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*ORIGINAL ARTICLE*

# Correlates of benefit from neoadjuvant chemotherapy before radiotherapy in non-small cell lung cancer: a meta-analytical approach with meta-regression analysis

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## Summary

***Purpose:*** *Induction chemotherapy before radiotherapy, although inferior to concomitant chemoradiotherapy, is still used in clinical practice, and improves survival compared to radiotherapy alone in unresectable non-small cell lung cancer (NSCLC). In this setting, we assessed the predictors of benefit from neoadjuvant chemotherapy before radiotherapy.*

***Methods:*** *Searches were made for randomized clinical trials (RCTs) that compared neoadjuvant chemotherapy with no treatment, administered before definitive radiotherapy. Relative risk (RR) was employed to define the risk of death at 2 and 3 years. Additionally, meta-regression analysis was conducted to explain heterogeneity.*

***Results:*** *Thirteen RCTs to date, encompassing 2776 patients, were identified. In this updated meta-analysis, neoadjuvant chemotherapy significantly reduced the risk of death, both at 2 and 3 years (RR = 0.91 and 0.94, respectively, both $p < 0.001$). Additionally, time to radiotherapy was inversely associated with the benefit from neoadjuvant chemotherapy at 2 ($t = 2.20$, $p = 0.050$) and 3 years ($t = 1.84$, $p = 0.093$).*

***Conclusion:*** *This meta-analysis confirms the importance of neoadjuvant chemotherapy before radiotherapy and highlights the importance of shorter time to radiotherapy to maximize NSCLC patients' survival.*

**Key words:** chemotherapy, meta-analysis, meta-regression, neoadjuvant, non-small cell lung cancer, radiotherapy

## Introduction

NSCLC has a dismal outcome and even in patients with non-metastatic disease 5-year overall survival (OAS) is poor [1]. In the setting of locally advanced disease, usage of chemotherapy in conjunction with radiotherapy has been shown to improve clinical outcome [2]. Likewise, the contribution of neoadjuvant chemotherapy to both surgery and radiotherapy has also been shown in various trials [3,4]. However, the clinical correlates of benefit from neoadjuvant chemotherapy have not been thoroughly explored. In addition, some previous meta-analyses in NSCLC had analysed trials of neoadjuvant chemotherapy administered before surgery or radiotherapy together with concomitant and / or adjuvant chemotherapy [5,6]. Moreover, although concomitant chemotherapy yields better overall survival compared to sequential chemotherapy, and thus is the current standard in suitable patients, it is more toxic and, in clinical practice, only a portion of patients with locally advanced NSCLC can receive this kind of treatment [7]. It is probable that for a significant proportion of patients with locally advanced disease who are not candidates for concomitant chemoradiotherapy due to unfavorable features associated with increased toxicity like weight loss, and poorer performance status [8], sequential chemoradiotherapy may be a more tolerable approach. Indeed, in clinical practice sequential chemotherapy is still used in a significant subgroup of NSCLC patients with unresectable disease [9,10], and is recommended for selected patients by some of the current guidelines [11]. Therefore, for the purpose of this paper, we evaluated in NSCLC the associates of benefit from neoadjuvant chemotherapy administered before radiotherapy (sequential chemoradiotherapy), in the form of an updated meta-analysis

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of the published literature, primarily aiming to explore the associates of benefit from this approach.

## Methods

*Search methodology*

PubMed, Cochrane, ScienceDirect and Ovid databases were searched for RCTs that performed a direct comparison between a neoadjuvant regimen incorporating arm and a no-treatment arm, before definitive radiotherapy. In the identification of suitable trials, usage of adjuvant chemotherapy was allowed for the arm receiving neoadjuvant chemotherapy (i.e. intervention arm, sequential chemoradiotherapy), and interaction of the effect of neoadjuvant chemotherapy with that of adjuvant chemotherapy was also evaluated. However, for the arm not receiving neoadjuvant chemotherapy (i.e. control arm, definitive radiotherapy), we did not allow any further chemotherapy if the intervention arm in that trial did not also receive the same additional chemotherapy. We also did not allow further chemotherapy during radiotherapy, for example, during the break interval of the split course radiotherapy. In trials with an arm not relevant for the purpose of this meta-analysis, only the relevant arms were included in the analysis.

The search was limited to RCTs published in English after 1966. Unpublished data was not considered. Multiple search strategies were employed. Firstly, the key words (neoadjuvant OR induction) AND chemotherapy AND (lung OR pulmonary) AND (cancer OR carcinoma) were used for the primary search. Secondly, databases were searched for all RCTs conducted so far in NSCLC. Thirdly, relevant references of review papers and of the RCTs identified by search strategies were also obtained. Fourthly, the most recent editions of the major reference textbooks in the field of oncology were further referred to. Two medical oncologists, first independently and then collaboratively, reviewed potential abstracts and obtained full text papers of relevant trials for further review.

*Quantitative data synthesis*

We decided to use the RR for death to determine any survival advantage yielded by neoadjuvant chemotherapy at 2 and 3 years. The primary reason for this choice was that hazard ratio (HR) and its variance, regarded as the most appropriate summary statistics for the survival data [12], were not possible to calculate for some of the trials, and omission of these trials would lead to significant loss of information (519 out of 2776 cases; 19%) [13,14].

We utilized the Mantel Haenszel method in fixed and random effects models to define the summary RRs and their 95% confidence intervals (CIs). Proportions surviving at 2 and 3 years were obtained either from the text, or if this was not available, estimated from the survival curves.

Time to radiotherapy was defined as the time period from the onset of neoadjuvant chemotherapy up to the onset of radiotherapy. It was calculated for each trial by the addition of the total duration of neoadjuvant chemotherapy and the average waiting period for radiotherapy after the last cycle.

Subgroup analyses were conducted for categorical variables that could potentially be associated with the effect size. Specifically, the usage of additional adjuvant chemotherapy in the study design (present vs. absent), and the type of neoadjuvant chemotherapy (doublets/single agents vs. triplets, i.e. $\leq 2$ vs. $>2$ agents), cycles of neoadjuvant chemotherapy delivered (2 vs. more cycles), and trial quality (as assessed according to Jadad score [15]; $<3$ vs. $\geq 3$ (out of 5)), were subjected to subgroup analysis. The impact of these categorical moderator variables was assessed by Analysis of Variance (ANOVA) using Q values and fixed and random effects estimates, depending on the heterogeneity of trials.

Heterogeneity of trials was evaluated by $x^{2-}$ based Q tests. In addition, Forest plots were constructed. Begg's funnel plot was used to test possible publication bias in this meta-analysis.

Meta-regression analysis was conducted with a view to explain the variations in effect size, and to explore the associates of benefit from neoadjuvant chemotherapy [16]. For these analyses, robust regression analysis was preferred over least squares regression analysis, since robust regression analysis works with less restrictive assumptions, and performs better in the case of outliers in the data, as is the case with our data [17]. In these analyses, RR at 2 and 3 years was used as the dependent variable. Firstly, trial features like trial size and publication year, secondly, patient and disease factors like proportion of patients with stage 3 disease, proportion of male patients, mean / median age, and proportion of patients having squamous cell histology, and thirdly, time to radiotherapy as a treatment factor, were separately entered into the robust regression analysis. A p value $\leq 0.05$ was considered to be significant in all statistical tests.

We used Comprehensive Meta-Analysis software (version 1.0.25, www.Meta-Analysis.com) for this meta-analysis. Meta-regression analysis was conducted by NCSS 2004 software [17]. We adhered to "The Quality of Reporting of Meta-analyses" (QUOROM) state-

ment for the purpose of reporting better the results of this meta-analysis [18].

## Results

*Trial flow*

At the initial stage, 103 RCTs were evaluated. A total of 13 randomized clinical trials met the inclusion criteria [3,13,14,19-28].

Figure 1 clearly shows the reasons for exclusion of various trials. As indicated in Figure 1, 2 trials were omitted at the last stage due to usage of additional chemotherapy during the split course radiotherapy [29,30]. In addition, since one other trial which was an updated report on the failure patterns [31] had the same survival data as the original report [26], it was also not included in this meta-analysis. The total number of patients evaluated in this meta-analysis was 2776.

*Individual studies*

Among the original publications included in this meta-analysis, 3 trials had indicated superior OAS with the neoadjuvant approach, with statistical significance [22,24,26]. In one trial, although univariate analysis did not indicate a change in OAS, Cox analysis had revealed improved survival with the neoadjuvant chemotherapy [21]. In 7 trials, neoadjuvant chemotherapy had not led to a statistically significant change in OAS. In the remaining 2 trials, no statistical testing among the randomized arms had been carried out [13,14].

Additionally, 2 trials included adjuvant chemotherapy in their design [3,27]. There were a total of 13 toxic deaths attributable to neoadjuvant therapy among 1135 patients that received this treatment (1.2%). Table 1 displays the characteristics of RCTs included in this meta-analysis. Funnel plots did not reveal publication bias.

*Quantitative data synthesis*

Overall survival analysis

Neoadjuvant chemotherapy before radiotherapy significantly reduced the risk of death, both at 2 and 3 years. With the fixed model, the associated RRs for mortality were 0.91 (95% confidence interval (CI) = 0.87 - 0.94, $p < 0.001$) at 2 years, and 0.94 (95% CI = 0.92 - 0.97, $p < 0.001$) at 3 years. The amount of heterogeneity did not reach statistical significance at 2 ($x^2 = 15.33$, df = 12, $p = 0.224$), and 3 years ($x^2 = 17.46$, df = 12, $p = 0.133$). Figures 2 and 3 depict the forest plots at 2 and 3 years.

Subgroup analysis

The effect of neoadjuvant chemotherapy did not differ with respect to administration of adjuvant chemotherapy, type of chemotherapy received (with $\leq 2$ vs. >2 agents), number of cycles of neoadjuvant chemotherapy delivered (2 cycles vs. 3 or more), and trial quality (Jadad score $< 3$ vs. $\geq 3$). The details of the subgroup analysis are shown in Table 2.

Meta-regression analysis

Time to radiotherapy was inversely associated with the benefit from neoadjuvant chemotherapy with statistical significance at 2 years ($t = 2.20$, $p=0.050$) and with a tendency for statistical significance at 3 years (t

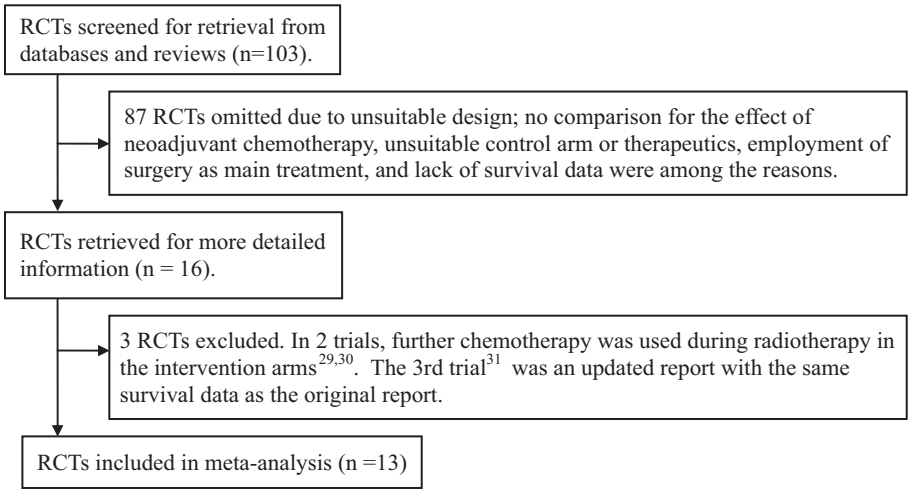


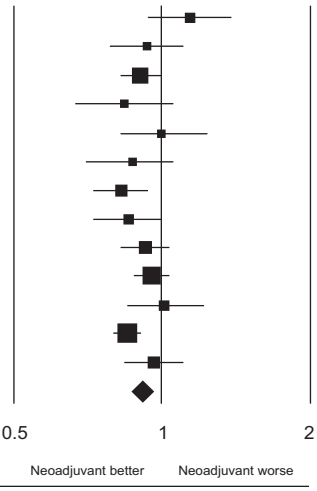

**Figure 1.** Flow diagram for the selection of studies included. Reasons for exclusion and inclusion of trials.

**Table 1.** Description of trials of neoadjuvant chemotherapy before radiotherapy in non small-cell lung cancer. Trial, patient, treatment characteristics, trial outcome and toxic death rate for individual studies

| *Trial* | *Reference number* | *N* Total* | *Trial quality (Jadad score)ℓ* | *Median/ mean age* | *Male %* | *Squamous histology %* | *Stage 3 %* | *Neoadjuvant chemotherapy* | *Additional chemotherapy*** | *Time to main treatment (days)* | *Outcome reported* | *Toxic deaths**** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Van Houtte 1988 | 14 | 59 | 2 | 63 | 91 | 64 | 85 | EPV[1] (3 cycles) | No | 84 | No statistical comparison, 3 years OAS[10] 7% in the neoadjuvant group, 13% in the control group | 1/27 |
| Morton 1991 | 27 | 114 | 2 | 63 | 71 | 48 | 95 | MACC[2] (2 cycles) | Further adjuvant MACC in the intervention group (2 cycles) | 55 | OAS and time to progression not changed | 1/56 |
| Le Chevalier 1991 | 3 | 353 | 3 | 59 | 97 | 86 | 88 | VCPC[3] (3 cycles) | Adjuvant VCPC if response or stable disease by induction (3 cycles) | 77 | OAS not changed | 0/156 |
| Crino 1993 | 20 | 61 | 2 | 62 | 95 | 67 | 100 | EP[4] (3 cycles) | No | 63 | OAS not changed | 0/33 |
| Gregor 1993 | 28 | 78 | 2 | 61 | 83 | 82 | 100 | P-Vin[5] (2 cycles) | No | 56 | OAS not changed | 0/78 |
| Wolf 1994 | 24 | 78 | 2 | 61 | 90 | 67 | 100 | IV[6] (2 cycles) | No | 55 | OAS improved by chemotherapy, 2 year OAS 24% vs. 12% (P=0.016) | 0/37 |
| Sause 1995 | 26 | 301 | 2 | Not given | 70 | 45 | 94 | P-V[7] (2 cycles) | No | 50 | OAS improved by chemotherapy (P=0.03); 1 year OAS 46% vs. 60% | 2/151 |
| Dillman 1996 | 22 | 155 | 2 | Not given | 75 | 39 | 100 | P-V (2 cycles) | No | 49 | OAS better in the neoadjuvant group, Meidan OAS 13.7 vs. 9.6 months (P=0.012) | 0/78 |
| Brodin 1996 | 21 | 302 | 2 | 64 | 84 | 100 | 81 | EP (3 cycles) | No | 56 | OAS not changed by univariate analysis (but Cox P is 0.04 in favor of neoadjuvant therapy) | 2/148 |
| Cullen 1999 | 19 | 446 | 2 | 64 | 77 | 70 | 100 | MIC[8] (4 cycles) | No | 84 | Median OAS not improved in the neoadjuvant group | 4/223 |
| Kim 2002 | 23 | 89 | 2 | 57 | 87 | 74 | 100 | PEV[9] (3 cycles) | No | 63 | OAS not changed | 1/43 |
| Sharma 2003 | 13 | 460 | 2 | 54 | 90 | 76 | 100 | MIC (3 cycles) | No | 63 | No statistical comparison, 3 year OAS 11.5% in the neoadjuvant group, 5.2% in the control group | 0/228 |
| Mattson 2003 | 25 | 274 | 2 | 62 | 80 | 62 | 100 | Taxotere (3 cycles) | No | 63 | OAS not changed | 2/134 |

*: Total number of subjects, **: Any additional chemotherapy used after neoadjuvant chemotherapy, ***: number of toxic deaths/number of patients that received neoadjuvant chemotherapy, ℓ: over a total score of 5, [1]: etoposide, cisplatin, vindesine, [2]: methotrexate, doxorubicin, cyclophosphamide and CCNU, [3]: vindesine, cyclophosphamide, cisplatin and lomustine, [4]: cisplatin and etoposide, [5]: cisplatin and vindesine, [6]: ifosfamide and vindesine, [7]: cisplatin and vindesine, [8]: mitomycin, ifosfamide and cisplatin, [9]: cisplatin, etoposide, vinblastine, [10]: overall survival

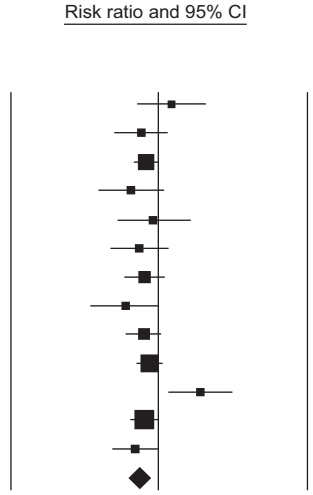
| Study name | Outcome | Risk Ratio | Lower limit | Upper limit | Z-Value | p-Value | Dead / Total: with neoadjuvant | Dead / Total: without neoadjuvant |
|---|---|---|---|---|---|---|---|---|
| Van Houtte 1988 | 2 year OAS | 1.140 | 0.935 | 1.389 | 1.296 | 0.195 | 25/27 | 26/32 |
| Morton 1991 | 2 year OAS | 0.930 | 0.780 | 1.109 | -0.809 | 0.418 | 44/56 | 49/58 |
| Le Chevalier 1991 | 2 year OAS | 0.900 | 0.814 | 0.994 | -2.070 | 0.038 | 136/176 | 152/177 |
| Crino 1993 | 2 year OAS | 0.837 | 0.661 | 1.058 | -1.488 | 0.137 | 24/32 | 26/29 |
| Gregor 1993 | 2 year OAS | 1.000 | 0.813 | 1.231 | 0.000 | 1.000 | 32/39 | 32/39 |
| Wolf 1994 | 2 year OAS | 0.862 | 0.695 | 1.069 | -1.353 | 0.176 | 28/37 | 36/41 |
| Sause 1995 | 2 year OAS | 0.825 | 0.717 | 0.949 | -2.697 | 0.007 | 100/152 | 122/153 |
| Dillman 1996 | 2 year OAS | 0.855 | 0.731 | 0.999 | -1.971 | 0.049 | 58/78 | 67/77 |
| Brodin 1996 | 2 year OAS | 0.925 | 0.822 | 1.041 | -1.298 | 0.194 | 112/148 | 126/154 |
| Cullen 1999 | 2 year OAS | 0.952 | 0.872 | 1.039 | -1.104 | 0.270 | 178/223 | 187/223 |
| Kim 2002 | 2 year OAS | 1.013 | 0.841 | 1.222 | 0.140 | 0.888 | 36/43 | 38/46 |
| Sharma 2003 | 2 year OAS | 0.849 | 0.789 | 0.913 | -4.404 | 0.000 | 182/228 | 220/234 |
| Mattson 2003 | 2 year OAS | 0.963 | 0.829 | 1.118 | -0.496 | 0.620 | 94/134 | 102/140 |
| FIXED MODEL (OVERALL) | | 0.906 | 0.874 | 0.939 | -5.378 | 0.000 | | |




OAS: overall survival

**Figure 2.** The effect of neoadjuvant chemotherapy before radiotherapy on 2-year overall survival in non-small cell lung cancer. Forest plot for the benefit from neoadjuvant as assessed by RR (relative risk for mortality) for the effect size. Symbols for individual study effect size are proportional to the square root of individual sample size.

| Study name | Outcome | Risk Ratio | Lower limit | Upper limit | Z-Value | p-Value | Dead / Total: with neoadjuvant | Dead / Total: without neoadjuvant |
|---|---|---|---|---|---|---|---|---|
| Van Houtte 1988 | 3 year OAS | 1.058 | 0.894 | 1.253 | 0.656 | 0.512 | 25/27 | 28/32 |
| Morton 1991 | 3 year OAS | 0.921 | 0.810 | 1.046 | -1.268 | 0.205 | 48/56 | 54/58 |
| Le Chevalier 1991 | 3 year OAS | 0.940 | 0.884 | 1.000 | -1.972 | 0.049 | 157/176 | 168/177 |
| Crino 1993 | 3 year OAS | 0.874 | 0.742 | 1.030 | -1.609 | 0.108 | 27/32 | 28/29 |
| Gregor 1993 | 3 year OAS | 0.971 | 0.811 | 1.162 | -0.325 | 0.745 | 33/39 | 34/39 |
| Wolf 1994 | 3 year OAS | 0.909 | 0.786 | 1.051 | -1.286 | 0.198 | 32/37 | 39/41 |
| Sause 1995 | 3 year OAS | 0.933 | 0.851 | 1.022 | -1.497 | 0.134 | 126/152 | 136/153 |
| Dillman 1996 | 3 year OAS | 0.844 | 0.729 | 0.978 | -2.258 | 0.024 | 59/78 | 69/77 |
| Brodin 1996 | 3 year OAS | 0.928 | 0.850 | 1.013 | -1.661 | 0.097 | 124/148 | 139/154 |
| Cullen 1999 | 3 year OAS | 0.956 | 0.898 | 1.018 | -1.412 | 0.158 | 196/223 | 205/223 |
| Kim 2002 | 3 year OAS | 1.214 | 1.045 | 1.411 | 2.541 | 0.011 | 42/43 | 37/46 |
| Sharma 2003 | 3 year OAS | 0.938 | 0.889 | 0.991 | -2.287 | 0.022 | 203/228 | 222/234 |
| Mattson 2003 | 3 year OAS | 0.896 | 0.796 | 1.007 | -1.839 | 0.066 | 102/134 | 119/140 |
| FIXED MODEL (OVERALL) | | 0.942 | 0.918 | 0.967 | -4.480 | 0.000 | | |




OAS: overall survival

**Figure 3.** The effect of neoadjuvant chemotherapy before radiotherapy on 3-year overall survival in non-small cell lung cancer. Forest plot for the benefit from neoadjuvant as assessed by RR (relative risk for mortality) for the effect size. Symbols for individual study effect size are proportional to the square root of individual sample size.

= 1.84, p=0.093). None of the other independent variables evaluated by the regression analysis, i.e. trial size, publication year, proportion of patients with stage 3 disease, proportion of male patients, mean / median age, and proportion of patients having squamous cell histology, were found to be significantly associated with the effect size. Table 2 displays the results of meta-regression and subgroup analysis. Figure 4 demonstrates the association between time to radiotherapy and the effect of neoadjuvant chemotherapy.

**Table 2.** Meta-regression and subgroup analyses of the correlates of benefit from neoadjuvant chemotherapy before radiotherapy. Assessment of the effect of the categorical and continuous moderator variables on the benefit from neoadjuvant chemotherapy

| *Correlates* | *Overall survival (RR)*[$] *2 years* | *3 years* |
|---|---|---|
| Trial characteristics | | |
| Trial size[#] | t = –0.98 (P=0.350) | t = 0.08 (P=0.938) |
| Publication year[#] | t = –0.18 (P=0.864) | t = –0.22 (P=0.828) |
| Trial quality (Jadad score < 3 vs. ≥3)[$] | Q = 0.02 (P=0.889) | Q = 0.02 (P=0.889) |
| Disease characteristics | | |
| Stage (% stage 3)[#] | t = -1.09 (P=0.300) | t = –0.957 (P=0.359) |
| Histology (% squamous cell type)[#] | t = 0.77 (P=0.456) | t = 1.18 (P=0.264) |
| Patient characteristics | | |
| Sex (% male)[#] | t = 0.16 (P=0.879) | t = 0.44 (P=0.666) |
| Mean/median age[#] | t = 0.74 (P=0.480) | t = –0.66 (P=0.525) |
| Treatment characteristics | | |
| Type of neoadjuvant chemotherapy[$*] | Q = 0.25 (P=0.615) | Q = 2.88 (P=0.090) |
| Cycles of neuoadjuvant chemotherapy[$**] | Q = 0.79 (P=0.376) | Q = 0.79 (P=0.376) |
| Adjuvant chemotherapy (yes or no)[$] | Q = 0.00 (P=0.973) | Q = 0.05 (P=0.834) |
| Time to radiotherapy[#***] | t = 2.20 (P=0.050) | t = 1.84 (P=0.093) |

n = 13 trials
[$]Effect size is given as relative risk, [#]Continuous moderator variables as assessed by robust regression analysis, [$]Subgroup analysis: the effect of categorical moderator variables are assessed by ANOVA tests for interaction, [*]regimen containing 1 or 2 vs. more agents, [**]2 cycles vs. 3 or 4 cycles, [***]days to radiotherapy from the onset of neoadjuvant treatment in the intervention arm

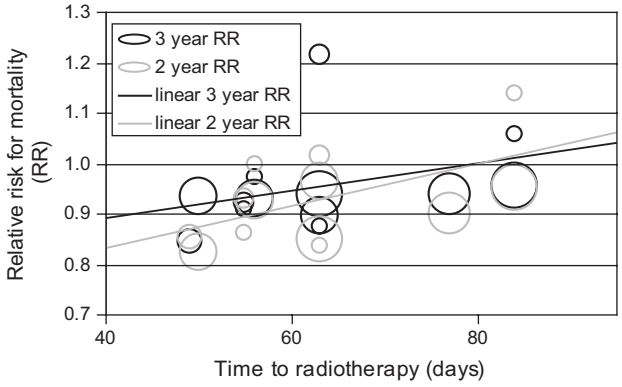



**Figure 4.** Benefit from neoadjuvant chemotherapy before radiotherapy at 2 and 3 years and time to radiotherapy. A scatter plot showing the association between relative risk (RR) for mortality and time to radiotherapy, separately for 2 and 3 years. The diameter of bubbles is proportional to the square root of sample size for each individual study.

## Discussion

One of the main findings from this meta-analysis of literature is that neoadjuvant chemotherapy before radiotherapy, in the form of sequential chemoradiotherapy, decreases mortality in NSCLC, by 9% and 6% at 2 and 3 years, over that by radiotherapy alone. This decrease is not large and is comparable to the findings of the 1995 NSCLCCG meta-analysis (10% reduction in hazard ratio for mortality) [6]. An updated 1995 meta-analysis, which will be a meta-analysis of individual patient data, is eagerly awaited to conclude more about the benefit of chemotherapy for patients treated with chemoradiotherapy, and will also enable direct comparison between sequential and concomitant chemoradiotherapy approaches.

Secondly, we also showed that the longer the time to radiotherapy from the onset of neoadjuvant chemotherapy, the less beneficial neoadjuvant chemotherapy could be. Our results imply that it may be rational not to delay radiotherapy beyond 6 to 9 weeks, as after this point the RR for mortality gets close to 1, or even above 1 (no effect, or detrimental). At present, it is not clear whether this decrease in benefit from neoadjuvant chemotherapy associated with increased time to treatment stems from diminished local control or other unnamed factors, however, this finding may have obvious clinical implications for NSCLC patients embarking on sequential chemoradiotherapy protocols.

Our work also has some important differences from the previous meta-analyses in this field; 3 previous meta-analyses [2,6,32] included radiotherapy trials incorporating concomitant chemotherapy, or adjuvant chemotherapy until progression or unacceptable toxicity, or adjuvant chemotherapy without neoadjuvant chemotherapy, whereas we concentrated on trials using neoadjuvant chemotherapy with or without predefined cycles of adjuvant chemotherapy. Likewise, the meta-analysis by Auperin et al. specifically questioned the role of concomitant chemoradiotherapy as opposed to radiotherapy only [33]. Thus, one of the primary differences of this updated meta-analysis is that it primarily focuses on the effect of neoadjuvant chemotherapy before radiotherapy with a specific emphasis on the predictors of its effect.

There are some other findings from this meta-analysis. Apart from time to radiotherapy, interestingly, meta-regression and subgroup analyses also show that the effect of neoadjuvant chemotherapy before radiotherapy, in the form of sequential chemoradiotherapy, is consistent regardless of other disease, patient, treatment, and trial characteristics. Thus, at this stage it is still unclear which patient subgroups and treatment characteristics are associated with greater benefit from neoadjuvant chemotherapy before radiotherapy. A new individual patient data meta-analysis will be useful also in this regard.

In the absence of contraindications, concomitant chemoradiotherapy is currently the standard approach for the treatment of unresectable disease, as concomitant approach in this setting has been shown to be superior to sequential chemoradiotherapy, but with more toxicity [7]. However, the data is still incomplete and limited, and firm conclusions still cannot be drawn about the superiority of concomitant approach.

We know that adjuvant chemotherapy in NSCLC is not free of morbidity or mortality. In one of the RCTs conducted, chemotherapy-related mortality after surgery was 0.8% [34]. Likewise, in a trial where adjuvant chemotherapy was administered after chemoradiotherapy, excessive toxicity was encountered [35]. Although, neoadjuvant chemotherapy before radiotherapy or surgery may be expected to cause less toxicity, in our meta-analysis of sequential chemoradiotherapy, toxic death risk was 1.2% after neoadjuvant therapy, which is very similar to the corresponding risk of adjuvant chemotherapy, as stated above. We believe this fact should be shared clearly with patients before starting neoadjuvant chemotherapy in sequential chemoradiotherapy protocols.

As with all meta-analyses based on abstracted data, there are limitations to our findings. Mainly, caution is required to interpret the results of subgroup analyses from this meta-analysis, as individual patient data meta-analysis is more reliable in this regard [36]. For this reason, our results need confirmation.

In short, this work confirms that neoadjuvant chemotherapy before radiotherapy improves survival in NSCLC in comparison to radiotherapy only. Additionally, our meta-analysis reveals that shorter time to radiotherapy may be associated with greater benefit of neoadjuvant chemotherapy.

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