**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 67114

**Manuscript Type:** EVIDENCE REVIEW

**Postoperative radiotherapy in resected non-small cell lung cancer: The never-ending story**

Serrano J *et al*. PORT in NSCLC

Javier Serrano, Patricia Calvo Crespo, Begoña Taboada, Ana Alvarez Gonzalez, Rafael Garcia García, Antonio Gomez Caamaño, Juan Carlos Trujillo Reyes, Xabi Mielgo Rubio, Felipe Couñago

**Javier Serrano,** Department of Radiation Therapy, Clinica Universidad de Navarra, Madrid 28027, Spain

**Patricia Calvo Crespo, Begoña Taboada,** Department of Radiation Oncology, Hospital Clínico Universitario Santiago de Compostela, Santiago de Compostela 15706, Spain

**Ana Alvarez Gonzalez,** Department of Radiation Oncology, HGU Gregorio Marañón, Madrid 28007, Spain

**Rafael Garcia García,** Department of Radiation Oncology, Hospital Ruber Internacional, Madrid 28034, Spain

**Antonio Gomez Caamaño,** Department of Radiation Oncology, Hospital Clínico Universitario Santiago de Compostela, A Coruña 15706, Spain

**Juan Carlos Trujillo Reyes,** Department of Thoracic Surgery, Hospital de La Santa Creu I Sant Pau, Barcelona 08026, Spain

**Xabi Mielgo Rubio,** Department of Medical Oncology, Hospital Universitario Fundación Alcorcón, Madrid 28922, Spain

**Felipe Couñago,** Department of Radiation Oncology, Hospital Universitario Quirónsalud Madrid, Hospital La Luz, Universidad Europea de Madrid, Madrid 28223, Spain

**Author contributions:** All authors have contributed equally; all authors have read and approved the final manuscript.

**Corresponding author: Javier Serrano, PhD, Consultant Physician-Scientist,** Department of Radiation Therapy, Clinica Universidad de Navarra, Calle Marquesado de Santa Marta 1., Madrid 28027, Spain. fserranoa@unav.es

**Received:** April 15, 2021

**Revised:** June 20, 2021

**Accepted:** September 14, 2021

**Published online:**

**Abstract**

This manuscript collects in a joint and orderly manner the existing evidence at the present time about postoperative treatment with radiotherapy in non-small cell lung cancer. It also systematically reviews the current evidence, the international recommendations in the most relevant guidelines, the most controversial aspects in clinical and pathological staging, the specific technical aspects of radiotherapy treatment, and also collects all the potential risk factors that have been postulated as significant in the prognosis of these patients, evaluating the possibility of segmenting a particularly sensitive subpopulation with a high risk of relapse on which an adjuvant treatment with radiotherapy could have an impact on their clinical evolution. Finally, currently active trials that aspire to provide more evidence on this topic are reviewed.

**Key Words:** Non-small lung cancer; Radiotherapy; Postoperative; Lung cancer

Serrano J, Crespo PC, Taboada B, Gonzalez AA, García RG, Caamaño AG, Reyes JCT, Rubio XM, Couñago F. Postoperative radiotherapy in resected non-small cell lung cancer: the never-ending story. *World J Clin Oncol* 2021; In press

**Core Tip:** The approach to the postoperative treatment of non-small cell lung cancer (NSCLC) is one of the pending subjects of the specialty of Radiation Oncology. Despite the enormous anticipation that the Lung-Art trial had produced, its results leave issues unresolved. In this article, we attempt to systematically recapitulate the currently existing evidence for the radiotherapeutic management of this pathology, in order to identify those patients who could potentially benefit more from postoperative treatment in NSCLC.

**INTRODUCTION**

***Historical evolution of postoperative radiotherapy***

One of the great historical controversies in the field of thoracic oncology is the use of Postoperative radiotherapy (PORT) in patients with non-small cell lung cancer (NSCLC). The rationale for this therapeutic strategy is the high risk of locoregional recurrence (LRR) after radical surgery, especially in patients with pN2 disease, who account for up to 30% of patients. The development of LRR in patients with NSCLC has important clinical implications and is associated with worse survival outcomes[1]. Several different pathological variables have been associated with a higher risk of developing LRR, including tumour size > 3 cm, lymphovascular invasion, visceral pleural invasion, and involvement of multiple lymph nodes[2].

The role of PORT in NSCLC remains controversial, mainly because studies carried out over the last few decades have reported conflicting safety and efficacy results. Although multiple retrospective and prospective studies have been performed, we still lack high-quality evidence to confirm or definitively rule out PORT in these patients. A meta-analysis published in 1998 found that PORT was associated with lower overall survival (OS) rates in patients with stage I-II disease, with 2-year OS rates of 43% in the non-PORT group *vs* 30% in the patients that received PORT, although there was no clear evidence that PORT negatively influenced outcomes in patients with stage III pN2 disease[3]. In older studies, the poor outcomes of PORT could be due to the high levels of morbidity and mortality associated with obsolete radiotherapy techniques or inappropriate doses, fractionations, and/or irradiation volumes. In fact, a more recent meta-analysis demonstrated that PORT improves OS outcomes when modern technology (linear accelerators vs. cobalt therapy units) is used to deliver the radiation dose[4].

Despite the contradictory findings described above, several studies have reported a clear benefit for PORT in patients with involved lymph nodes (pN2) in terms of improved local control and even OS[5-7].  Among those studies with positive findings, the most important is the study carried out by Mikell *et al*[7], who evaluated 2115 patients with pN2 NSCLC based on data retrieved from the National Cancer Database (NCBD). In that study, PORT was associated with a significant increase in OS (42 mo *vs* 38 mo, *P* = 0.048) in patients treated according to the therapeutic standards of the modern era [three-dimensional conformal radiotherapy (3D-CRT), adjuvant chemotherapy (ChT), *etc.*][7].

The long-awaited preliminary results of the Lung ART trial (NCT00410683)[8], which included patients with NSCLC who underwent complete resection with adjuvant ChT, were recently presented at the ESMO 2020 meeting. Lung ART is a multi-institutional randomized phase III trial which included stage III N2 NSCLC cases comparing mediastinal PORT (54 Gy/27-30 fractions) to no PORT in very selected patients: PS 0-2, complete resection with optimal nodal exploration and proven N2 disease. The main endpoint was disease-free survival (DFS). Between August 2007 and July 2018, 501 patients were randomized after surgery or after ChT: 252 patients allocated to PORT, and 249 to no PORT. With a median FU of 4.8 years DFS HR was 0.85 (95%CI [0.67-1.07]); median DFS was 30.5 mo with PORT and 22.8 without PORT; 3-year DFS was 47.1% with PORT *vs* 43.8% without PORT (*p* = ns), and finally, 3-year OS was 66.5% with PORT *vs* 68.5% without PORT (*p* = ns). Early and late Gr 3-5 cardio-pulmonary toxicity was respectively 7% and 20% in PORT arm *vs* 3.2% and 7.7% in control arm. Nonetheless, PORT significantly decreased LRR in the mediastinum (46.1% *vs* 25% with and without PORT, respectively), a finding that suggests that PORT could offer a clinical benefit in a well-selected subgroup of patients.

However, these preliminary results raised further doubts about the role of PORT in NSCLC. The findings of this landmark trial are extremely important and may come to redefine the role of radiotherapy in NSCLC.

According to these data, PORT should not be routinely recommended to all resected stage III N2 NSCLC patients. The decision to prescribe o not PORT must be individualised according to the patient’s specific characteristics. In general, PORT should be indicated only in highly selected patients with good performance status (PS 0-1), significant mediastinal lymph node involvement (pN2, extracapsular extension), and/or residual disease (R1-R2) after surgery. In addition, PORT must be only performed in cases with a favourable dose distribution that fulfils the dose restriction criteria for the organs of risk (OARs), especially cardiopulmonary restrictions.

**Current evidence and recommendations for PORT**

The role of PORT in the treatment of NSCLC remains controversial. Although this therapeutic strategy has been evaluated in numerous retrospective and prospective studies, robust evidence to definitively support the value of PORT is still lacking, as can be seen in the lack of consensus among the clinical guidelines published by the main international scientific societies[9-13].

Currently, the most widely accepted indication for PORT, with the most evidence, is for the treatment of residual disease (including extracapsular extension) after radical surgery. Most international guidelines recommend PORT in patients with involved surgical margins (R1-R2) at the surgical bed due to the high risk of ​​recurrence in this region, with a recommended dose ranging from 54-60 Gy (1.8-2 Gy/fraction)[14].

By contrast, in patients with stage pN2 disease, the current evidence suggests that the treatment decision should be assessed on a case-by-case basis by a multidisciplinary team to determine if the patient would be likely to benefit from PORT. The treatment decision should consider several key clinical characteristics, including the number of mediastinal nodal stations involved (≥ 1), the patient’s general physical condition (PS 0-1), and cardiopulmonary function. Table 1 summarizes the recommendations proposed by the main international guidelines.

**Management of cases with involved surgical margins**

The rate of incomplete resections (microscopic or macroscopic; R1-R2) after radical surgery for lung cancer ranges from 1%-17%[15]. In these cases, the aim of PORT is to reduce the risk of local recurrence and improve OS. Although various clinical guidelines recommend salvage surgery in patients with positive surgical margins, this approach is not supported by robust data. Ghiribelli *et al*[16] evaluated OS in a series of patients with incomplete resections (R1), finding that survival was not correlated with the type of infiltration, nodal involvement, or histological type. As a result, in patients with microscopic residual tumours, the authors recommended salvage surgery only in patients with early stage (I-II) disease; by contrast, the recommended treatment in stage III pN2 disease is adjuvant radiotherapy.

A study published in 2012 evaluated the efficacy and toxicity of PORT according to histological subtype in patients (*n* = 41) with incompletely resected NSCLC[17]. Of the 41 patients, 23 had microscopic (R1) and 18 macroscopic (R2) residual disease. The histologic distribution was as follows: squamous cell carcinoma (SCC) (*n* = 23), adenocarcinoma (14), and other histologies (4). The predominant progression pattern was distant disease, observed in 13% of patients with SCC and 64% of those with adenocarcinoma (*p* < 0.01). Survival rates at 5-years were as follows: OS, 56%; local control (LC), 63%; DFS, 37%; and metastasis-free survival (MFS), 49%. On the multivariate analysis, the only significant predictors of better survival (DFS and MFS) were SCC histology, stage N0-1, and R1 surgical margins. The authors concluded that, in patients with R1 margins, PORT provides good LC without severe toxicity, but systemic therapy should always be considered due to the high risk of distant metastasis.

Hancock *et al*[18] evaluated 3102 surgically treated NSCLC patients included in the NCDB registry. Of these, 1688 had microscopically positive margins (R1). The authors compared patients according to margin status (R1 *vs* R0), with significantly lower 5-year OS rates in the R1 group for all stages: stage I, 37% *vs* 62% (*p* <0.0001); stage II, 29% *vs* 41% (*p* < 0.0001); and stage III, 19% *vs* 33% (*p* < 0.0001). Administration of adjuvant ChT with PORT in the R1 group was associated with better OS than surgery alone, regardless of stage (stage I, 44% *vs* 35%, *P* = 0.05; stage II, 33% *vs* 21%, *P* = 0.0013; stage III, 30% *vs* 12%, *p* < 0.0001).

In a study published in 2015, Wang *et al*[19] evaluated 3395 patients with incompletely resected stage II-III NSCLC to determine the influence of PORT on survival outcomes, finding that PORT was associated with significantly better 5-year OS (32.4% *vs* 23.7%). Radiation doses between 50-70 Gy improved survival rates in the PORT group *vs* the non-PORT group. However, when higher doses (> 70 Gy) were administered, there were no between-group differences in OS. The authors of that study concluded that PORT improves OS in patients with incompletely resected stage II-III NSCLC and should therefore be considered as an adjuvant treatment. They also suggested that the radiation dose in patients with macroscopic residual disease (R2) should be the same as those used for radical radiotherapy (60-66 Gy).

**Mediastinal staging**

***Preoperative mediastinal staging***

The appropriate management of NSCLC depends on accurate mediastinal staging. Contrast-enhanced chest computed tomography (CT) is currently the diagnostic test of choice for preoperative mediastinal staging. On CT imaging, nodes with a short-axis diameter ≥ 1 cm are considered pathological[20]. In recent years, 18F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)-CT has transformed lung cancer staging due to its greater sensitivity. However, PET-CT has some limitations in cases with small nodes (< 1 cm) and in certain histologies in which FDG uptake is limited. PET-CT also has a high false positive rate (20%-25%) in the presence of intercurrent infections and inflammatory processes. Consequently, histopathologic confirmation of mediastinal node involvement is usually required, especially when the therapeutic approach depends directly on the results of this assessment[21-23]. Histological confirmation can be omitted in certain patients with small (≤ 3 cm) peripheral tumours without radiological evidence of suspected mediastinal involvement.

Mediastinal nodes can be obtained endoscopically through endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS) guided puncture, or surgically, through mediastinoscopy or video-assisted thoracoscopy (VATS). Endobronchial ultrasound (EBUS/EUS) is usually the first step in evaluating suspected mediastinal node involvement[24,25]. These minimally invasive endoscopic techniques are usually preferred to surgical approaches due to their good sensitivity and specificity profile and relatively low risk of morbidity. If the sample is negative, not assessable, or insufficient (despite radiological suspicion), staging should be completed with invasive techniques, which have a higher negative predictive value (NPV). For many years, conventional mediastinoscopy was the main surgical staging technique, despite the technical limitations of this procedure for the study of the posterior and inferior mediastinum, in which either extended cervical mediastinoscopy or VATS is necessary[26].

***Mediastinal restaging after neoadjuvant therapy***

Mediastinal restaging after neoadjuvant therapy (ChT or ChT+RT) is controversial. Some patients with stage IIIA, low volume N2 disease are classified as potentially resectable and may benefit from neoadjuvant therapy, which could increase the likelihood of achieving a complete response (CR) in the mediastinum, thus permitting surgical resection of the tumour[27]. In this clinical scenario, however, the value of CT for mediastinal restaging is questionable since CT-based assessment, although highly predictive of pathologic CR, tends to underestimate the true CR rate.

PET-CT is an excellent tool to assess the response of both the primary tumour and metastatic lesions, but it is less reliable in evaluating mediastinal involvement due to high rates of false negative and false positives (20% and 25%, respectively)[28,29]. Therefore, histopathologic confirmation is necessary in cases with radiological response if surgical resection is being considered.

EBUS/EUS restaging after neoadjuvant therapy has a low sensitivity and a low NPV. If the test is negative, the surgical technique should be escalated to reduce the false negative rate[30]. Restaging *via* mediastinoscopy has a high sensitivity (> 60%), specificity (≈100%), positive predictive value (PPV; 100%) and NPV (> 73%); however, this procedure is not routinely performed due to its technical complexity in this clinical context. Rather, the recommended strategy is initial confirmation of stage N2 disease by EBUS or EUS-guided transbronchial aspiration during the initial workup, thus reserving mediastinoscopy for restaging[31].

**Selection of candidates for PORT**

Numerous studies have explored a wide range of prognostic factors potentially associated with an increased risk of LRR in order to identify high-risk patients suitable for adjuvant radiotherapy. In patients with NSCLC, the histological type is not currently considered a prognostic factor for adjuvant treatment due to the poor quality of the available data and contradictory findings in the literature. While some studies have found that SCC histology is associated with worse OS rates than adenocarcinoma[32,33], findings from other studies point in the opposite direction[34].

The findings of a recent meta-analysis involving 25780 patients from 13 studies (most retrospective) underscored the prognostic value of multiple mediastinal node involvement. That study showed that, in patients with pN2 disease with ≥ one positive node and/or multiple N2 station involvement, PORT significantly improved both DFS (HR 0.57, 95% confidence interval [CI], 0.38–0.85) and OS (HR 0.85, 95%CI, 0.79–0.92)[35].

The lymph node ratio (LNR)—defined as the number of involved nodes divided by the total removed or examined—has also been significantly associated with survival outcomes. A recent study evaluated 11,341 patients with NSCLC and postoperative nodal involvement included the SEER (Surveillance, Epidemiology, and End Results Database) registry. The authors established three risk categories according to the LNR (LNR1 ≤ 0.28, LNR2 <0.81, and LNR3 > 0.81), finding that LNR3 was an independent prognostic factor for cancer-specific survival (CSS) (HR 2.54; 95%CI, 2.30–2.80; *p* < 0.001)[36].

Other parameters, such as the positive and negative lymph node counts (PLN and NLN, respectively), have been developed to quantify the tumour load in mediastinal nodes. Zhou *et al*[37] reviewed data from 39959 surgically-treated cases of NSCLC, demonstrating a significant association between mediastinal tumour burden and OS (PLN > 5; HR 2.0128, 95%CI: 1.6996–2.3836; NLN> 5; HR 0.7493, 95%CI: 0.7211–0.7785; LNR > 0.30; HR 1.7949, 95%CI: 1.5329–2.1016); and with CSS (PLN > 5; HR 2.2147, 95%CI: 1.8095–2.7106; NLN > 5; HR 0.7214, 95%CI: 0.6869–0.7575; LNR > 0.30; HR 1.9627, 95%CI: 1.6219–2.3752). In this same line of research, another study evaluated 5168 patients with stage IIIA-N2 NSCLC, finding that patients with PLN > 5 who underwent PORT had significantly better OS outcomes (HR 0.637, 95%CI: 0.518–0.784), a benefit that persisted even when compared to adjuvant ChT alone (HR 0.726, 95%CI: 0.564–0.934)[38].

The studies that have generated the most interest are those that have sought to stratify risk groups according to multiple clinical, pathologic, and molecular parameters. In this regard, the study by Deng and colleagues[39] is worth highlighting. Those authors evaluated numerous characteristics — age, sex, surgical technique, histological type, degree of differentiation, tumour size, number of nodes evaluated (LNR index) — in a large sample (*n* = 2329) of patients included in the SEER database. Based on that analysis, the authors proposed a prognostic scoring model that classified patients into two risk categories (high and low), which was a significant predictor of survival outcomes (OS and CSS)[40].

Jiang *et al*[40] recently developed a model that incorporated several molecular biomarkers, together with other well-known clinical variables, to predict clinical outcomes in patients with stage IIIA pN2 NSCLC. In that study, the following variables were significantly associated with the risk of LRR: epidermal growth factor receptor (EGFR) status: wild-type *vs* native (HR 3.666, 95%CI: 1.724-7.797); lymphocyte to monocyte ratio (LMR) < 4.69 (HR 2.364, 95%CI: 1.221-4.574); surgical procedure (VATS *vs* thoracotomy) (HR 0.348, 95%CI: 0.175 -0.693); and pN2 LNR ≥ 38.9% (HR 3.597, 95%CI: 1.832-7.062). The authors then used those data to develop a predictive model (Table 2) based on the four independent risk factors to determine the individual risk of LRR in each patient. This score, in turn, could be used to recommend or not adjuvant radiotherapy[41].

**Technical recommendations for the treatment of PORT**

***Simulation***

The generally accepted recommendations provided by clinical guidelines for the management of NSCLC should be followed for positioning, immobilization, and treatment simulation. Systems designed to improve immobilization and control respiratory motion (4D-CT) should be used, preferably with image-guided radiotherapy (IGRT), to obtain smaller treatment volumes and more precise radiotherapy to achieve a better dosimetric distribution.

In general, CT imaging (slice thickness, 2-3 mm) should be performed with intravenous contrast to improve contouring of the nodal areas[42,43]. The use of 5FDG-PET-CT for postoperative simulation is not recommended due to the lack of robust data; moreover, interpretation of these images in the immediate postoperative period can be challenging due to the inflammation, which can lead to false positives. Image interpretation after ChT is also difficult and it is easy to underestimate the residual disease (false negatives)[44].

***Target volumes***

The most important data for target volume definition were described in the Lung-ART clinical trial and based on contouring performed by 17 experienced thoracic radiation oncologists in two representative cases[45]. The clinical target volume (CTV) should include the bronchial stump, ipsilateral hilum, adjacent mediastinal pleura, and involved nodes (according to the pathology report). The involved nodal station and those immediately superior and inferior to that region should also be contoured, being careful to avoid oversizing the CTV. To generate the PTV (planning target volume), a margin of at least 0.5 cm in the mediolateral and dorsoventral directions (1 cm in the craniocaudal direction) should be applied to the CTV to minimize uncertainties related to tumour motion and patient positioning[46].

The definition of critical organs (OARs)[47] and dose restrictions are the same as in NSCLC, although with more restrictive lung criteria. In post-lobectomy patients, Boonyawan *et al*[47], proposed limiting the lung volume that receives 10 and 20 Gy (V10 and V20) to < 30% and < 20%, respectively[48]. In patients older than age 65, the lung V5 should be reduced to ≤ 36%[49]; if IMRT is performed, the recommended V5 is < 64.9%, with mean lung dose (MLD) < 10.8 Gy[50]. In patients undergoing pneumonectomy, to ensure safety, these limitations should be even more restrictive, as follows: V5 < 30%, V20 < 13%, and MLD < 7.5 Gy[51]. If 3D-CRT is used, the V20 should be < 10%[52].

***Dose and fractionation***

In completed-resected (R0) surgeries, the recommended dose is 50-54 Gy using a conventional fractionation scheme (1.8-2 Gy/d)[53]. However, in high risk patients with R1 or R2 margins, the total dose may be increased up to 54-60 Gy, or even up to radical doses of 60-66 Gy if there is evidence of macroscopic residue in the surgical bed or mediastinal region.

The use of hypofractionated regimens is not advised due to the risk of increased toxicity. Currently, accelerated fractionation radiotherapy schemes (2 Gy/d, 7 d/wk) are being explored (NCT02189967)[54].

In terms of treatment sequencing, PORT should be administered after completing ChT if the surgical resection is complete (R0); however, in patients with postoperative R1-R2 margins, there is some controversy surrounding the use of concomitant or sequential RT and ChT. As a result, the treatment sequence should be individualized based on the expected tolerance[55,56].

Although several radiotherapy techniques — 3D-CRT, intensity modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and tomotherapy — all provide optimal dosimetric results in the postoperative context[57], data from prospective studies support the routine use of the IMRT in NSCLC due to lower cardiac doses and a lower risk of severe pneumonitis.

**Future lines of research in PORT**

At present, there is broad consensus among radiation oncologists that the current level of evidence is insufficient to recommend PORT for all patients with stage III pN2 NSCLC, which is mainly attributable to the heterogeneous characteristics of patients with pN2 disease and treatment-related cardiopulmonary toxicity, which remains high despite efforts to reduce it.

In terms of the lack of homogeneity, it is evident that TNM staging in patients with pN2 NSCLC does not provide sufficient information to indicate or not adjuvant therapy. Consequently, it is essential to explore and evaluate new clinical, pathological, and molecular factors to better differentiate between different risk subpopulations, which would then allow us to tailor the treatment indication based on the patient’s unique characteristics.

It is important to note that most of the prognostic factors identified to date have been derived from data obtained in large retrospective series or epidemiological records. Clearly, due to the important methodological limitations of those studies, it is difficult to extrapolate the findings of those studies into routine clinical practice without stronger supporting data. In this regard, new studies with more robust methodological designs are needed to obtain a higher level of evidence. Table 3 lists the main trials currently underway to evaluate PORT in NSCLC.

The studies performed to date have consistently found an association between PORT and a higher risk of cardiopulmonary morbidity and mortality, a finding that undermines the clinical benefits of this treatment. However, some studies have shown that IMRT is superior to 3D-CRT in NSCLC in terms of dosimetry and survival outcomes[58]. Heavy particle therapy seems to show certain dosimetric advantages *vs* IMRT in terms of protection of OARs, and could significantly reduce cardiopulmonary toxicity, although prospective studies confirming this clinical benefit are not yet available[59].

For all the reasons described above, it is evident that only advanced radiotherapy techniques, such as VMAT or IMRT, which allow for better dose conformity, should be used for the treatment of NSCLC. In addition, these techniques should be used in all future clinical trials of PORT to better determine the true value of PORT in patients with NSCLC.

**CONCLUSION**

In patients with stage pN2 disease, current evidence suggests that the treatment decision should be evaluated on a case-by-case basis by a multidisciplinary team to determine whether the patient is likely to benefit from PORT. The treatment decision should consider several key clinical features, such as the volume of nodal mediastinal tumor burden, physical condition (performance status) and individual cardiopulmonary risk, but another technological issues, like availability to modern functional imaging devices or high dosimetric conformation radiotherapy (IGRT or VMAT), may be critical for a correct indication.

**REFERENCES**

1 **Péchoux CL**, Mercier O, Belemsagha D, Bouaita R, Besse B, Fadel E. Role of adjuvant radiotherapy in completely resected non-small-cell lung cancer. *EJC Suppl* 2013; **11**: 123-130 [PMID: 26217121 DOI: 10.1016/j.ejcsup.2013.07.022]

2 **Lopez Guerra JL**, Gomez DR, Lin SH, Levy LB, Zhuang Y, Komaki R, Jaen J, Vaporciyan AA, Swisher SG, Cox JD, Liao Z, Rice DC. Risk factors for local and regional recurrence in patients with resected N0-N1 non-small-cell lung cancer, with implications for patient selection for adjuvant radiation therapy. *Ann Oncol* 2013; **24**: 67-74 [PMID: 23002278 DOI: 10.1093/annonc/mds274]

3 . Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. *Lancet* 1998; **352**: 257-263 [PMID: 9690404]

4 **Billiet C**, Decaluwé H, Peeters S, Vansteenkiste J, Dooms C, Haustermans K, De Leyn P, De Ruysscher D. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. *Radiother Oncol* 2014; **110**: 3-8 [PMID: 24100149 DOI: 10.1016/j.radonc.2013.08.011]

5 **Feng QF**, Wang M, Wang LJ, Yang ZY, Zhang YG, Zhang DW, Yin WB. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. *Int J Radiat Oncol Biol Phys* 2000; **47**: 925-929 [PMID: 10863061 DOI: 10.1016/s0360-3016(00)00509-5]

6 **Lally BE**, Zelterman D, Colasanto JM, Haffty BG, Detterbeck FC, Wilson LD. 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 [PMID: 16769986 DOI: 10.1200/JCO.2005.04.6110]

7 **Mikell JL**, Gillespie TW, Hall WA, Nickleach DC, Liu Y, Lipscomb J, Ramalingam SS, Rajpara RS, Force SD, Fernandez FG, Owonikoko TK, Pillai RN, Khuri FR, Curran WJ, Higgins KA. Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. *J Thorac Oncol* 2015; **10**: 462-471 [PMID: 25384064 DOI: 10.1097/JTO.0000000000000411]

8 Abstract LBA3\_PR ‘An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small cell lung cancer (NSCLC) and mediastinal N2 involvement. Primary end-point analysis of Lung ART (IFCT-0503, UK NCRI, SAKK) NCT00410683 ’ will be presented by Cécile Le Pechoux during the Presidential Symposium II, on Sunday. 2020; **18**: 25

9 **Ettinger DS**, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, Dilling TJ, Dowell J, Gettinger S, Gubens MA, Hegde A, Hennon M, Lackner RP, Lanuti M, Leal TA, Lin J, Loo BW Jr, Lovly CM, Martins RG, Massarelli E, Morgensztern D, Ng T, Otterson GA, Patel SP, Riely GJ, Schild SE, Shapiro TA, Singh AP, Stevenson J, Tam A, Yanagawa J, Yang SC, Gregory KM, Hughes M. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 2.2021. *J Natl Compr Canc Netw* 2021; **19**: 254-266 [PMID: 33668021 DOI: 10.6004/jnccn.2021.0013]

10 **Rodrigues G**, Choy H, Bradley J, Rosenzweig KE, Bogart J, Curran WJ Jr, Gore E, Langer C, Louie AV, Lutz S, Machtay M, Puri V, Werner-Wasik M, Videtic GMM. Adjuvant radiation therapy in locally advanced non-small cell lung cancer: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline. *Pract Radiat Oncol* 2015; **5**: 149-155 [PMID: 25957185 DOI: 10.1016/j.prro.2015.02.013]

11 **Guckenberger M**, Belka C, Bezjak A, Bradley J, Daly ME, DeRuysscher D, Dziadziuszko R, Faivre-Finn C, Flentje M, Gore E, Higgins KA, Iyengar P, Kavanagh BD, Kumar S, Le Pechoux C, Lievens Y, Lindberg K, McDonald F, Ramella S, Rengan R, Ricardi U, Rimner A, Rodrigues GB, Schild SE, Senan S, Simone CB 2nd, Slotman BJ, Stuschke M, Videtic G, Widder J, Yom SS, Palma D. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An ESTRO-ASTRO consensus statement. *Radiother Oncol* 2020; **146**: 223-229 [PMID: 32342863 DOI: 10.1016/j.radonc.2020.04.001]

12 **Postmus PE**, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, Escriu C, Peters S; ESMO Guidelines Committee. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28**: iv1-iv21 [PMID: 28881918 DOI: 10.1093/annonc/mdx222]

13 **Kris MG**, Gaspar LE, Chaft JE, Kennedy EB, Azzoli CG, Ellis PM, Lin SH, Pass HI, Seth R, Shepherd FA, Spigel DR, Strawn JR, Ung YC, Weyant M. Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. *J Clin Oncol* 2017; **35**: 2960-2974 [PMID: 28437162 DOI: 10.1200/JCO.2017.72.4401]

14 **Robinson CG**, Patel AP, Bradley JD, DeWees T, Waqar SN, Morgensztern D, Baggstrom MQ, Govindan R, Bell JM, Guthrie TJ, Colditz GA, Crabtree TD, Kreisel D, Krupnick AS, Patterson GA, Meyers BF, Puri V. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base. *J Clin Oncol* 2015; **33**: 870-876 [PMID: 25667283 DOI: 10.1200/JCO.2014.58.5380]

15 **Wind J**, Smit EJ, Senan S, Eerenberg JP. Residual disease at the bronchial stump after curative resection for lung cancer. *Eur J Cardiothorac Surg* 2007; **32**: 29-34 [PMID: 17466532 DOI: 10.1016/j.ejcts.2007.04.003]

16 **Ghiribelli C**, Voltolini L, Paladini P, Luzzi L, Di Bisceglie M, Gotti G. Treatment and survival after lung resection for non-small cell lung cancer in patients with microscopic residual disease at the bronchial stump. *Eur J Cardiothorac Surg* 1999; **16**: 555-559 [PMID: 10609907 DOI: 10.1016/s1010-7940(99)00310-3]

17 **Ohguri T**, Yahara K, Moon SD, Yamaguchi S, Imada H, Hanagiri T, Tanaka F, Terashima H, Korogi Y. Postoperative radiotherapy for incompletely resected non-small cell lung cancer: clinical outcomes and prognostic value of the histological subtype. *J Radiat Res* 2012; **53**: 319-325 [PMID: 22327172 DOI: 10.1269/jrr.11082]

18 **Hancock JG**, Rosen JE, Antonicelli A, Moreno A, Kim AW, Detterbeck FC, Boffa DJ. Impact of adjuvant treatment for microscopic residual disease after non-small cell lung cancer surgery. *Ann Thorac Surg* 2015; **99**: 406-413 [PMID: 25528723 DOI: 10.1016/j.athoracsur.2014.09.033]

19 **Wang EH**, Corso CD, Rutter CE, Park HS, Chen AB, Kim AW, Wilson LD, Decker RH, Yu JB. Postoperative Radiation Therapy Is Associated With Improved Overall Survival in Incompletely Resected Stage II and III Non-Small-Cell Lung Cancer. *J Clin Oncol* 2015; **33**: 2727-2734 [PMID: 26101240 DOI: 10.1200/JCO.2015.61.1517]

20 **Gelberg J**, Grondin S, Tremblay A. Mediastinal staging for lung cancer. *Can Respir J* 2014; **21**: 159-161 [PMID: 24914606 DOI: 10.1155/2014/890108]

21 **Gould MK**, Kuschner WG, Rydzak CE, Maclean CC, Demas AN, Shigemitsu H, Chan JK, Owens DK. Test performance of positron emission tomography and computed tomography for mediastinal staging in patients with non-small-cell lung cancer: a meta-analysis. *Ann Intern Med* 2003; **139**: 879-892 [PMID: 14644890 DOI: 10.7326/0003-4819-139-11-200311180-00013]

22 **Zhao L**, He ZY, Zhong XN, Cui ML. (18)FDG-PET/CT for detection of mediastinal nodal metastasis in non-small cell lung cancer: a meta-analysis. *Surg Oncol* 2012; **21**: 230-236 [PMID: 22197027 DOI: 10.1016/j.suronc.2011.11.001]

23 **Lv YL**, Yuan DM, Wang K, Miao XH, Qian Q, Wei SZ, Zhu XX, Song Y. Diagnostic performance of integrated positron emission tomography/computed tomography for mediastinal lymph node staging in non-small cell lung cancer: a bivariate systematic review and meta-analysis. *J Thorac Oncol* 2011; **6**: 1350-1358 [PMID: 21642874 DOI: 10.1097/JTO.0b013e31821d4384]

24 **Stigt JA**, Boers JE, Boomsma MF. Ultrasound-Guided Tissue Core Biopsies in Supraclavicular Lymph Nodes in Patients with Suspected Thoracic Malignancies. *Respiration* 2015; **90**: 412-415 [PMID: 26484528 DOI: 10.1159/000441301]

25 **Vilmann P**, Clementsen PF, Colella S, Siemsen M, De Leyn P, Dumonceau JM, Herth FJ, Larghi A, Vazquez-Sequeiros E, Hassan C, Crombag L, Korevaar DA, Konge L, Annema JT. Combined endobronchial and oesophageal endosonography for the diagnosis and staging of lung cancer. European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). *Eur Respir J* 2015; **46**: 40-60 [PMID: 26034128 DOI: 10.1183/09031936.00064515]

26 **Hammoud ZT**, Anderson RC, Meyers BF, Guthrie TJ, Roper CL, Cooper JD, Patterson GA. The current role of mediastinoscopy in the evaluation of thoracic disease. *J Thorac Cardiovasc Surg* 1999; **118**: 894-899 [PMID: 10534695 DOI: 10.1016/s0022-5223(99)70059-0]

27 **Milleron B**, Westeel V, Quoix E, Moro-Sibilot D, Braun D, Lebeau B, Depierre A; French Thoracic Cooperative Group. Complete response following preoperative chemotherapy for resectable non-small cell lung cancer: accuracy of clinical assessment using the French trial database. *Chest* 2005; **128**: 1442-1447 [PMID: 16162741 DOI: 10.1378/chest.128.3.1442]

28 **Cerfolio RJ**, Bryant AS. When is it best to repeat a 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography scan on patients with non-small cell lung cancer who have received neoadjuvant chemoradiotherapy? *Ann Thorac Surg* 2007; **84**: 1092-1097 [PMID: 17888953 DOI: 10.1016/j.athoracsur.2007.05.050]

29 **Eschmann SM**, Friedel G, Paulsen F, Reimold M, Hehr T, Budach W, Langen HJ, Bares R. 18F-FDG PET for assessment of therapy response and preoperative re-evaluation after neoadjuvant radio-chemotherapy in stage III non-small cell lung cancer. *Eur J Nucl Med Mol Imaging* 2007; **34**: 463-471 [PMID: 17103167 DOI: 10.1007/s00259-006-0273-5]

30 **Zielinski M**, Szlubowski A, Kołodziej M, Orzechowski S, Laczynska E, Pankowski J, Jakubiak M, Obrochta A. Comparison of endobronchial ultrasound and/or endoesophageal ultrasound with transcervical extended mediastinal lymphadenectomy for staging and restaging of non-small-cell lung cancer. *J Thorac Oncol* 2013; **8**: 630-636 [PMID: 23584295 DOI: 10.1097/JTO.0b013e318287c0ce]

31 **Rami-Porta R**, Call S. Invasive staging of mediastinal lymph nodes: mediastinoscopy and remediastinoscopy. *Thorac Surg Clin* 2012; **22**: 177-189 [PMID: 22520285 DOI: 10.1016/j.thorsurg.2011.12.003]

32 **Wang BY**, Huang JY, Chen HC, Lin CH, Lin SH, Hung WH, Cheng YF. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. *J Cancer Res Clin Oncol* 2020; **146**: 43-52 [PMID: 31705294 DOI: 10.1007/s00432-019-03079-8]

33 **Nakamura H**, Sakai H, Kimura H, Miyazawa T, Marushima H, Saji H. Difference in Postsurgical Prognostic Factors between Lung Adenocarcinoma and Squamous Cell Carcinoma. *Ann Thorac Cardiovasc Surg* 2017; **23**: 291-297 [PMID: 28966230 DOI: 10.5761/atcs.oa.17-00020]

34 **Bennouna J**, Senellart H, Hiret S, Vaissiere N, Douillard JY. Impact of histology on survival of resected non-small cell lung cancer (NSCLC) receiving adjuvant chemotherapy: subgroup analysis of the adjuvant vinorelbine (NVB) cisplatin (CDDP) versus observation in the ANITA trial. *Lung Cancer* 2011; **74**: 30-34 [PMID: 21371774 DOI: 10.1016/j.lungcan.2011.02.004]

35 **Liu T**, Mu Y, Dang J, Li G. The role of postoperative radiotherapy for completely resected pIIIA-N2 non-small cell lung cancer patients with different clinicopathological features: a systemic review and meta-analysis. *J Cancer* 2019; **10**: 3941-3949 [PMID: 31417638 DOI: 10.7150/jca.28680]

36 **Kai L**, Zhoumiao C, Shaohua X, Zhao C, Zhijun L, Zhengfu H, Xiujun C. The lymph node ratio predicts cancer-specific survival of node-positive non-small cell lung cancer patients: a population-based SEER analysis. *J Cardiothorac Surg* 2021; **16**: 13 [PMID: 33468199 DOI: 10.1186/s13019-020-01390-x]

37 **Zhou X**, Wu C, Cheng Q. Negative Lymph Node Count Predicts Survival of Resected Non-small Cell Lung Cancer. *Lung* 2020; **198**: 839-846 [PMID: 32683563 DOI: 10.1007/s00408-020-00378-7]

38 **Gao F**, Li N, Xu Y, Yang G. Effects of Postoperative Radiotherapy on Survival of Patients With Stage IIIA Resected Non-Small Cell Lung Cancer: Analysis of the SEER Database. *J Natl Compr Canc Netw* 2020; **18**: 718-727 [PMID: 32502986 DOI: 10.6004/jnccn.2020.7537]

39 **Deng W**, Xu T, Xu Y, Wang Y, Liu X, Zhao Y, Yang P, Liao Z. Survival Patterns for Patients with Resected N2 Non-Small Cell Lung Cancer and Postoperative Radiotherapy: A Prognostic Scoring Model and Heat Map Approach. *J Thorac Oncol* 2018; **13**: 1968-1974 [PMID: 30194035 DOI: 10.1016/j.jtho.2018.08.2021]

40 **Jiang G**, Huang J, Cui T, Lin X, Lin G. A biomarker-based prediction model for risk of locoregional recurrence in pathologic stage IIIA-N2 non-small cell lung cancer. *Int J Clin Exp Pathol* 2020; **13**: 3060-3082 [PMID: 33425107]

41 **Nestle U**, De Ruysscher D, Ricardi U, Geets X, Belderbos J, Pöttgen C, Dziadiuszko R, Peeters S, Lievens Y, Hurkmans C, Slotman B, Ramella S, Faivre-Finn C, McDonald F, Manapov F, Putora PM, LePéchoux C, Van Houtte P. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. *Radiother Oncol* 2018; **127**: 1-5 [PMID: 29605476 DOI: 10.1016/j.radonc.2018.02.023]

42 **De Ruysscher D**, Faivre-Finn C, Moeller D, Nestle U, Hurkmans CW, Le Péchoux C, Belderbos J, Guckenberger M, Senan S; Lung Group and the Radiation Oncology Group of the European Organization for Research and Treatment of Cancer (EORTC). European Organization for Research and Treatment of Cancer (EORTC) recommendations for planning and delivery of high-dose, high precision radiotherapy for lung cancer. *Radiother Oncol* 2017; **124**: 1-10 [PMID: 28666551 DOI: 10.1016/j.radonc.2017.06.003]

43 **Spoelstra FO**, Senan S, Le Péchoux C, Ishikura S, Casas F, Ball D, Price A, De Ruysscher D, van Sörnsen de Koste JR; 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**: 1106-1113 [PMID: 19560881 DOI: 10.1016/j.ijrobp.2009.02.072]

44 **Seol HY**, Kim YS, Kim SJ. Predictive Value of 18F-Fluorodeoxyglucose Positron Emission Tomography or Positron Emission Tomography/Computed Tomography for Assessment of Occult Lymph Node Metastasis in Non-Small Cell Lung Cancer. *Oncology* 2021; **99**: 96-104 [PMID: 32980838 DOI: 10.1159/000509988]

45 **Gómez A**, González JA, Couñago F, Vallejo C, Casas F, de Dios NR. Evidence-based recommendations of postoperative radiotherapy in lung cancer from Oncologic Group for the Study of Lung Cancer (Spanish Radiation Oncology Society). *Clin Transl Oncol* 2016; **18**: 331-341 [PMID: 26280402 DOI: 10.1007/s12094-015-1374-z]

46 **Kong FM**, Ritter T, Quint DJ, Senan S, Gaspar LE, Komaki RU, Hurkmans CW, Timmerman R, Bezjak A, Bradley JD, Movsas B, Marsh L, Okunieff P, Choy H, Curran WJ Jr. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat Oncol Biol Phys* 2011; **81**: 1442-1457 [PMID: 20934273 DOI: 10.1016/j.ijrobp.2010.07.1977]

47 **Boonyawan K**, Gomez DR, Komaki R, Xu Y, Nantavithya C, Allen PK, Mohan R, Liao Z. Clinical and Dosimetric Factors Predicting Grade ≥2 Radiation Pneumonitis After Postoperative Radiotherapy for Patients With Non-Small Cell Lung Carcinoma. *Int J Radiat Oncol Biol Phys* 2018; **101**: 919-926 [PMID: 29976504 DOI: 10.1016/j.ijrobp.2018.04.012]

48 **Shepherd AF**, Iocolano M, Leeman J, Imber BS, Wild AT, Offin M, Chaft JE, Huang J, Rimner A, Wu AJ, Gelblum DY, Shaverdian N, Simone CB 2nd, Gomez DR, Yorke ED, Jackson A. Clinical and Dosimetric Predictors of Radiation Pneumonitis in Patients With Non-Small Cell Lung Cancer Undergoing Postoperative Radiation Therapy. *Pract Radiat Oncol* 2021; **11**: e52-e62 [PMID: 33068790 DOI: 10.1016/j.prro.2020.09.014]

49 **Tang X**, Li Y, Tian X, Zhou X, Wang Y, Huang M, Ren L, Zhou L, Xue J, Ding Z, Zhu J, Xu Y, Peng F, Wang J, Lu Y, Gong Y. Predicting severe acute radiation pneumonitis in patients with non-small cell lung cancer receiving postoperative radiotherapy: Development and internal validation of a nomogram based on the clinical and dose-volume histogram parameters. *Radiother Oncol* 2019; **132**: 197-203 [PMID: 30385172 DOI: 10.1016/j.radonc.2018.10.016]

50 **Yu JH**, Wang CL, Liu Y, Wang JM, Lv CX, Liu J, Zhang Q, Fu XL, Cai XW. Study of the predictors for radiation pneumonitis in patient with non-small cell lung cancer received radiotherapy after pneumonectomy. *Cancer Radiother* 2021; **25**: 323-329 [PMID: 33446419 DOI: 10.1016/j.canrad.2020.11.001]

51 **Zhao L**, Ji W, Ou G, Lv J, Liang J, Feng Q, Zhou Z, Wang L, Yin W. Risk factors for radiation-induced lung toxicity in patients with non-small cell lung cancer who received postoperative radiation therapy. *Lung Cancer* 2012; **77**: 326-330 [PMID: 22512813 DOI: 10.1016/j.lungcan.2012.03.017]

52 **Bütof R**, Simon M, Löck S, Troost EGC, Appold S, Krause M, Baumann M. PORTAF - postoperative radiotherapy of non-small cell lung cancer: accelerated versus conventional fractionation - study protocol for a randomized controlled trial. *Trials* 2017; **18**: 608 [PMID: 29262836 DOI: 10.1186/s13063-017-2346-0]

53 **Corso CD**, Rutter CE, Wilson LD, Kim AW, Decker RH, Husain ZA. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. *J Thorac Oncol* 2015; **10**: 148-155 [PMID: 25325781 DOI: 10.1097/JTO.0000000000000406]

54 **Francis S**, Orton A, Stoddard G, Tao R, Hitchcock YJ, Akerley W, Kokeny KE. Sequencing of Postoperative Radiotherapy and Chemotherapy for Locally Advanced or Incompletely Resected Non-Small-Cell Lung Cancer. *J Clin Oncol* 2018; **36**: 333-341 [PMID: 29236592 DOI: 10.1200/JCO.2017.74.4771]

55 **Verma V**, Moreno AC, Haque W, Fang P, Lin SH. Sequential Versus Concurrent Chemoradiation Therapy by Surgical Margin Status in Resected Non-Small Cell Lung Cancer. *J Natl Compr Canc Netw* 2018; **16**: 508-516 [PMID: 29752325 DOI: 10.6004/jnccn.2018.7007]

56 **Zhang Y**, Han A, Fu Z, Xu S, Zhang Z. The Dosimetric Comparisons of CRT, IMRT, ARC, CRT+IMRT, and CRT+ARC of Postoperative Radiotherapy in IIIA-N2 Stage Non-Small-Cell Lung Cancer Patients. *Biomed Res Int* 2019; **2019**: 8989241 [PMID: 31011583 DOI: 10.1155/2019/8989241]

57 **Chun SG**, Hu C, Choy H, Komaki RU, Timmerman RD, Schild SE, Bogart JA, Dobelbower MC, Bosch W, Galvin JM, Kavadi VS, Narayan S, Iyengar P, Robinson CG, Wynn RB, Raben A, Augspurger ME, MacRae RM, Paulus R, Bradley JD. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. *J Clin Oncol* 2017; **35**: 56-62 [PMID: 28034064 DOI: 10.1200/JCO.2016.69.1378]

58 **Kong M**, Hong SE. Comparison of survival rates between 3D conformal radiotherapy and intensity-modulated radiotherapy in patients with stage III non-small cell lung cancer. *Onco Targets Ther* 2016; **9**: 7227-7234 [PMID: 27920560 DOI: 10.2147/OTT.S124311]

59 **Boyce-Fappiano D**, Nguyen QN, Chapman BV, Allen PK, Gjyshi O, Pezzi TA, De B, Gomez D, Lin SH, Chang JY, Liao Z, Lee P, Gandhi SJ. Single Institution Experience of Proton and Photon-based Postoperative Radiation Therapy for Non-small-cell Lung Cancer. *Clin Lung Cancer* 2021 [PMID: 33707003 DOI: 10.1016/j.cllc.2021.02.002]

**Footnotes**

**Conflict-of-interest statement:** None of the authors have any conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** April 15, 2021

**First decision:** June 7, 2021

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** Spain

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ko R **S-Editor:** Gong ZM **L-Editor: P-Editor:**

**Table 1 Recommendations for postoperative radiotherapy according to the main international guidelines**

|  |  |  |
| --- | --- | --- |
| Guidelines | Clinical scenario | Recommendation for PORT |
| NCCN[9] | Stage pN0-1 Stage pN2, negative surgical margins (R0)Microscopic or macroscopic surgical margins (R1-R2) | Not recommendedSequentialConcomitant (selected cases) or sequential |
| ASTRO[10] | Stage pN2 Microscopic or macroscopic surgical margins (R1-R2)ESTRO-ASTRO[11]Multiple nodal stations involvedExtracapsular nodal extension | SequentialConcomitant (selected cases) or sequentialSequentialSequential |
| ESMO[12] | Early stage (I-II) disease (R0) Positive margins or chest wall involvement (R1-R2)Stage pN2 | Not recommendedSequentialOnly in selected cases |
| ASCO[13] | Early stage (I-II) disease (R0) Stage pN2 | Not recommendedOnly in selected cases |

NCCN: National Comprehensive Cancer Network; ASTRO: American Sociedad of Radiation Oncology; ESTRO: European Society for Radiotherapy & Oncology; ESMO: European Society for Medical Oncology; ASCO: American Society of Clinical Oncology; PORT: Postoperative radiotherapy.

**Table 2 Proposed predictive model for locoregional recurrence in stage IIIA N2 non-small cell lung cancer[41]**

|  |
| --- |
| **Risk model for LRR in stage pIIIA-N2 NSCLC** |
| **Factor** | **Category** | **Score** |
| EGFR status | Wild- type | 4 |
| LMR | LMR < 4.69 | 2 |
| Type of surgery | Thoracotomy | 3 |
| LNR | LNR ≥ 38.9 | 4 |
| **Risk group** | **Score** | **3-yr LRFS** |
| Low risk | 0-2 | 71.4% |
| Medium risk | 3-5 | 57.3% |
| High risk | 6-13 | 13.6% |

LRFS: locoregional recurrence-free survival; LRR: locoregional recurrence; NSCLC: non-small cell lung cancer; LNR: lymph node ratio; LMR: lymphocyte-to-monocyte ratio.

**Table 3 Registered active studies related to postoperative radiotherapy**

|  |  |  |
| --- | --- | --- |
| **NCT** | **Title** | **Study type** |
| NCT02977169 | To Evaluate the Role of Postoperative Radiotherapy in Patients With IIIA(N2) Non-Small Cell Lung Cancer | Interventional |
| NCT02974426 | To Evaluate the Optimal Timing of Postoperative Radiotherapy in Patients With IIIA(N2) Non-Small Cell Lung Cancer | Interventional |
| NCT04073745 | Single Fraction Stereotactic Body Radiation Therapy After Surgery in Treating Patients with Non-small Cell Lung Cancer | Interventional |
| NCT03006575 | Study of Split-course Chemoradiotherapy For Postoperative Locoregional Recurrence of Non-small Cell Lung Cancer | Interventional |
| NCT02555592 | Strategy of Surgical Resection with Adjuvant Therapy for IIIA NSCLC and N2 Disease Only in Subaortic or Paraaortic Level | Observational |
| NCT02189967 | Postoperative Radiotherapy of Non-small Cell Lung Cancer: Accelerated vs. Conventional Fractionation | Interventional |
| NCT00880971 | Postoperative Radiotherapy for Patients with IIIA (N2) Non-small Cell Lung Cancer | Interventional |
| NCT01112631 | Prospective Study of Quality of Life in Non-small Cell Lung Cancer (NSCLC) Patients Treated With/Without Postoperative Radiotherapy | Observational |