Clin Transl Oncol (2016) 18:331–341
DOI 10.1007/s12094-015-1374-z

REVIEW ARTICLE

Evidence-based recommendations of postoperative radiotherapy in lung cancer from Oncologic Group for the Study of Lung Cancer (Spanish Radiation Oncology Society)

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Received: 29 June 2015 / Accepted: 4 August 2015 / Published online: 18 August 2015

Abstract Locally advanced non-small cell lung cancer (NSCLC) is a diversified illness in which postoperative radiation therapy (PORT) for complete resection with positive hiliar (pN1) and/or mediastinal (pN2) lymph nodes is controversial. Although several studies have shown that PORT has beneficial effects, randomized trials are needed to demonstrate its impact on overall survival. In this review, the Spanish Radiation Oncology Group for Lung Cancer describes the most relevant literature on PORT in NSCLC patients stage pN1–2. In addition, we have outlined the current recommendations of different national and international clinical guidelines and have also specified practical issues regarding treatment volume definition, doses and fractionation.

Keywords Postoperative radiation therapy · Non-small cell lung cancer · Pathologic N2 · Adjuvant treatment

Introduction

Some patients with early stage NSCLC have an elevated risk for local and systemic recurrence despite complete resection. As a result, evaluation of different adjuvant approaches [1] has been performed.

In the last years, the benefit of chemotherapy (Cht) has been confirmed in different clinical trials [2] and meta-analyses [3] that included patients with stage II and III

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NSCLC. In contrast with the expanding consensus about adjuvant Cht, the role of PORT remains controversial.

Different retrospective and prospective studies have suggested that adjuvant Cht may benefit selected patients but the impact on overall survival (OS) is scarce [4]. A meta-analysis published in 1998 conditioned the exclusion of PORT in diverse multimodal approaches [5].

At present, technical developments in treatment planning and an increase in the knowledge of radiobiological concepts of doses and fractionation have allowed an escalation in the therapeutic index of radiation therapy [6]. Therefore, it seems appropriate to re-examine the role of PORT in the clinical context of personalized and effective systemic treatment [7].

Materials and methods

A comprehensive review of the clinical literature of the following databases was performed from January 1980 to January 2015: MEDLINE (Pubmed), EMBASE (Ovid), Web of science (Web of Knowledge). Article selection in this review was undertaken by six radiation oncologists with extensive experience in lung cancer. Articles which were excluded evaluated the role of PORT in R1 and R2 and after neoadjuvant chemotherapy. The key words selected were: postoperative radiation therapy, non-small cell lung cancer, and pathologic N2 and adjuvant treatment.

What is the rationale of port in NSCLC?

The argument in favor of PORT is based on three fundamental issues: the high risk of local recurrence (LR) in these patients, the potential of radiation to eliminate residual malignant cells in the surgical bed, resection margin or regional lymph nodes and finally, a favorable balance between the benefit of locoregional control and the risk of toxicity and the consequent impact on OS.

It is difficult to determine the risk of LR after surgery because of the absence of local failure patterns in different studies (some of which only establish the first site of failure) as well as the non-existent definition of these patterns. In general, the LR rate is proportional to the risk of failure, increasing according to the stage and grade of lymph node involvement: 5–20 % in stage I, 20–40 % in stage II and 30–60 % in stage IIIA [8, 9] (Table 1). Even after adjuvant or neoadjuvant Cht, approximately 20–40 % of patients present LR [10]. Different clinical and pathological factors are related to a major risk of LR. Among these, massive primary tumors, non-squamous histology, positive margins, limited surgery (segmentectomy), inadequate lymph node dissection and the number of lymph nodes affected are the most remarkable [11, 12].

Table 1 Relapse patterns in selected studies

Nodal stage	Locoregional relapse (%)	Systemic relapse (%)
N_0	6–17	18–30
N_1	9–28	22–64
pN_2	17–41	70
cN_2	14–54	38–55

A patient with an elevated risk of LR is theoretically the ideal candidate for studying the benefits of PORT. Nonetheless, it must be taken into account that patients at high risk for LR also have a high risk of systemic disease and thus, the expectations of cure are limited with a local approach.

Investigators by the Mayo Clinic evaluated the role of PORT in completely resected pN2 patients stratified by risk [13]. Their results suggested a proportional benefit of PORT in local control with an increase in the risk of LR and death. On the other hand, despite systemic failure continuing to be the primary cause of death in NSCLC, long-term survival is increasing with the use of adjuvant Cht. Adequate patient selection is necessary so that the possible benefit in survival surpasses the risk of potential toxicity.

What is the evidence against port?

The meta-analysis on PORT performed in 1998 analyzed individual patient data (>2000 patients) in 9 clinical trials of surgery versus surgery followed by adjuvant radiation therapy [14–20] (Table 2). In general, the results suggested a negative effect on OS probably in relation to the increase of intercurrent death (relative risk of death around 21 % with an absolute two-year decrease in OS of 7 %).

The detrimental effect on survival was evident in pN0-1 (stage III and pN2 results favor PORT, albeit not being statistically significant). This meta-analysis demonstrated a 24 % reduction in the risk of LR.

A follow-up of the PORT study published in 2005 included former data correction and with the inclusion of a new trial [21] and showed the same conclusions [22].

This meta-analysis by Burdett et al. was updated by the Cochrane group and included 2343 patients from 11 trials [23]. Their results demonstrated an 18 % increase in the risk of death limited to stage I/II (pN0–N1). There is no clear evidence of a detrimental effect on survival in pN2 patients but there is a clear benefit in local control (74 versus 59 %).

Table 2 Summary and comments in PORT Meta-analysis Trialists Group

Trial (recruitment/no. patients)	Hazard ratio	Comments
Belgium (1966–1977/202)	1.48 (0.99–2.22) $p = 0.012$	Some patients stage I. TD: 60 Gy in all cases. Co-60 in all cases. CMT. Use of SCB and LF
LCSG 773 (1978–1985/230)	1.12 (0.75–1.68) $p = 0.457$	Co-60 in some cases. CMT. Use of SCB and LF
CAMS (1981–1995/317)	1.02 (0.70–1.51) $p = 0.874$	ETD: 60 Gy in all cases. Co-60 in some cases. CMT. Use of SCB and LF
Lille (1985–1991/163)	1.53 (0.92–2.54) $p = 0.032$	Stage I all patients. TD: 60 Gy in some cases. Co-60 in some cases. Use of SCB and LF
EORTC 08861 (1986–1990/106)	1.64 (0.76–3.54) $p = 0.098$	CMT
MRC LU11 (1986–1993/308)	0.96 (0.69–1.34) $p = 0.748$	EDpF: 2.6 Gy all cases. Co-60 some cases. CMT and SCF. Use of SCB and LF
GETCB 04CB86 (1986–1994/189)	1.17 (0.74–1.85) $p = 0.378$	Some patients stage I. ETD: 60 Gy all cases. EDpF: Up to 2.5 Gy in some cases. Co60 some cases. CMT. Use of SCB and LF
Slovenia (1988–1992/74)	0.85 (0.44–1.63) $p = 0.517$	EDpF: 2.5–3.0 Gy in all cases. CMT. Use of LF
GETCB 05CB88 (1988–1994/539)	1.45 (1.06–1.99) $p = 0.002$	Some patients stage I. ETD: 60 Gy in all cases. EDpF: Up to 2.5 Gy some cases. Co-60 some cases. CMT. Use of SCB and LF
Italy (1989–1997/104)	0.71 (0.35–1.45) $p = 0.215$	All patients stage I
Total (2232)	1.18 (1.07–1.31) $p = 0.002$	

LCSG Lung Cancer Study Group, *CAMS* Chinese Academy of Medical Sciences, *EORTC* European Organization for Research and Treatment of Cancer, *MRC* Medical Research Council, *GETCB* Groupe d'Etude et de Traitement des Cancers Bronchiques, *ETD* excessive total dose, *Co-60* Cobalt-60 machine, *CMT* complete mediastinal treatment, *SCB* spinal cord block, *LF* lateral fields, *EDpF* excessive dose per fraction

Several authors have analyzed these data and concluded that the majority of these studies lack adequate design methods and radiation treatment [24], with the main critical issues being (Table 2): (a) scarce sample (low probability of detecting differences); (b) inadequate staging according to current standards (unspecified surgery details and lymph node staging); (c) patients with low risk for LR selected (four trials with stage I or pN0, thereby possibly reducing the survival benefit of PORT due to the absence of risk stratification; subgroup analysis depending on the risk and an unplanned re-analysis which, indeed, showed statistical power similar to a retrospective study); (d) outdated technology (cobalt units in most of the trials with a published 5-year OS being lower compared to linacs and CT-based planning, 8 versus 30 %) [25]; (e) Outdated planning (most trials used lateral beams—extensive lung volumes exposed to moderate doses—and/or posterior medullar blocks—lower dose in mediastinum); (f) Inadequate doses and fractionation (most of the studies used very high total doses and/or doses per fraction); and (g) Absence of quality assurance.

Two other randomized trials showed no detrimental effect of radiation therapy and were excluded; both appeared to provide benefits in survival for N-positive patients.

The study of Dautzenberg et al. [20], which clearly presented the previously mentioned inconveniences, included more than one-third of the patients in the PORT meta-analysis (728 patients). Taking into account the aforementioned concepts, if the studies included had been analyzed in the context of modern therapy, neither would have been considered acceptable. Suboptimal PORT would be equivalent to adjuvant alkylating agents in resected NSCLC which is also associated with a detrimental effect on survival [26]. It is important to look back on postmastectomy radiation; for a long time it was considered detrimental until two well-designed clinical trials using modern techniques demonstrated its benefit in terms of event-free survival and OS [27, 28].

What evidence favors port?

PORT in pN2 Most of the evidence that favors PORT comes from retrospective studies (Table 3). Two unicenter experiences in the USA have suggested benefits in a

Table 3 Evidence in support of PORT for pN2

Trial Recruitment date No. patients/No. PORT)	Survival PORT versus no PORT	Comments
Sawyer et al. [29]	OS: 43 versus 22 %	Unicentral experience
Cl Mayo	$p = 0.0001$	
Retrospective		
1987–1993		
224/88		
Lally et al. [31]	OS: 27 versus 20 %	Retrospective nature of the analysis Consider stage N2 heterogeneity (comorbidity, type of surgery, examined and lymph nodes affected), Cht and radiation therapy treatment details.
Retrospective	$p = 0.036$	
SEER database	RFS: 36 versus 27 %	
1988–2002	$p = 0.298$	The analysis excludes dead patients in the first 4 months after surgery.
7465/3531		
Douillard JY [32]	OS: 47.4 versus 34 %	ANITA trial randomizes 840 patients (stages IB–IIIA) to adjuvant Cht (cisplatin/vinorelbine) versus observation. PORT administered according to participant center preferences. This unplanned analysis showed that N2 patients have a benefit with PORT associated with Cht.
1994–2000		
840/232		
Zou B [33]	OS: 30.5 versus 22.2 %	PORT/Cht versus adjuvant Cht
Retrospective	$p = 0.007$	
1998–2005	RFS: 14.4 versus 9.3 %	
183/104	$p = 0.003$	
Dai H [34]	OS: 36.6 versus 30.6 %	161 patients (72.9 %) treated with adjuvant Cht and 96 patients (43.4 %) received PORT (of whom 61–63.5 %, also received Cht)
Retrospective	$p = 0.046$	
2003–2005	RFS: 32.1 versus 16.5 %	
221/96	$p = 0.009$	
Shen W [35]	OS: 37.9 versus 27.5 %	PORT/Cht versus adjuvant Cht
Randomized clinical trial	$p = 0.073$	Closed due to slow accrual
2004–2009	RFS: 30.3 versus 18.8 %	
135/66	$p = 0.041$	
Billiet C [37]	Overall survival analysis depending on the use of cobalt or Linac treatment or both	
Meta-analysis		
1980–2002	PORT significantly increased overall survival when administered with a Linac. RR 0.76, 95 % CI 0.61–0.95, $p = 0.02$	
11 trials (2387 patients)		

selected group of patients. A series from the Mayo Clinic included 224 pN2 patients resected between 1987 and 1993; 88 of whom had received adjuvant radiation [29]. Both groups (PORT versus no PORT) were well balanced. Regression analysis confirmed that PORT is an independent prognostic factor for LR (17 versus 60 %; $p = 0.0001$) and survival (43 versus 22 %; $p = 0.0001$).

In the experience of the University of Pennsylvania, 200 patients with NSCLC stage II and III showed the need for moderate doses of radiation (risk of intercurrent death with <54 Gy of 2 %) to achieve benefits in local control and survival [30].

Analysis of a SEER database (Surveillance Epidemiology and End Results), with more than 7400 NSCLC stage pT1–3 N1–2 patients treated between 1988 and 1995, showed no evidence of a benefit with PORT in OS, which was even negative in pN0–N1 patients despite the use of modern radiation techniques [31]. However, in contrast to this meta-analysis, PORT in pN2 was associated with an increase in cancer-specific survival (30 versus 25 %) and 5-year OS (22 versus 16 %). The analysis showed an early divergence in pN0–1 curves and a late divergence in pN2 curves (3 years after treatment).

The first observation would be that PORT is a marker for aggressive tumoral type or for macroscopic residual disease; the second indicates a late beneficial effect of PORT, as a consequence of the elimination of residual microscopic disease. Nonetheless, this study could be criticized because of the lack of a SEER database and the methods applied.

First of all, the retrospective essence of the analysis did not consider the heterogeneity of pN2 (comorbidity, type of surgery, number of resected and affected lymph nodes), the use of Cht and radiation therapy. Next, the analysis excluded patients that died in the first 4 months after surgery. A proportion of these patients could have been affected by cardiopulmonary disease secondary to radiation therapy. The median follow-up of the study (3.5 years) was too short to evaluate the late effects of radiation.

The ANITA study randomized 840 patients (stages IB-IIIA) to adjuvant Cht (cisplatin/vinorelbine) versus observation [32]. PORT (45–60 Gy) was given after Cht according to the preferences of the participating center. An unplanned analysis shows that pN2 patients presented benefits with PORT when associated with Cht (5-year OS 47 % versus 34 %), while pN0-1 patients presented a decrease in survival with this combination. These patients showed an increase in survival when treated with radiation therapy alone (5-year OS 21 versus 17 %).

A retrospective multicenter study from China compared PORT associated with Cht ($n = 104$) to Cht alone ($n = 79$) in pN2 patients [33]. Their results showed that disease-free survival (DFS) and OS were significantly higher in the group receiving both PORT and Cht. (5-year OS: 30.5 versus 0.22.2 %, $p = 0.007$; SLE 14.4 versus 9.3 % $p = 0.003$). LR-free survival was much higher in the PORT + Cht group (73.2 % versus 33.8 %, $p = 0.027$). Metastasis-free survival did not achieve statistical significance, although it was higher in the PORT + Cht group (35.8 % versus 18.9 %, $p = 0.394$). In the multivariate analysis, PORT + Cht treatment and receiving more than 3 cycles of Cht showed a positive effect in terms of DFS and OS. The association of pN1+ and pN2+ was correlated with a significantly worse DFS and OS than with pN1+ alone.

Another retrospective unicenter study from Pekin [34] evaluated 221 stage IIIA-pN2 patients treated between 2003 and 2005; 161 patients (72.9 %) received adjuvant Cht and 96 (43.4 %) received PORT (of whom 61–63.5 % also received Cht). The OS was significantly superior in the PORT group: 94.8 %, 59.1 and 36.6 % for 1, 3 and 5 years, respectively, versus 77.6, 45.4 and 30.6 % in patients who did not receive PORT. The DFS was also higher in the PORT group (76.1, 39.8 and 32.1 versus 56.4, 28.2 and 16.5 % for 1, 3 and 5 years). Multivariate analysis showed that PORT, cN2, number of lymph nodes affected and adjuvant Cht were independent prognostic factors for OS.

An analysis to assess the impact of different treatment combinations showed that the group treated with surgery, adjuvant Cht and radiation therapy (RT) had the longest median survival time (48.3 months versus 38.3 months for surgery + RT, 33.1 months for surgery + Cht and 21.6 months for surgery alone) and the highest OS at 1, 3 and 5 years (at 5 years: 38.2, 33.7, 31.9 and 23.1 %, respectively) although the difference was not statistically significant. PORT had a powerful positive impact on LR-free survival and metastasis-free survival.

A randomized clinical trial, which was prematurely closed due to slow accrual, analyzed the OS and DFS of 135 stage pN2 patients in two arms, Cht ($n = 69$) and PORT + Cht ($n = 66$) [35].

The DFS in the combination group was significantly higher (28 months) than in Cht alone, (18 months, $p = 0.041$). The median survival and the global survival rate at 5 years was 40 months (37.9 %) in the combination arm and 28 months (18.8 %) in the Cht alone arm although the result was not statistically significant ($p = 0.073$) .

Recently, Mikell et al. published the results of 2115 NSCLC patients staged pN2 postoperatively and treated with adjuvant Cht, included in the National Cancer Data Base between 2004 and 2006. Patients treated with Co-60 RT or patients who received neoadjuvant treatment were excluded: 918 patients (43.4 %) received PORT and 1197 (56.6 %) received no RT. The median OS was 42 versus 38 months, respectively. This event was significant on multivariate analysis and also in the Cox model (HR = 0.87, 95 % CI 0.78–0.98, $p = 0.026$ and HR = 0.89, 95 % CI 0.79–1.00, $p = 0.046$).

On multivariate analysis, younger age, female, adenocarcinoma histology, high social status, lower T, 1–2 lymph node involvement versus ≥3 and number of analyzed lymph nodes were related to a better OS ($p = 0.05$). No direct relationship was observed between PORT and number of lymph nodes affected [36].

Finally, a meta-analysis evaluated the clinical impact of technology in patients with PORT [37]. The study included 11 clinical trials (2387 patients) published between 1980 and 2002 and compared the OS using cobalt unit treatments, Linac treatments or both. PORT significantly increased the survival when administered with a Linac (RR 0.76, 95 % CI 0.61–0.95, $p = 0.02$). In addition, patients treated with a Linac showed a significant decrease in LR with a relative risk of 0.31 (95 % CI 0.12–0.79, $p = 0.01$). Based on these results, the investigators hypothesized that the administration of PORT with a Linac and a modern technique could lessen LR by 20 % and increase the OS by 13 % [37].

PORT in patients with pN1 Several recently published studies have evaluated the role of PORT in patients with pN1. These studies concluded that it is reasonable to re-examine the possible benefit of PORT using modern techniques because of the high LR in this population.

A retrospective multicenter study analyzed the recurrence pattern of 60 patients surgically treated between 2000 and 2006 and staged pN1 with a median follow-up of 30 months [38].

Local relapse as a first site of recurrence was shown in 33, 33 and 46 % at 2, 3 and 5 years, being more frequent than distant metastases (26 % at 2 and 3 years and 32 % at 5 years). The most frequent site of relapse was the ipsilateral mediastinum followed by the bronchial stump and contralateral mediastinum.

On comparing the results of the 440 pN0 patients in the same retrospective study, LR and distant recurrence rates were significantly higher in pN1 patients ($p = 0.03$ for LR and $p = 0.01$ for distant metastases).

The only significant factor associated with a higher risk for LR was Cht. This probably means that Cht can prevent or delay distant metastases and allows LR to be clinically evident [38].

In a retrospective series of 335 patients with surgically resected stage pN0–pN1 NSCLC, the first site of relapse was LR in 37 %, local and distant in 35 % and distant alone in 28 % [39]. Multivariate analysis showed that the risk of LR was higher in the presence of lymphovascular invasion and T3–4.

A unicenter study including 198 stage pN1 patients treated between 1995 and 2008 showed a risk of LR of 40 % at 5 years. The factors associated with a higher risk of LR were visceral pleural invasion, the number of lymph nodes affected and video-assisted thoracoscopic resection. The most frequent sites of recurrence were the mediastinum (53 %), the bronchial stump/ipsilateral hilum (26 %) and both (21 %) [40].

Another retrospective study of 199 patients stage pN1 treated between 2007 and December 2008 also showed an elevated rate of LR (20.6 %) in comparison with both distant and LR (12.6 %); distant disease was found in only 39.7 % [11]. Multivariate analysis showed that station 10 infiltration and incomplete mediastinal dissection (less than 3 stations) were associated with a worse locoregional failure-free survival; 158 patients received postoperative Cht but there was no difference in LR between these patients and the 41 others not receiving Cht.

A review of 1402 consecutive stage I–III (N0–N1) NSCLC patients who underwent surgery at MD Anderson between January 1999 and 2009 showed that the extent of surgical resection (single/multiple wedges + segmentectomy versus lobectomy + bilobectomy + pneumonectomy), tumor size >2.7 cm, and visceral pleural invasion were independently significant risk factors for LR. Second, they found that pathologic N1 stage, visceral pleural invasion, and lymphovascular space invasion were risk factors for regional failure. Finally, they found that multiple factors, including the presence of LR, were associated with an increased risk of mortality. As the authors state, this information could be used to help identify patients with a high risk of recurrence who would be candidates for more aggressive postoperative treatment [41].

Is there any role for adjuvant chemoradiation?

An Eastern Cooperative Oncology Group study (ECOG 3590) compared PORT versus PORT with concurrent cisplatin and etoposide in stage II and IIIA patients [42] and found no difference in LR and survival. Toxicity was more frequent in the combined arm, although treatment-related mortality was less than 2 %. The intercurrent death rate was not significantly different compared to the death rate in controls of the same age and sex [43].

A phase II trial of the RTOG (RTOG 9705) evaluated PORT concurrent with carboplatin and paclitaxel in stage II and IIIA patients [44]. The median progression-free survival and median survival were 35.6 and 56.3 months, respectively.

Toxicity of port

If radiation therapy increases the mortality of surgically treated lung cancer patients, we must ask ourselves what the cause and mechanism of toxicity are.

Studies based on equivalent biologic dose parameters suggest that the adverse effects of PORT are related to dose [45]. Survival curve analysis has shown that mortality is detected after the fourth month of randomization and builds up during the following 8 months.

There seems to be a radiation-induced noxious process which becomes evident at 3–12 months after treatment, coinciding with the natural history of radiation pneumonitis.

It is of note that noxious PORT effects have not been demonstrated in stage III patients. However, radiation-induced mortality is not expected to be lower in this group than in patients with lesser disease burden.

It is clear that these patients with stage III were probably treated with wider radiation fields. This could mean that radiation therapy increases the cancer-specific survival in patients with more advanced stages.

Is it possible to decrease toxicity with modern radiation therapy?

University of Pennsylvania investigators reviewed their experience of PORT with modern techniques. Their study determined the intercurrent death rate in patients with NSCLC surgically treated and irradiated compared to death rates in the general population. The administration of radiation therapy (Linacs, reduced target volumes and 3D planning) with 55 Gy resulted in a modest increase in the intercurrent death rate with no statistical significance (13.5 versus 10 %) [30].

A prospective study with 151 stage pN2 patients evaluated PORT with modern techniques; radiation therapy was administered to pN2 patients while patients with pN1 were managed as a control group. Two studies reviewed the results. The first [46] described cardiopulmonary toxicity and quality of life which where similar in both groups (pN1 patients treated with surgery alone and pN2 patients received PORT). In addition, respiratory and cardiac symptoms were evaluated as well as pulmonary function tests with no differences in the two groups.

The second [47] review analyzed the results and described an actuarial survival of 27.1 % at 5 years; distant metastases alone or with local relapse in 55 % and LR in 19.2 %, of whom 9 % had both LR and distant metastases.

Port recommendations in clinical guidelines

Several international clinical guidelines have established recommendations of PORT in lung cancer. The leading protocols are compiled in Table 4. Despite being one of the most prominent, the British guideline NICE did not consider PORT in the last update in 2011 [48] and is therefore not included in the table.

The almost undivided consensus is that PORT has a negative effect on survival in completely resected (R0) stage pT1–2 and pN0–1 patients, whereas this effect apparently does not exist in pN2 patients in whom PORT could provide an improvement in OS and locoregional control.

Likewise, PORT should be indicated for incomplete microscopic (R1) or macroscopic (R2) Resections. There is agreement in that some issues should be solved related to the potential influence of new radiation therapy techniques in the aspects mentioned (limiting cardiac and lung dose and/or enhancing treatment volume definition and coverage), as well as the currently unknown total dose and fractionation that should be recommended for PORT.

In general, the indications of PORT in guidelines are brief and barely describe concrete situations of its use in common clinical scenarios.

The American College of Radiology guidelines [49] are the most exhaustive and meticulous and specifically identify the following situations:

- The potential indication of PORT in unsatisfactory surgical technique (insufficient mediastinal lymphadenectomy) even in stages I–II.
- The sequence of chemoradiation: if R0, sequential chemoradiation; if R1-2 concurrent chemoradiation.
- Specific clinical scenarios: (a) patients staged cT2N1 at diagnosis (Dx) and pT2N2 after surgery (Sx): sequential chemoradiation better than Cht alone (equivalent recommendation strength of the latter if only one pN2

Table 4 Clinical guidelines summary

Guideline	Indication
SIGN (2005) [52]	Consider PORT in a clinical trial
CCO 7–1–2 (2006) [53]	Stages I–II: PORT not recommended
	Stage IIIA: Role of PORT in combination with Cht controversial
CCO-ASCO (2007) [54]	Stage I–II: PORT not recommended
	Stage IIIA: PORT not routinely recommended Possible role in pN2
CCO 7–1–1	Stages I–II: PORT not recommended
V.2 (2012) [53]	Stage IIIA: Recommendations not conclusive. Individualized setting.
ESMO (2013) [55]	Stages I–II: PORT not recommended
	Stage IIIA: Consider PORT if pN2
ACR N2adj (2013) [49]	Stages I–II: PORT not recommended. Consider if inadequate mediastinal sampling (not performed or insufficient)
	pN2: Consider sequential PORT after Cht
NCI (2013) [50]	Stages I–II: PORT not recommended
	Stage III: Evidence of the negative effect and possible OS increase in multiple pN2 or extracapsular invasion not conclusive.
SEOM (2013) [56]	Stages I–II: PORT not recommended
	Stage IIIA: Consider PORT if pN2 (sequential after Cht)
NCCN (V2 2014) [51]	Stages I–II: PORT not recommended
	Stage IIIA: Consider PORT if pN2 or extracapsular invasion (sequential after Cht)

All aforementioned indications for completely resected patients (R0)

PORT postoperative radiation therapy, *RT* radiation therapy, *Cht* chemotherapy, *N2* mediastinal lymph nodes affected, *OS* overall survival

station affected). (b) cT2 pN2 patients at Dx and pT1pN1 patients after induction Cht and Sx: consider PORT in selected patients (especially if more than one N1 lymph nodes affected). (c) Patients staged cT2pN2 at Dx: The treatment of choice is radical concurrent chemoradiation versus induction chemoradiation followed by Sx, both with the same strength of recommendation. As an alternative, induction Cht followed by Sx ± PORT as necessary, with a lower strength of recommendation.

NCI [50] and NCCN [51] guidelines stand out in favor of PORT when extracapsular extension is present.

Lastly, ASTRO (American Society for Radiation Oncology) published the second "Choosing Wisely" list [57] and clinical practice guideline [58] in which they suggest: "Don't routinely offer radiation therapy for patients who have resected NSCLC with negative margins and N0–1 disease".

Port technique

Target volume definition

A rational design of the radiation fields based on CT images, the administration of moderate doses and the use of 3D planning and verification techniques establish the basic pillars of PORT for NSCLC.

There are currently no data from available prospective studies that define optimal target volumes. At least, the bronchial stump, ipsilateral hilum and affected mediastinal lymph nodes must be included. Other locations must be covered in an individualized manner depending on the knowledge of pulmonary drainage, failure patterns after surgery and pulmonary function.

The currently ongoing phase III trial that will help to clarify the utility of PORT in NSCLC is the Lung Adjuvant Radiotherapy Trial—Lung ART which applies a mandatory CTV contouring protocol for every patient included [59]. This study is based on a preliminary study in which 17 radiation oncologists were encouraged to contour their regular CTVs in two model patients employing a previously validated contouring program [60]. The cited protocol recommends:

1. *rCTV(resected clinical target volume)* Includes affected lymph node fields described in the pathological surgical report. All affected areas reported in CT or PET-CT should not routinely be included. The bronchial stump, ipsilateral hilum and the extension of mediastinal pleura adjacent to surgical bed should be included in the rCTV.
2. *Mediastinal CTV (clinical target volume)* Includes rCTV plus a margin that incorporates the immediately superior and inferior lymph node station related to the affected lymph node area. All lymph node areas in between non-adjacent affected lymph node areas must be included in the CTV. Lymph node areas 4 (lower paratracheal lymph nodes) and 7 (subcarinal lymph nodes) should always be included in the CTV due to frequent infiltration. Lymph node areas 5 and 6 (subaortic and para aortic lymph nodes) in left tumors should always be included in the CTV also because of frequent infiltration. The supraclavicular region should not be routinely included in the CTV. Table 5 describes the levels and limits depending on the lymph node region affected.
3. *PTV (planning treatment volume)* To compensate for errors due to organ movement and patient position inaccuracy, a minimum margins of 0.5 cm (lateral, anterior and posterior) and 1 cm (cephalad-caudal)

Table 5 CTV according to lymph node level affected

Affected lymph node level	Lymph node levels to be included in CTV	Superior and inferior maximal limits of the radiation fields	
		Superior	Inferior
1–2	1–2, 4 and 10 ipsilateral; 7	1 cm over the sternal notch. Supraclavicular fossae can be included if necessary (N1–2)	4 cm below the carina
3	3, 4 and 10 ipsilateral; 7		
4	2, 4 and 10 ipsilateral; 7	Sternal notch	
5	2 and 4L, 5, 6 and 7	Superior aortic arch	
6		Sternal notch	
7	4R and 7 if right tumor.	Superior aortic arch	5 cm below the carina
	4L, 5, 6 and 7 for left tumor		
8	4R, 7 and 8 if right tumor		Gastroesophageal union
	4L, 5, 6, 7 and 8 for left tumor		

must be added to CTV. These margins are specific to individual treatment facilities and depend on the availability of 4D-CT and distinct set-up errors.

A recently published trial analyzed the LR pattern and suggested the use of CTV in 250 stage IIIA (N2) patients treated surgically between 2005 and 2011 in whom PORT was not performed [12]. Locoregional relapse was noted as a first relapse in 31.2 %. The lymph node stations most affected in left lung cancer were 4R followed by 7, 4L, 6, 10L and 5. The most frequent relapses in right lung cancer were 2R, followed by 10R, 4R and 7. The CTV suggested for right lung tumors includes lymph node stations 2R, 4R, 7, 10R, 11R; in the left lung: 2R, 4R, 4L, 5, 6, 7, 10L and 11L. For patients with left lung cancer, all relapses are included in the proposed irradiation volume; for right lung tumors, 83 % of the latter.

Doses

Little data are available on adequate doses in adjuvant treatment for NSCLC. Recommendations are based on scant retrospective series and estimates from other tumor locations. In general, 50 Gy in 1.8–2 Gy per fraction is considered adequate, increasing the dose to 54–60 Gy if close or affected margins and 66 Gy if remaining disease present.

Conclusions and recommendations (box 1)

Currently, there is no role for PORT in completely resected NSCLC stages I and II with adequate mediastinal lymphadenectomy. In fact, there is no established impact on survival and local control rates and it may even increase the risk of death not related to cancer.

Notwithstanding, several recent publications analyzing the recurrence pattern in stage pN1 patients suggest that the role of PORT should be reevaluated as a result of the high locoregional relapse rate taking into consideration that there are no studies with limited fields and modern techniques with which there might be no deleterious effect.

Although some data support the role of PORT in local control and survival in completely resected N2 patients, the evidence available is not sufficiently strong. Indeed, two ongoing multicenter randomized clinical trials will try to enlighten this indication (LungART—NCT00410683; NCT00880971) [59, 61].

However, there are increasing data that encourage the use of PORT. Once the risk benefit balance has been evaluated, PORT might be a reasonable option in this group of patients. As discussed above, the concerns about its application can be reduced with modern radiation techniques. To enhance treatment results, some strict conditions are necessary, such as a good performance status (ECOG PS 0–1), adequate pulmonary function, meticulous staging, proper treatment volume definition, 3D planning, 50 to 50,4 Gy dose (1.8–2 Gy per fraction), possible toxicity assessment according to dose–volume histograms and lastly, short- and long-term monitoring.

In the near future, progress in surgery, pathology, genetics and molecular biology will allow an optimal selection of candidates for PORT according to prognostic and predictive biomarkers.

Compliance with ethical standards

Conflict of interest The authors indicate no potential conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

Box 1

Phase III trials and a PORT meta-analysis in resected NSCLC demonstrate an increase in local control but not a survival benefit. Most of these trials were undertaken before the implementation of adjuvant chemotherapy

A recent PORT meta-analysis update suggests a benefit in N2 patients (local control increases without an adverse effect on survival)

EORTC is actually addressing the Only clinical trial (LUNG ART) that randomizes patients to PORT versus observation after radical surgery and adjuvant Cht for NSCLC

Consider PORT after adjuvant Cht in selected patients (N2) to increase local control. It is recommended to use modern planning techniques and moderate radiation doses (50 Gy)

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