tumor size, histological type, age and sex. While the most favorable outcome is seen in patients with minimal N2 disease, bulky and/or multilevel N2 disease carries a significantly higher LR rate and worse prognosis.[20,31-33] Most of our experts considered extent of the LNs (ENE, bulky/multiple LNs, multistation/-level LNs) relevant, their consideration was even more prominent after the presentation of the LungART results.

Although the LungART data have not yet been published as a full-length paper, the study has already changed the decision-making for PORT in daily practice for some of the experts. Overall, the recommendation for PORT decreased. In particular for completely resected pN2 NSCLC without risk factors, only four experts still used PORT compared to ten before LungART presentation.

Although the LungART trial mainly included pN2 patients (98% in the control arm and 96% in the PORT arm), three experts also changed their decision-making for pN1 patients toward a more conservative strategy with less PORT.

Toxicity is an important concern related to PORT, in particular, as several studies could not demonstrate a clear benefit. In the past, many clinics used suboptimal radiation techniques and large treatment fields, which were criticized for causing locoregional toxicity. Subsequently the improvement of radiotherapy technologies such as three-dimensional conformal radiation therapy (3D-CRT), IMRT or VMAT could have potential benefits for the toxicity profile.[8,34-37] The use of protons may be another step toward reducing RT-induced toxicity.[38,39]

However, patients in the LungART were mainly treated with 3D-CRT, only 11% of the patients in the study received IMRT, which makes it difficult to draw any conclusions to more modern techniques.

Most of our experts preferred IMRT over 3D-RT for adjuvant mediastinal radiotherapy.

LA-NSCLC patients often have significant comorbidities, which possibly predispose them to cardiac and pulmonary toxicities. Especially for those patients, the potential benefit of PORT must be balanced against the higher risk of cardio-pulmonary toxicity, as was shown in the LungArt trial. These results are very relevant for daily decision-making and our analysis demonstrated that after the LungART presentation more experts mentioned cardio-pulmonary comorbidities as a relevant decision criterion.

When considering the toxicity of PORT, the total dose, fractionation and the treated volume should also be discussed. Corso et al.[18] demonstrated a significantly better 5-year-OS in completely resected NSCLC patients who received 45 to 54 Gy compared to patients without PORT, while patients who received more than 54 Gy had an equivalent survival to patients treated without PORT. Additionally, fractionation schedules with more than 2.5 to 3 Gy per fraction have been associated with a higher rate of cardiac and pulmonary morbidity and mortality.[40-42] Most of our experts recommended an RT dose between 50 and 54 Gy (a 2 Gy) for completely resected pN2 patients, most of them suggested an RT dose of 54 Gy as per the LungART trial. All centers used radiation schedules with 2 Gy fractions per day, only one expert used >2 Gy per fraction (24 × 2.42 Gy).When performing PORT the optimum sequence of RT and chemotherapy should be considered. Thus, we also asked our experts about their preferred procedure. There was a clear trend toward chemotherapy first followed by RT. This sequence is in accordance with the literature, only one expert recommended PORT first. Two recent analyses of the National Cancer Database (NCDB) registry found that for completely resected pN2 NSCLC patients (747 patients) sequential chemotherapy and PORT was associated with superior survival compared with concomitant chemoradiotherapy[43,44]. Toxicity-related factors might help explain these results.

About 1%-17% of surgical resections for NSCLC result in positive surgical margins or gross residual disease.[45] Incomplete resection is associated with increased local failures and negatively impacts survival. PORT is often recommended to improve LR and OS in patients with incompletely resected NSCLC.[45,46] Indeed, for R1/2 resected NSCLC, all experts in our analysis recommended PORT. While for R1 resections an adjuvant chemotherapy followed by RT was recommended by most of our experts, nearly all recommended concurrent radiochemotherapy for R2 resected NSCLC.

The current ESMO and NCCN guidelines support the use of PORT alone or with chemotherapy in selected patients, depending on the extent of residual disease, nodal status, and disease stage.[29,30] However, there is limited supporting evidence, the literature consists of mostly small retrospective studies collected over many years. The current guidelines do not take into account the recent results of the LungART trial, but it can be expected that future versions of guidelines will become even more hesitant to recommend PORT, especially for completely resected LA NSCLC.

The International Association for the Study of Lung Cancer (IASLC) staging committee proposed a definition of complete resection, requiring in brief: microscopically free resection margins, systematic nodal dissection or lobe-specific systematic nodal dissection, no extracapsular nodal extension and the highest mediastinal node removed negative for tumor.[47-49] Interestingly, a recent analysis of resection margins on the IASLC database was not able to determine the exact impact of ENE in the setting of R0, R1 or R (uncertain). The relevance of ENE remains unclear,[50] as is the interplay between ENE and PORT. For extracapsular node positive mediastinal lymph nodes, the resection status of the overlying extranodal tissue should be reported as per LungART protocol. If this margin is negative, resection may be considered as complete. On the contrary, if there is evidence of extracapsular extension in an isolated sampled node, this will be considered as an incomplete resection. It seems these criteria are closely considered in clinical routine, as our analysis demonstrated. The decision-making of our experts who recommended PORT in pN+ NSCLC patients relied on the IASLC definition of incomplete resection by Rami-Porta et al. The most relevant risk factors defined by the majority of experts was ENE followed by incomplete lymph node resection. In the LungART trial, patients with ENE were not included. Regardless, after ESMO 2020 the use of ENE as decision-criterion changed

for five experts. Two excluded it from their list of risk factors and three others included it.

The heterogeneous use of decision criteria among the participating experts may have multiple causes. These may include local standards, personal experience as well as the availability of different guidelines and analyses used as a basis for decision-making.

As the LungART trial excluded some high-risk factors and the radiotherapy technique was mostly based on older non-IMRT/VMAT techniques it remains unclear how to apply the results to high-risk patients when modern techniques are applied. In the most recently published randomized Chinese PORT-C trial IMRT was (with 89%) the preferred treatment technique. However, the oncological outcome, especially OS data, were comparable to the LungART trial.[51]

The clinical decision-making process is rarely a one-to-one extraction from published data, this is why we believe this work adds to the understanding of how literature is applied to clinical practice.

In summary, after the presentation of LungART trial results at ESMO 2020, PORT is still used for stage III pN2 NSCLC patients with risk factors by 82% of the participating European thoracic radiation oncology experts. The recommendation rate for PORT in completely resected pN2 patients without risk factors decreased from 45% to 18%. All of our lung cancer experts recommended PORT after R1/2 resection. Cardiopulmonary comorbidities became more relevant in decision-making for PORT.

The full publication and subgroup analysis of the LungART trial will hopefully shed additional light on the dilemma of the decision-making process for PORT in completely resected pN+ patients and identify appropriate patients who might benefit from PORT.

Clinical Practice Points

- The role of PORT in stage III N2 NSCLC patients remains controversial.
- The ESMO and NCCN guidelines support the use of PORT alone or with chemotherapy in selected patients, depending on the extent of residual disease, nodal status and disease stage.
- PORT is still widely used among European thoracic radiation oncology experts with a clear decrease in its use for patients with completely resected pN+ NSCLC after the presentation of LungART trial results at ESMO 2020.
- PORT is recommended after R+ resection.
- Toxicity is an important concern related to PORT. LA-NSCLC patients often have significant comorbidities. Especially for those patients the potential benefit of PORT must be put into balance with the higher risk of cardiopulmonary toxicity. These results are very relevant for daily decision-making and our analysis showed that after the LungART presentation more experts mentioned cardio-pulmonary comorbidities as relevant decision criterion.

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