Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: A meta-analysis

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A B S T R A C T

Background: We hypothesized that modern postoperative radiotherapy (PORT) could decrease local recurrence (LR) and improve overall survival (OS) in patients with stage IIIA-N2 non-small-cell lung cancer (NSCLC).

Methods: To investigate the effect of modern PORT on LR and OS, we identified published phase III trials for PORT and stratified them according to use or non-use of linear accelerators. Non-individual patient data were used to model the potential benefit of modern PORT in stage IIIA-N2 NSCLC treated with induction chemotherapy and resection.

Results: Of the PORT phase III studies, eleven trials (2387 patients) were included for OS analysis and eight (1677 patients) for LR. PORT decreased LR, whether given with cobalt, cobalt and linear accelerators, or with linear accelerators only. An increase in OS was only seen when PORT was given with linear accelerators, along with the most significant effect on LR (relative risk for LR and OS 0.31 (p = 0.01) and 0.76 (p = 0.02) for PORT vs. controls, respectively).

Four trials (357 patients) were suitable to assess LR rates in stage III NSCLC treated with surgery, in most cases after induction chemotherapy. LR as first relapse was 30% (105/357) after 5 years. In the modeling part, PORT with linear accelerators was estimated to reduce LR rates to 10% as first relapse and to increase the absolute 5-year OS by 13%.

Conclusions: This modeling study generates the hypothesis that modern PORT may increase both LR and OS in stage IIIA-N2 NSCLC even in patients being treated with induction chemotherapy and surgery.

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Despite advances in treatment, lung cancer remains the leading cause of cancer mortality in most countries [1,2]. About one third of patients with non-small cell lung cancer (NSCLC) presents with locally advanced non-metastatic disease (stages IIIA and B) [3]. Current 5-year survival rates in this heterogeneous stage group are about 20–25% when patients are treated with combined modality treatments including chemotherapy, radiotherapy, and/or surgery [4–6]. In the majority of cases concurrent chemoradiation is used as treatment. Patients with potentially resectable stage IIIA-N2 can be treated with induction chemotherapy followed by radical surgery. Prospective studies report 5-year survival rates from 20% to 30%, with about 30% of the patients reporting local recurrence (LR) [7–9].

Several phase III trials investigated the role of post-operative radiotherapy (PORT) after surgical resection in NSCLC. The PORT

Meta-analysis Trialist Group reported a meta-analysis based on individual patient data of both published and unpublished trial data [10]. For the whole patient group, PORT decreased the survival at two years by 6% (52% vs. 58%), although there may be a role for PORT in patients with N2 disease. The deleterious effect of PORT has been attributed to an excess of intercurrent deaths, with a high incidence of cardiac and respiratory complications due to poor radiotherapy techniques [11,12]. In support of this hypothesis, several more recent trials with contemporary radiation techniques did not report an increase of death from intercurrent disease [13–19]. Kepka et al. did not detect a difference in QoL scores, cardiopulmonary morbidity or non-cancer related deaths between patients receiving PORT and those treated with surgery alone [19].

In a literature based meta-analysis, we investigated the effect on LR and overall survival (OS) of PORT given with modern techniques. Then we modeled the possible gain with PORT in view of the present-day still high LR rates after induction chemotherapy and resection in patients with stage IIIA-N2 NSCLC.
Methods

Literature based meta-analysis

A MEDLINE search was done to identify published phase III studies including patients with completely resected and pathologically documented stage I to III NSCLC, recruited after January 1, 1965, and randomly assigned to a control group or a group with PORT. Trials were listed as to whether PORT was given with cobalt only, linear accelerators (LINAC) only, or a combination of both. Beam quality was thus used as a surrogate for more contemporary patient selection and therapy. The relative risk (RR) was computed for the overall survival and local tumor failure. A follow up time of minimum two years was required. Chi-square heterogeneity tests were used to test for statistical heterogeneity among trials. As we anticipated that the trial results would be heterogeneous, all analyses were performed using a random effects model. The biological equivalence of the radiotherapy schedules was calculated. We used the equivalent dose in 2-Gy fractions without (EQD2) or with correction for the overall treatment time (EQD2,T), which was calculated in two steps [20]. First, an adjustment for dose per fraction was made:

\[
\text{EQD}_2 = D \cdot \left( \frac{d + \frac{\delta}{2}}{2 + \frac{\delta}{2}} \right)
\]

where \(D\) is the total radiation dose, \(d\) the dose per fraction and \(\delta = 10\) Gy for the tumor [21].

To take into account proliferation of tumor cells, we used the formula:

\[
\text{EQD}_{2T} = \text{EQD}_2 - \text{MAX}\left(\frac{T - T_k}{T_k}, 0\right) \cdot D_{\text{prolif}}
\]

where \(T_k\) is the kick-in time of accelerated repopulation, assumed in our case to be 30 days. The function \(\text{MAX}(T - T_k, 0)\) will have the value of \(T - T_k\) if this difference is positive, and zero in all other cases. The parameter \(D_{\text{prolif}}\) is the dose recovered per day. For this parameter we used \(D_{\text{prolif}} = 0.66\) Gy per day [21].

The correlation between the radiotherapy parameters total dose, EQD2, for tumor, EQD2,T for tumor, EQD2 for the lungs and the dose per fraction and the RR for survival and for local tumor failure were calculated using Spearman’s two-tailed test.

Based on the published results of OS in the phase III trials using linear accelerators only, we used the RR to graphically depict the theoretical gain in absolute percentage on overall survival with PORT in stage I to III NSCLC. Results are based on non-individual patient data. They are expressed as mean ± 95% confidence intervals. Standard error and upper and lower limits of the 95% confidence intervals were calculated, \(p\)-values of less than 0.05 were considered to be significant.

Statistical analyses for the meta-analysis were performed with RevMan (Review Manager), Version 4.2 for Windows.

Modeling of the effect of PORT on LR and OS after induction chemotherapy

We performed another MEDLINE search to identify recently published data investigating locoregional recurrence in stage IIIA-N2 NSCLC treated with a surgical resection, in most cases following after induction chemotherapy. Trials were eligible for inclusion provided that they were prospective, that the study population was at least 40 patients with at least 2 years of follow-up and that cisplatin-based chemotherapy was used in case chemotherapy was administered. We included only trials from the year 2000 until October 30, 2012.

From the collected data we calculated the mean of the first relapse rates. 95% confidence intervals were calculated. These results were used as a starting point in the hypothesis-generated model specifically in stage III NSCLC. To get an estimation of the effect of a decrease of local recurrence on overall survival, to the best of our knowledge, for N2 NSCLC, the most robust data come from a meta-analysis based on individual patient data comparing sequential and concurrent chemotherapy and radiotherapy [22]. In this study, a decrease in LR of 6% favoring the concurrent approach, without differences in the incidence of distant metastases was observed. This 6% absolute gain in LR was translated into a 4.5% absolute benefit in OS at 5 years. Although these results were obtained in non-surgical patients, we used these figures for the current modeling. \(p\)-Values of less than 0.05 were considered to be significant.

Results

Eleven randomized phase III trials, with a total of 2.387 patients, were included for survival analysis [23–33]. One trial used Cobalt only [23], six both Cobalt and linear accelerators [24–29], and four linear accelerators only [30–33]. The trial characteristics and the biological equivalence of the radiotherapy schedules used are listed in Table 1. Mostly doses between 50 and 60 Gray (Gy) delivered in conventional fractionation were used. The mean follow up time ranges from 30 to 63 months. For the whole group, there was no improvement in OS with PORT (RR 1.02 (95% CI 0.84–1.24), \(p = 0.84\)). PORT only significantly improved OS when given with linear accelerators (RR 0.76 (95% CI 0.61–0.95), \(p = 0.02\)) (Fig. 1). Using this relative risk ratio we calculated the theoretical gain in absolute percentage on overall survival with modern PORT in stage I–III NSCLC (ex. 1/0.76 = 1.32) (Fig. 2).

Eight randomized phase III trials, for a total of 1.677 patients were suitable to assess LR rates [23–31,33]. Three trials used linear accelerators only, LR rates in these more recent series were 27.0% (10/37), 23.6% (17/72) and 22.6% (12/53), respectively [30,31,33] in the group without PORT, and thus very consistent. LR rates significantly decreased with PORT using either beam quality (Fig. 3). The most significant decrease was observed in the group treated with linear accelerators only, with a relative risk (RR) of 0.31 (95% CI 0.12–0.79, \(p = 0.01\)).

Four trials within a total of 357 patients, with N2 involvement treated with surgery and in most cases induction chemotherapy, were identified for LR analysis [34–36,7]. The mean LR rate as first relapse at 5 years was 105/357 (29.4%) (95% CI 0.26–0.32) (Table 2). In three trials patients received induction chemotherapy, consisting of three cycles of a platinum based regimen [34,35,7]. LR rates were about 30% in all four trials, although in the trial of Pepek only surgery was performed [36]. In two trials postoperative radiotherapy was given in the case of incomplete resection or involvement of the upper mediastinal lymph nodes [34,7]. Cumulative recurrence rate was only reported in one trial [34]. In this trial, the cumulative LR rate was 60.0% (45/75) (95% CI 0.57–0.63) after a mean follow up of 5 years.

Based on the previous results, a hypothesis-generating modeling study was performed. We have shown that modern PORT with linear accelerators reduces LR rates with a RR of 0.31. These results are based on general outwaited studies. Using current LR rates in stage III NSCLC patients, we hypothesize that PORT might reduce first and cumulative LR rates from 30% and 60% without PORT to 10% and 20% with the addition of PORT, respectively.

Based on the results of Auperin et al. [22], we more conservatively assumed that two thirds of the increase in LR rates (LR from 30% to 10% with PORT = 20% absolute gain) would lead to improved OS of 13% (≈20%×2/3) at 5 years.

Discussion

The current standard of care for most patients with IIIA-N2 NSCLC patients is concurrent chemoradiotherapy [37]. However,
long-term outcomes with this treatment are poor, due to a high rate of distant metastases and of local recurrence. In an individual patient meta-analysis, Aupérin et al. reported local tumor progression in 36% of patients with locally advanced NSCLC treated with concurrent chemoradiation [22]. The true incidence of LR when more thoroughly assessed, is even higher [38]. Importantly, this meta-analysis demonstrated that about two-thirds of the magnitude of improvement in local control was translated in improved overall survival.

An alternative option is using surgery as part of the treatment in potentially resectable patients, most frequently after induction chemotherapy that has resulted in downstaging [39–41]. Several phase II studies showed 5-year survival rates of about 20–30% in these patients [7,34], which is in the same range as treatment with concurrent chemoradiation. However, still about 30% of patients have local tumor failure as first site of recurrence, even after downstaging with chemotherapy [7,8,34,42]. In view of the suboptimal LR rates both after induction chemotherapy and surgery and after concurrent chemoradiotherapy, we hypothesized that a tri-modality approach combining chemotherapy, radiotherapy and surgery may be worth investigating. Although most recent series report on induction chemoradiotherapy followed by surgery [43,44], a viable alternative could be sequential chemotherapy, surgery and postoperative radiotherapy (PORT), the latter tailored according to risk groups for local recurrence. This strategy would allow optimization of the systemic treatment, which may be hampered when delivered concomitantly with radiotherapy, and avoids possible increased complications with preoperative radiotherapy.

The results of the PORT meta-analysis group [10] showed however a detrimental effect of PORT when all patients with completely resected NSCLC were considered [45]. Also a recent update of this meta-analysis, adding two trials, could not demonstrate

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th># Patients</th>
<th>Stage</th>
<th>Beam quality</th>
<th>Dose/fraction (Gy)</th>
<th>EQD2 (tumor) (Gy)</th>
<th>EQD2T (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium [23]</td>
<td>224</td>
<td>I–III</td>
<td>Cobalt only</td>
<td>60/30</td>
<td>60</td>
<td>50.76</td>
</tr>
<tr>
<td>CAMS [24]</td>
<td>317</td>
<td>II, III</td>
<td>Cobalt and Linac</td>
<td>60/30</td>
<td>60</td>
<td>50.76</td>
</tr>
<tr>
<td>GETCB 04CB86 [25]</td>
<td>189</td>
<td>I–III</td>
<td>Cobalt and Linac</td>
<td>60/24–30</td>
<td>60</td>
<td>50.76</td>
</tr>
<tr>
<td>GETCB 05CB88 [26]</td>
<td>539</td>
<td>I–III</td>
<td>Cobalt and Linac</td>
<td>60/24–30</td>
<td>62.50</td>
<td>57.88</td>
</tr>
<tr>
<td>LCC 773 [27]</td>
<td>230</td>
<td>II, III</td>
<td>Cobalt and Linac</td>
<td>50/25–28</td>
<td>50</td>
<td>43.38</td>
</tr>
<tr>
<td>Lille 1985 [28]</td>
<td>163</td>
<td>I</td>
<td>Cobalt and Linac</td>
<td>45–60/22–30</td>
<td>45</td>
<td>43.68</td>
</tr>
<tr>
<td>MRC LUI I [29]</td>
<td>308</td>
<td>II, III</td>
<td>Cobalt and Linac</td>
<td>40/15</td>
<td>42.23</td>
<td>42.23</td>
</tr>
<tr>
<td>Slovenia 1988 [30]</td>
<td>74</td>
<td>III</td>
<td>Linac only</td>
<td>30/10–12</td>
<td>32.50</td>
<td>32.50</td>
</tr>
<tr>
<td>Austria [31]</td>
<td>155</td>
<td>III</td>
<td>Linac only</td>
<td>50–56/28</td>
<td>50</td>
<td>45.38</td>
</tr>
<tr>
<td>EORTC [32]</td>
<td>106</td>
<td>II, III</td>
<td>Linac only</td>
<td>56/28</td>
<td>55.07</td>
<td>48.47</td>
</tr>
<tr>
<td>Italy [33]</td>
<td>104</td>
<td>I</td>
<td>Linac only</td>
<td>50.40/28</td>
<td>49.56</td>
<td>42.96</td>
</tr>
</tbody>
</table>

PORT, post-operative radiotherapy; Linac, linear accelerator; EQD2, equivalent dose at 2 Gy per fraction; EQD2T, equivalent dose at 2 Gy per fraction corrected for the overall treatment time; Tumor, α/β = 10 Gy; T, 30 days.

![Table 1](image)

**Table 1** Characteristics of the included studies using PORT.

**Fig. 1.** Overall survival as a function of the beam quality used. PORT, post-operative radiotherapy; RR, relative risk.
better results. However no data are available from these trials, leading to unreliable results [46]. Because of the recruitment of patients in the studies of the PORT meta-analysis went from 1966 to 1995, they included also patients treated with cobalt machines without CT-based planning. The excess of toxicity (mostly cardiac and pulmonary) and non-cancer related deaths observed in the post-operative radiotherapy arm of the trials included in the meta-analysis can probably be explained by excessive volumes of radiation, old radiation techniques, too large doses and fraction sizes [11,12]. Trials with contemporary radiotherapy techniques demonstrated that there was no increase of death from intercurrent disease [13–18]. A recently published non-randomized trial could not detect a difference in cardiopulmonal morbidity or excess in non-cancer related deaths between patients receiving 3D-planned PORT in comparison to a control group [19]. Modern radiotherapy can thus probably be delivered with acceptable toxicity, on the condition that advanced radiation techniques are used as well as a clinically and biologically individualized treatment can be accomplished [47,48]. Recent trials with different fractionation schedules or radiation dose escalation revealed promising results for further optimizing radiotherapy, alone or in the context of chemoradiation. A phase III trial (CHART) showed an improved survival after continuous hyperfractionated accelerated radiotherapy compared to standard fractionation in NSCLC patients [49]. The CHARTWEL trial could not confirm these results, but however demonstrated a significant trend for a decrease in LR [50]. With individualized, isotoxic, accelerated radiotherapy (INDAR) biological doses of over 80 Gy can be delivered, but with toxicity levels that are comparable to 65 Gy [51]. Results show an increase in both the median survival as well as the 5-year survival rates of patients with stage III NSCLC. Another important parameter of radiotherapy quality is the time factor. Delay before the start of treatment as well as overall treatment time can influence the outcome [52].

We therefore hypothesized that the distinction between Cobalt vs. linear accelerators could be used as a very rough estimate of the radiation treatment quality. We performed a literature study for phase III trials comparing surgery with or without PORT in stage I–III NSCLC. Results from these non-individual patient data show a significant decrease of LR and increase in OS when this treatment was delivered with linear accelerators [23–29,31–33] even though these series were performed in the beginning of the 1990’s and radiotherapy has improved much since then [53]. Modern PORT decreased the risk for LR (RR 0.31; p = 0.01) and death (RR 0.76; p = 0.02). This is in line with a population-based cohort study including 17485 patients with stage II and III resected NSCLC [54], in which PORT was suggested to improve the 5-year survival of N2 patients from 20% to 27% after surgical resection. Also in this study, it was pointed that most patients were probably treated with linear accelerators, as the inclusion period was from 1988 to 2002. Another trial using linear accelerators only, demonstrated a decrease in LR in patients with stage III N2 NSCLC receiving PORT compared to surgery alone [55]. A subgroup analysis of the ANITA trial suggests that PORT may indeed improve long-term survival [56].

**Fig. 2.** Estimated benefit on OS with Linac-based PORT. Theoretical gain in absolute percentage in overall survival at 5 years. Results are expressed as mean ± 95% confidence intervals. OS, overall survival; LR, local recurrence; PORT, post-operative radiotherapy.

**Fig. 3.** Local tumor failure as a function of the beam quality used. PORT, post-operative radiotherapy; RR, relative risk.
Having estimated the theoretical gain of PORT on LR and OS, we reviewed recent studies from the year 2000 onward to gain insight in current local recurrences after surgery particularly for the stage IIA-N2 disease. Only prospective trials were included. Overall, the mean LR rate as first relapse was 29% after 5 years, with cumulative rates of 60%, reported in one trial (Table 2) [34–36,7]. Unfortunately, only limited data on this particular endpoint were found in the literature. The only study of Lou et al. included patients treated with induction chemotherapy and followed by surgery in the case of nodal downstaging, resulting in a 30% LR rate without adding PORT [35].

We estimated that with Linac-based PORT, LR rates could be reduced from 30% to 10%. In the phase III study of Thomas et al. in patients with locally advanced NSCLC – most patients probably having quite a bulky lymph node spread in the arm with PORT – LR rates were 20% after induction chemotherapy and surgery, which is in line with our assumptions [57]. According to our estimations, in stage IIA-N2 NSCLC patients, Linac-based PORT could increase the absolute overall survival by 13%. In the ANITA trial, the addition of PORT to resection and adjuvant chemotherapy increased the 5-year survival from 34% to 47% in pN2 disease, which is very close to our assumptions [56].

This study has many limitations and should therefore be considered merely hypothetical. First, no individual patient data were used and many assumptions were underlying our estimations because no direct comparisons between the different treatment modalities are available in the literature. The ongoing randomized phase III trial Lung Adjuvant Radiotherapy Trial (Lung ART), comparing 3D conformal PORT to no PORT in pathological N2 NSCLC, will hopefully shed new light on this dilemma [58]. Second, the phase III studies were performed before PET-CT scans and minimal invasive staging was available. The use of PET-CT can result in an upstaging of patients, because of the superiority over other imaging techniques in staging both nodal and metastatic diseases. Third, even the Linac-based radiotherapy techniques used in these studies are, according to current standards, outdated. Unfortunately this makes the comparability restricted, this is seen in the significant p-values of the test for heterogeneity of the included studies. As a consequence this makes the implementation in clinical practice less reliable, however we may expect an even more pronounced effect after these recent enhancements in staging and treatment techniques.

In conclusion we believe that PORT deserves an in-depth investigation in terms of LR, OS and overall toxicity in patients with stage IIA-N2 disease even in patients having received induction chemotherapy and a complete surgical resection after downstaging.

Conflict of interest

None.

Table 2
Characteristics of the included studies reporting locoregional recurrence rates.

<table>
<thead>
<tr>
<th>Trial</th>
<th># patients</th>
<th>Stage</th>
<th>Treatment</th>
<th>LR at first relapse</th>
<th>Cumulative LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betticher et al. [34]</td>
<td>75</td>
<td>III-N2</td>
<td>CT(DC) – S (PORT&lt;sup&gt;a&lt;/sup&gt;)</td>
<td>29.3% (22/75)</td>
<td>60.0% (45/75)</td>
</tr>
<tr>
<td>Lou et al. [35]</td>
<td>153</td>
<td>III-N2</td>
<td>CT(PT) – S</td>
<td>30.0% (46/153)</td>
<td>–</td>
</tr>
<tr>
<td>Pepek et al. [34]</td>
<td>23</td>
<td>III</td>
<td>S</td>
<td>30.0% (7/23)</td>
<td>–</td>
</tr>
<tr>
<td>Lorent et al. [7]</td>
<td>106</td>
<td>III-N2</td>
<td>CT(VIP) – S (PORT&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>28.3% (30/106)</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>29.4% (105/357)</td>
<td>60.0% (45/75)</td>
</tr>
</tbody>
</table>

CT, chemotherapy; DC, docetaxel-cisplatin, 3 cycles; S, surgery; PORT, post-operative radiotherapy; PT, platinum-taxane chemotherapy, 3 cycles; VIP, vindesine-ifosfamide-cisplatin, 3 cycles.

<sup>a</sup> PORT in 23/75 patients, in case of R1/R2 resection or upper lymph node involvement.

<sup>b</sup> PORT in 19/75 patients after surgery in case of incomplete resection.

<sup>c</sup> Derived from %.

References


Post-operative radiotherapy for stage III NSCLC


