Review Article

A narrative review of postoperative adjuvant radiotherapy for non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Objective: To summarize the principal studies investigating the role of postoperative radiation therapy (PORT) for non-small cell lung cancer (NSCLC) and to discuss the recent major breakthroughs deriving from the Lung ART trial, in order to provide a real-world scenario of the management of resected NSCLC patients.

Background: Surgery followed by platinum-based chemotherapy remains the mainstay of adjuvant treatments for completely resected stage II and IIIA NSCLC. Less consistent is the employment of PORT, as no significant benefit was clearly identified from the previous published meta-analysis. Furthermore, the recent results of Lung ART trial questioned for the first time the efficacy of PORT for pathological N2 (pN2) NSCLC patients. Hence, the need to define if PORT still has a role for resected NSCLC and which subgroup of patients could benefit most from this treatment.

Methods: A literature search of PubMed was performed to identify publications, including prospective and retrospective clinical studies, meta-analysis and systematic review of PORT for NSCLC. No limit concerning years of publication or publication status were applied. Only papers using the English language were selected. The ESMO 2020 and ESMO 2021 online resources were used to analyze the Lung ART trial results. The authors provide a narrative summary of the findings and implications of these studies and how they improve the clinical practice.

Conclusions: PORT was considered the standard of care for patients with completely resected pN2 NSCLC based on the results of an old meta-analysis that did not demonstrate a detrimental effect. The more recent randomized phase III Lung ART trial concluded that PORT could not anymore be recommended for pN2 NSCLC as a significant benefit in terms of 3 years disease-free survival (DFS) was not reached and an increased rate of radiotherapy related toxicity was observed. Retrospective studies suggest a possible role of PORT for incompletely resected NSCLC patients and those with an extranodal extension (ENE), but this issue needs to be reinforced from randomized prospective trials. The extensive publication of Lung ART trial is largely awaited to define if there is a role of PORT for resected NSCLC patients.

Keywords: Postoperative radiation therapy (PORT); adjuvant radiotherapy; non-small cell lung cancer (NSCLC); stage IIIA; pathological N2 (pN2)

Received: 10 July 2021; Accepted: 28 December 2021; Published: 25 March 2022.

doi: 10.21037/med-21-31

View this article at: https://dx.doi.org/10.21037/med-21-31

Introduction

Background

Worldwide, lung cancer is the leading cause of cancer death, with more than one million new cases diagnosed every year, and about 80–90% of them are non-small cell lung cancer (NSCLC) (1-3). Surgery followed by platinum-based chemotherapy represents the standard of care for stage II and IIIA NSCLC, however, the locoregional recurrence (LRR) for pathological N2 (pN2) disease remains high with a worse associated overall survival (OS) (4,5). Actually, stage IIIA pN2 patients constitute a large population with different clinical and pathological characteristics influencing the prognosis. Many factors such as N2 metastases, number of involved stations, tumor size, histological type, age and sex have been associated with OS. However, it is still impossible to predict which patients will benefit most from adjuvant treatments (6-10). Postoperative radiation therapy (PORT) was commonly employed for resected pN2 NSCLC patients in order to reduce LRR and increase OS based on the results of randomized controlled trials, which didn't prove a clear detrimental effect of PORT in this setting. The presentation of the primary endpoint analysis of Lung ART trial at ESMO 2020 changed the attitudes of radiation oncologists, as for the first time the efficacy of PORT for pN2 NSCLC was questioned (11). Furthermore, the spread of the COVID-19 pandemic during the last years affected lung cancer patients more than others, as they were considered more fragile and with a higher risk to develop severe respiratory symptoms. This pushed clinicians to decrease hospital access and to reduce, where possible, those treatments with a high pulmonary toxicity rate. Considering all those issues, this narrative review wants to answer whether PORT is still a role for resected pN2 NSCLC and give practical advice for the clinical management of these patients.

Objectives

This narrative review aimed to assess the current role of PORT for resected NSCLC patients, taking into account the recent results of the Lung ART trial in the scenario of the COVID-19 pandemic. An analysis of the main trials evaluating the efficacy of PORT was performed, focusing on the limitations and weak points of these studies. The major breakthroughs from the Lung ART trial were reported to update these patients' practical management.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-21-31/rc).

Methods

A literature search of PubMed was performed to identify publications pertaining PORT for NSCLC. The keywords used for the research were PORT, postoperative radiation therapy, resected NSCLC, pN2 NSCLC and adjuvant radiotherapy. Prospective and retrospective published and unpublished trials, systematic and narrative review and meta-analysis were included. No limits regarding the years of publication were applied, while only papers written using the English language were accepted. The results concerning the Lung ART trial come from the online library of ESMO 2020 and ESMO 2021 conferences. Eleven published and unpublished trials, two meta-analyses and a real-world clinical series were included in the final analysis.

Discussion

The Lung ART trial primary end points analysis (11)

The primary endpoint analysis of the randomized Lung ART trial has been presented at ESMO 2020 conference. The study aimed to evaluate the role of PORT in NSCLC patients with N2 involvement. It was initiated in 2007, and the inclusion criteria were completed resected NSCLC with N2 proved nodal involvement. Patients needed to be eligible for pre-operative or postoperative chemotherapy. Enrolled subjects were randomized to control *vs.* conformal PORT delivered at the dose of 54 Gy in 27 fractions. The stratifications factors were the center, administration or not of neo-adjuvant or adjuvant chemotherapy, histology, the extent of mediastinal lymph node involvement (0 *vs.* 1 *vs.* 2+) and the use of pre-treatment positron emission tomography (PET) scan. The primary endpoint was disease-free survival (DFS), while secondary endpoints were OS, the pattern of relapse, local failure, second cancers and treatment-related toxicities. The initial target accrual was 700 patients to show a 10% of improvement at 3-year DFS. In 2017, because of the start of several trials with neo-adjuvant immunotherapy and also because of an accrual slower than expected, it was decided to lower patient recruitment at 500 to show a 12% of difference at 3-year DFS. The statistical study hypothesis was that the 3-year DFS should improve from 30% of the control arm to 42% of the PORT arm with a hazard ratio (HR) =0.72. The analysis was performed on the Cox model

adjusted on the stratification factors. Five hundred and one patients were included in the final analysis in a little bit over 10 years, while for the safety analysis, only 487 patients were considered. The median follow-up was 4.8 years. The two populations were well balanced. About 34% of patients were single N2 NSCLC. The vast majority of the population was adenocarcinoma and received neo-adjuvant or adjuvant chemotherapy. The majority of patients had a lobectomy, the median size of tumor was about 34 mm, and most patients (about 98%) were pN2. The most involved nodal sites were stations 4 and 7 (for right side) and stations 5 and 7 (for the left side). In terms of PORT, the compliance to radiotherapy was good, and the main parameters regarding lungs and heart were well respected. The main PORT techniques were 3D conformal radiotherapy in 89% of cases and intensity-modulated radiation therapy (IMRT) for the other 11%. The results showed a 3-year DFS rate in the control arm of 43.8% *vs.* 47.1% in the PORT group, with a median DFS of 22.8 *vs.* 30.5 months for the control and PORT arm, respectively; HR =0.85; 95% confidence interval (CI): 0.67–1.07; P=0.16. The 3-year OS was 68.5% in control and 66.5% in the PORT group, confirming no significant differences in OS or DFS between the two arms. Looking at the DFS components in terms of the first event the authors observed that 46% of patients in the control arm had a mediastinal relapse *vs.* 25% in the PORT group. At the same time, there were more death events in the PORT arm, 13 out of 21 deaths were related to cardiopulmonary or PORT toxicity. In terms of variation of treatment effects according to the stratification factors a trend of outcomes in favor of PORT was observed but this was not significant. No difference in terms of OS was seen between the two arms, but there were more deaths related to recurrence or progression in the control arm. In contrast, more deaths related to cardio-pulmonary causes were observed in the PORT group, 3 of which were due to treatment toxicities. In terms of safety, most toxicities were G1 or G2, and as expected, there were more early G3–4 and late G3–4 toxicities in the PORT arm. In particular, 14.6% *vs.* 8.9% of G3–4 late toxicity and 11.6% *vs.* 7.7% early G3-G4 toxicity were observed in the PORT *vs.* control arm, respectively. In terms of G5 late toxicity, there was no difference in the two arms. Second cancers and possible late cardiopulmonary toxicities were more frequent in the PORT arm, and these findings will be issues for further deeper analysis by the authors. The authors conclude that PORT cannot be recommended anymore for stage IIIA pN2 completely resected NSCLC. An update of Lung ART trial was reported at ESMO 2021 conference (12). The results showed that PORT was associated with a significant improvement of the 3 years mediastinal relapse with 86.06% (81.2–89%) *vs.* 72.26% (65.9–77.4%) in the PORT and control arm, respectively. No impact of PORT on 3 years metastatic free survival was observed. Quality of resection, the extent of mediastinal involvement and lymph node ratio (involved/explored) were identified as significant prognostic factors for DFS.

The Lung ART trial represents the first phase III randomized study questioning the efficacy of PORT for resected pN2 NSCLC. The study methodology was very well structured: PORT was administered following the currently available guidelines, using proper doses (54 Gy in 27 fractions) and proper modern radiotherapy techniques [3D conformal radiation therapy (RT) and IMRT]. The two study populations were well balanced without significant clinical and pathological characteristics differences. These factors ensure the reliability and accuracy of the obtained results. The higher rate of observed cardio-pulmonary toxicities in the PORT arm may be explained by the most frequent use of 3D conformal radiotherapy (89%) compared to IMRT (11%), which is notably associated with a lower rate of damage to organs at risks. Final results showed that PORT was associated with an increased DFS, although the results were not statistically significant for the study hypothesis, without a significant impact on OS. It may suggest the presence of a subgroup of patients who could benefit from PORT, whose characteristics needed further investigations to be defined.

PORT employment before ESMO 2020

The first meta-analysis, which defined the role of PORT for completely resected NSCLC, was published in 1998 and evaluated 9 among published and unpublished randomized trials (13). Two thousand one hundred and twenty-eight patients affected by NSCLC stage I to IIIA were randomized to receive PORT *vs.* no immediate further treatment, included chemotherapy (14-22). The median dose used for PORT was between 30 and 60 Gy given in 15 to 30 fractions. After a median follow up of 3.9 (range, 2.3–9.8) years a clear pattern in favor of surgery alone was found both in terms of OS (HR =1.21; 95% CI: 1.08–1.34; P=0.001), loco-regional free survival (LRFS) (HR =1.16; 95% CI: 1.05–1.29; P=0.005) and DFS (HR =1.13; 95% CI: 1.02–1.23; P=0.007). A detriment of 7% at 2 years corresponding to a reduction in OS from 55%

Table 1 Trials characteristics summary

Study	Recruitment	Number of patients	Stage	Total dose (Gy)	Fractions	Machine
Belgium (5)	1966–1977	202	I, II, III	60	30	Cobalto 60
LCSGS 773 (6)	1978–1985	230	II, III	50	25–27.5	Cobalto 60 + Linac
CAMS 12 (7)	1981–1995	317	II, III	60	30	Cobalto 60 + Linac
Lille 13 (8)	1985–1991	163	I	45–60	22.5–30	Cobalto 60 + Linac
EORTC 08861 (12)	1986–1990	106	II, III	56	28	Linac
MRC LU 11 (9)	1986–1993	308	II, III	40	15	Cobalto 60 + Linac
GETCB 04CB86 (11)	1986–1994	189	I, II, III	60	24–30	Cobalto 60 + Linac
Slovenia (10)	1988–1992	74	III	30	10–12	Cobalto 60 + Linac
GETCB 05CB88 (11)	1988–1994	539	I, II, III	60	24–30	Cobalto 60 + Linac
The Italy trial (12)	1989–1997	104	I	50.4	28	Linac
The Korea trial (13)	1989–1998	111	III	50.4–55.8	28–31	NR
Lung ART trial (3)	2007–2018	501	II, III	54	27	Linac

to 48% was found. Eighty-one percent of deaths were attributed to NSCLC, 4% to treatment and 15% to other causes. Notably, all radiotherapy treatments included large volumes and obsolete techniques no more standard. Subgroups analysis confirmed clear detrimental effects of PORT for stage I and II NSCLC, while no clear evidence of detriment was observed for stage IIIA pN2 disease (P=0.005). The authors concluded that PORT cannot be routinely recommended in completed resected early-stage NSCLC and should be considered only for pN2 patients. Although this meta-analysis defined PORT as the standard treatment for pN2 NSCLC patients, it was very criticized. Patients enrolled were treated after 1965 with radiotherapy techniques no longer considered standards, such as cobalt machine, single field delivery and large daily fractions. Moreover, most trials used a total dose now considered palliative for NSCLC. The data collected from this meta-analysis were afterwards updated with the addition of two trials, the Italy trial and the Korea trial (23,24). Trials characteristics are summarized in *Table 1*. A total of 2,343 patients treated after 1965 were included. After a median follow up of 4.4 (range, 2.3–11.4) years surgery alone showed improved outcomes both in terms of OS (HR =1.18; 95% CI: 1.07–1.31; P=0.001), LRFS (HR =1.12; 95% CI: 1.01–1.23; P=0.003) and DFS (HR =1.13; 95% CI: 1.02–1.24; P=0.002). A detriment of 5% at 2 years corresponding to a reduction in OS from 58% to 53% was found in the PORT arm. Eighty-two percent of deaths were attributed to NSCLC, 4% to treatment and 14% to other causes. The most important updates of this meta-analysis regarded the stage disease, converted from IV to VI TNM edition, and the use of the Fisher test to assess the possible treatment bias (25). The major impact was that patients previous classified as T3N0M0, stage IIIA, were reclassified as stage IIB. This analysis put an end to the use of PORT for pN0 and pN1 patients and define the pN2 population as the subjects for further investigations.

Many other authors tried to investigate the role of PORT for pN2 NSCLC. Robinson *et al.* published a real-world clinical series of patients who underwent to complete surgical resection and adjuvant chemotherapy from 2006 to 2010 (26). They identified 4,483 patients from the National Cancer database, 1,850 treated with PORT with doses ranging from 45 to 60 Gy and 2,633 without PORT (control arm). After a median follow-up of 22 months on univariate analysis factors associated with improved OS were younger age, treatment at an academic facility, female sex, urban population, higher income, lower Charlson score, smaller tumor size, multi-agents chemotherapy, resection with at least a lobectomy and the use of PORT. The positive effect of PORT on OS was also confirmed at multivariate analysis. These results reinforced the role of PORT for pN2 NSCLC patients especially when modern radiotherapy techniques are employed.

Although this was considered the best evidence on PORT before the Lung ART trial, many biases are

detectable in the included trials. First of all, the patient selection including a very heterogeneous population as for clinical and for disease characteristics (es: from stage I to III); secondly, patients were randomized to PORT *vs.* no further treatments, which is not the standard of care for stage II and III NSCLC for whom adjuvant chemotherapy remains the standard of care; thirdly the employed dose, fractionations, radiotherapy volumes and techniques were obsolete and obviously associated with a higher rate of related toxicities and deaths. Furthermore, a clear benefit was never reached, even from the meta-analysis, and the validation of the use of PORT for pN2 completely resected NSCLC based on a not demonstrated detrimental effect. Despite the value of the meta-analysis, the data supporting the use of PORT were not consistent, considering the poor methodology and the study design of the included trials.

The importance of modern radiotherapy techniques

The impact of radiotherapy techniques on outcomes was further investigated by two meta-analyses. Billiet *et al.* (27) analyzed 11 randomized trials with a total of 2,387 patients (14,15,17-21,23,28,29): one trial used cobalt only, six both cobalt and linear accelerators and four linear accelerators only. The median follow-up ranged from 30 to 63 months, and the total dose ranged from 50 to 60 Gy, delivered with conventional fractionation. The authors found that, on the whole population, PORT significantly improved OS only when administered with linear accelerators (P=0.002). Eight trials were suitable to assess LRR with a total of 1,677 patients. Only 3 of these trials used modern radiotherapy techniques. Authors found that LRR decreased with PORT, and this was most significant in the group treated with linear accelerators (P=0.01).

Similar findings have been reported from another meta-analysis by Patel *et al.* (30). The authors included 11 prospective and retrospective studies, with a total of 2,728 patients with pN2 disease, among which 1,360 received PORT from 1982 and 2005 (7,27,29,31-38). Thirty-seven percent of patients received platinum-based adjuvant chemotherapy across 7 of the included trials. Radiotherapy volumes covered bronchial stump, hilum and mediastinum. The results showed that PORT was associated with increased OS (P=0.02) and a reduction of the LRR (P<0.001). The most common related toxicities were mild esophagitis, dysphagia, odynophagia with no severe adverse events observed. These findings suggest that, as expected, radiotherapy techniques have a strong impact on outcomes. The use of modern linear accelerators may improve the OS and LRR, reducing treatment-related toxicities.

PORT: when to use it?

Although surgical resection is the mainstay for early-stage NSCLC patients, from 1% to 17% result for positive surgical margins or gross tumor residual (39,40). As already discussed, many studies concluded that PORT should not be recommended for pN0 and pN1 disease but no study has specifically investigated the role of PORT for the subgroup of patients with residual disease. Thus Wang *et al.* (41), identified 3395 patients from the National Cancer Database treated with surgical resection from 2003 and 2011, resulting in pN0–2 positive margins disease, defined as follows: R1: microscopic or R2: macroscopic residual disease. PORT was delivered in 1,207 patients using dose ≥50 Gy and IMRT or 3D conformal radiotherapy or megavoltage photon external beam radiotherapy. A total of 1,892 patients had R1 disease, 129 R2 and 1,374 were defined as a residual disease not otherwise specified (NOS). At survival analysis, 1,304 patients were included, and the use of PORT resulted in an improved OS, 33.5 months in the PORT arm *vs.* 23.7 months in the control arm (P<0.001), respectively. Stratifying by nodal stage, PORT significantly improved OS for pN0, pN1 and pN2 patients. Examining the effect of doses, patients who received dose >70 Gy resulted in a similar OS to those not receiving PORT. In conclusion, the authors found that the use of PORT for pN0–2 incompletely resected NSCLC showed a significant benefit in OS. In the absence of randomized trials these findings suggest that PORT should be carefully evaluated in selected NSCLC patients with the incompletely resected disease.

Another important factor to consider in evaluating PORT is the presence of extranodal extension (ENE) defined as the extension of metastatic cells through the nodal capsule into the peri-nodal tissue. A systematic review and meta-analysis published in 2017 showed a negative prognostic role of the ENE for R1 resected NSCLC patients (42). Thirteen prospective and retrospective trials with a total of 1,709 patients (573 ENE+ *vs.* 1,136 ENE–) were included. After a median follow-up of 60 months, the authors found that the presence of ENE was associated with a significantly higher risk of death, HR =1.3, 95% CI: 1.01–1.67, P=0.04, and with a higher risk of disease recurrence, HR =1.93, 95% CI: 11.53–2.44, P<0.0001. A prospective trial evaluated the impact of ENE in 80 R1

resected NSCLC patients (43 ENE– *vs.* 37 ENE+), treated with PORT from 2002 and 2011 (43). Patients with ENE+ were mostly adenocarcinoma and presented a higher stage of disease (II and IIIA). Patients with pN2 involvement underwent elective nodal irradiation that was optional for the pN0–1 patients. The clinical target volume (CTV) included the bronchial stump, the pathologically involved nodes and the elective nodal stations with a high probability of microscopic invasion; prescribed doses ranged from 50 to 60 Gy delivered in fractions of 2 Gy. After a median follow-up of 42 months, the median OS was 31 *vs.* 24 months for ENE– and ENE+ patients, respectively. The ENE was confirmed to be a significant negative prognostic factor for OS, HR =3.02, 95% CI: 1–9.16, P=0.05. Locoregional failure was 14.5% in ENE– *vs.* 14.1% in ENE+ patients, while distant failure was 37.5% *vs.* 49% in ENE– and ENE+ patients, respectively. For pN0–1 patients, the use of PORT showed an improvement in locoregional failure rate, 7.7% *vs.* 20.8% in PORT– *vs.* PORT+, respectively, P=0.2. In conclusion, the authors found that the presence of ENE is associated with a worse OS and that the distant failure remains very high for ENE+ patients. The omission of nodal irradiation for pN0–1 ENE+ patients is associated with an unacceptable local failure rate. These findings suggest that PORT should be considered for ENE+ R1 resected NSCLC patients even with pN1 disease.

How COVID-19 pandemic impact the management of NSCLC patients?

No reports are available regarding a higher incidence of SARS-Cov-2 infections in cancer patients, but limited data from China and more recently from Italy and USA seem to confirm that older people and patients affected by chronic diseases such as cancer are more vulnerable. ESMO recommendations for cancer patients management during COVID-19 pandemic suggest that the Benefit/Risk ratio of cancer treatments may need to be considered carefully (44). The categories at increased risk are just patients who receive chemotherapy and extensive field thoracic radiotherapy. For these reasons, ESMO guidelines suggest giving priority to adjuvant therapy in patients with resected high-risk diseases who are expected to derive a significant survival benefit. Considering the new findings from the Lung ART trial, completely resected stage IIIA pN2 NSCLC patients are no longer deemed suitable to thoracic adjuvant radiotherapy. These results are even more recommendable during the COVID-19 pandemic. We can conclude that COVID-19 pandemic challenged the current indication for adjuvant treatments by leaning the clinicians to carry out only those treatments considered not deferrable and for whom a significant clinical benefit was expected. Thus PORT for completely resected pN2 NSCLC patients was no more considered an urgent and necessary adjuvant treatment.

Summary

Although since 1998, PORT had been considered the standard of care for completely resected pN2 NSCLC patients, the preliminary results of the Lung ART suggested that it could not be anymore recommended. This is more indicated in the scenario of COVID-19 pandemic where unnecessary treatments have to be avoided and cancer patients protected. In conclusion, PORT should be reserved only for well selected incompletely resected NSCLC patients and for patients with ENE. The long-term results of the Lung ART trial are awaited to understand if there is a subgroup of completely resected patients who still benefit from PORT. Future research should focus on incompletely resected patients, prospective randomized trials are much needed for this setting. Further studies about the possible use of hypofractionated or stereotactic radiotherapy on micro or macro residual of disease are also warranted. Although Lung ART trial seems to put an end to PORT, many questions remains open and future research are necessary.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Giuseppe Banna and Alfredo Addeo) for the series “Changes in management of mediastinal tumours following the surge of COVID-19 pandemic” published in *Mediastinum*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-21-31/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-21-31/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-21-31/coif). The series "Changes in management of mediastinal tumours following the surge of COVID-19 pandemic" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/med-21-31
Cite this article as: Olmetto E, Perna M, Cerbai C, Aquilano M, Banini M, Mariotti M, Livi L, Scotti V. A narrative review of postoperative adjuvant radiotherapy for non-small cell lung cancer. Mediastinum 2022;6:4.