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ORIGINAL ARTICLE

Risk factors for recurrence in patients with resected N1 non-small cell lung cancer – a systematic review and meta-analysis

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Summary

Purpose: *To evaluate the rates of locoregional failure (LRF) vs distant metastasis (DM), and find risk factors for recurrence in patients with completely resected N1 non-small cell lung cancer (NSCLC).*

Methods: *By searching Pubmed, Embase and the Cochrane Controlled Trials Register from 1995 through 2014, eligible randomized clinical trials (RCTs) were identified. In addition, the reference lists of articles and conference abstracts were searched. The logarithm of the risk ratio (RR) and its standard error (SE) were calculated, and a fixed-effect model was used to combine the estimates.*

Results: *3 RCTs and 9 retrospective studies, which included 889 patients, were identified and selected. All studies dealt with resected N1 NSCLC, LRF vs DM, and risk factors such as visceral pleural invasion (VPI) and lymphovascular invasion (LVI). There was statistically significant benefit on 5-year overall survival (OS) for LRF (RR=0.68, 95% CI=0.60–0.78, p<0.00001). Further analysis for patients with LRF also showed that VPI (RR=1.25, 95% confidence interval/CI=1.09-1.42, p=0.0009), LVI (RR=1.16, 95% CI=1.04-1.30, p=0.009), were the main risk factors for recurrence.*

Conclusions: *The present study indicates that in patients with resected N1 NSCLC, the incidence of LRF is lower than DM. Advanced T stage classification, VPI, and LVI were predictors of poor survival. These patients represent a subgroup with N1 disease who might benefit from additional therapy, including adjuvant radiotherapy (RT). However, large, well-designed prospective studies should be conducted to confirm this conclusion.*

Key words: *distant metastasis, locoregional recurrence, lymphovascular invasion, meta-analysis, non small cell lung cancer, visceral pleural invasion*

Introduction

Lung cancer is the leading cause of cancer related deaths in many countries. Due to the rapid course of the disease after diagnosis, standardized mortality rates are quite similar to those of incidence for both sexes and in more than 75% of the cases the disease is diagnosed in advanced stages [1]. NSCLC is the most common form of lung cancer and approximately 70% of the patients with NSCLC present with advanced disease [2]. NSCLC, including adenocarcinoma, squamous cell and large cell anaplastic carcinomas, comprises 80-85% of lung cancers overall. Surgical resection is regarded as the current standard procedure for stage I-IIIA patients. However, the long-term survival, even after surgical resection, is rather disappointing. Five-year OS for patients with pathologic stage I NSCLC is only 60–70% and falls to 35–40% for those with stage II tumors [3]. For stage III NSCLC patients palliative chemotherapy increases OS and quality of life when compared to best supportive care, and these patients have an average survival of 8 to 10 months when treat-

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ed with platinum-based regimens [4]. Nevertheless, the reported rates of LRF after surgery for NSCLC vary, and have been reported to be as high as 40% [5-7]. The postoperative prognosis is much worse for patients with N1 disease than for those with N0 disease. The 5-year OS rates of patients with N1-stage II disease vary from 33 to 65% for stage IIA and from 27 to 56% for stage IIB [8]. Despite the well known predominance of distant vs locoregional relapse in patients operated for primary NSCLC, there are few reports specifically addressing the pattern of relapse including the exact onset of relapse, the way of detecting relapse (symptom-based/controls) and treatment, taking into account tumor- and patient-related characteristics [9]. In an effort to improve survival rates after recurrence, adjuvant RT has been explored as a therapeutic option.

The rates of LRF compared to DM for resected N1 NSCLC remain unclear, and risk factors for recurrence in patients with completely resected N1 NSCLC are not classified as yet. Individual trials have shown inconclusive and conflicting results. A number of randomized controlled trials were conducted, and some studies have found that VPI and LVI can increase the risk of LRF, so no survival benefit for patients with LRF was observed. A meta-analysis of randomized trials and retrospective studies have reported that postoperative RT had a detrimental effect on OS in patients with N0 and N1 NSCLC [10-13]. However, limitations of flaws in study design and outdated radiation techniques can produced potential biases. Lopez Guerra et al. found that patients with N0-N1 disease have low rates of LRF after surgical resection and identified patients who may benefit from adjuvant RT [14].

Despite the fact that several trials have demonstrated the prognostic importance of mediastinal nodal downstaging or pathologic response to adjuvant RT, LRF or DM rates for N1 staged groups are rarely reported. Older randomized studies indicated that the toxicity of postoperative RT outweighed the potential improvement in local control, but studies using more modern irradiation techniques show significantly reduced toxicity, inferring that selected patients may benefit.

A systematic review and quantitative meta-analysis were therefore undertaken to distinguish the risk factors and evaluate adjuvant RT in patients with recurrent N1 NSCLC.

Methods

Literature search

Potentially eligible studies were identified using Pubmed, Embase, and the Cochrane Controlled Trials from January 1995 to March 2014. We used the following search terms: locoregional recurrence or LR, DM or recurrence/failure, relapse, VPI, LVI, risk factors, N1 non small cell lung cancer, randomization, and clinical trial. Proceedings of major conferences were also searched for abstracts using the same keywords. The reference sections of selected papers were manually searched for relevant publications. Experts and investigators who took part in the meta-analysis were asked to help in identifying other trials. When there was uncertainty about the eligibility of a trial, this was discussed and resolved by consensus among the study authors.

Definition of recurrence

Disease recurrence at the surgical resection margin was considered as local failure, while mediastinal, hilar, and supraclavicular fossa recurrence were defined as regional failure. The recent lymph node map proposed by the International Association for the Study of Lung Cancer [15] was used for illustrating the regional recurrences. DM was defined as disease recurrence in the contralateral lung or outside the hemithorax and mediastinum. In patients with subsequently confirmed brain or bone metastases and the appearance of first specific symptoms was accepted as the time of the relapse onset. Cancer relapse within the first 12 postoperative months was particularly analyzed. Univariate and multivariate analyses of factors influencing the OS and the relapse occurrence included the interval between the onset of symptoms and operation, radiographic appearance, bronchoscopic appearance, tumor diameter, T and N stage, VPI, extent of resection and adjuvant treatment.

Literature criteria

All patients must have been previously diagnosed with NSCLC and treated with standard therapies. Trials had to be properly randomized. Non-English language papers were not included in the review. To be eligible for inclusion, studies had to meet the following criteria: LVI and VPI were measured in surgical tumor samples; the relationship between LVI/VPI and survival was investigated; stage I-IIIA disease; N1 disease; complete resection; systematic lymphadenectomy with at least 6 different lymph node groups examined; exact data about tumor histology. Treatment should contain the following information: locoregional recurrence and DM; and the results should be published as a full paper. Abstracts were not included, because of issues with incompleteness of the data and potential issues with the quality of data abstracted from non–peer-reviewed sources. To avoid duplication of patient data, we carefully noted the author names and the research centers involved for all authors.

Individual patient data

The following information was obtained from each

source article: year of publication, study period, number of patients, sex, clinical stage, performance status, therapeutic method, objective response rate, OS, LRF or DM. Each study was assessed for quality and potential bias using a structured checklist based on the Method for Evaluating Research and Guideline Evidence criteria [16]. Study characteristics were quality of randomization, blinding, outcome measures, measure assessment, arm comparability, loss to follow-up, and intention to treat analysis.

Statistics

The main end point was OS, defined as the time between date of random assignment and date of death, or last date of follow-up for censored patients. Findings of the meta-analysis were depicted in classical Forest plots, with point estimates and 95% CIs for each trial and overall; size of the squares was proportional to study size. For all analyses, a two-sided p value of ≤0.05 was considered statistically significant. Differences between outcomes in the control groups of the different trials were measured against the logarithm of the hazard ratio to give an estimate of the relation between risk and benefits for LRF and DM. Statistical analyses were performed using Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK). The observed and expected number of events and associated variances were used to calculate individual trial and overall combined RR and their 95% CIs by the fixed-effects mode. Heterogeneity tests were used to test for statistical heterogeneity among trials with the x^2-based Q test [17]. When the effects were assumed to be homogeneous, the fixed-effect model was used; otherwise, the random effect model based on the Mantel-Haenszel method was applied [18]. These were used to calculate absolute differences in the survival rates at annual intervals. Publication bias was assessed using funnel plots with an asymmetric plot suggesting a possible publication bias.

Results

From the literature search we obtained 28 references. A final manual cross-reference search of these selected papers did not identify additional relevant articles. The excluded records included 2 reviews, 3 case reports, 5 non-English studies and 6 studies without available survival information. Thirty patients were excluded from two trials because of complete absence of information in the study database. One was excluded because of ineligible histology (small-cell lung cancer). Finally, 12 eligible studies published from 1994 to 2014 and satisfying the inclusion criteria for the systematic review and meta-analysis were identified. Each of the 12 trials was reported in a full paper [7,9,14,19-27].

Baseline characteristics of the 12 trials are listed in Table 1. Of all the eligible patients, 249 (40.6%) had been assigned to the LRF group, and 364 (59.4%) were assigned to the DM group. All of the patients received curative resection. Curative resection was defined as an agreement between surgeon and histopathologist that the margins of the resected tissue contained no tumor. Median patient age was 61 years (range 34-84). Most of the patients were males (77%), had a good PS (0 or 1 in 90%). OS was obtained from the original papers.

In our analysis, 10 studies were selected for inclusion as LRF [7,9,19-26]. Five studies identified VPI as a significant risk factor for LRF [14,22,24,26-27], and 6 identified LVI as a significant risk factor for LRF [14,22-24,27]. Other risk factors such as advanced T stage and smoking history were not included in the analysis because of the low number of patients.

Table 1. Characteristics of population and survival in the eligible studies of the locoregional recurrence group

First author [Ref]	*Year*	*Patients (N)*	*Treatment*	*Tumor stage*	*Nodal stage*	*Metastasis status*	*MFU (months)*
Sawyer [7]	1999	107	S	UN	N1	M0	38
Osaki [9]	2003	82	S	T1-2	Ni	M0	44
Fujmoto [19]	2005	180	S	T1-4	N1	M0	40
Matsuoka [20]	2007	128	S	T1-2	N1	M0	48
Subotic [21]	2009	30	S	T1-3	N1	M0	46
Saynak [22]	2011	335	S	T1-4	N0-1	M0	40
Varlotto [23]	2011	60	S	UN	N1	M0	30
Higgins [24]	2011	198	S	UN	N1	M0	51
Shin [25]	2013	305	S	UN	N1	M0	48
Fan [26]	2013	199	S	T1-3	N1	M0	53.8
Kelsey [27]	2009	975	S	T1-2	N0-1	M0	48
Guerra [14]	2013	1402	S	T1-3	N0-1	M0	42

MFU: median follow-up, UN: unknown, S: surgery

LRF vs DM for resected N1 NSCLC

The baseline characteristics of the 10 studies [7,9,19-26] about LRF and DM are included in Table 1. The effect of LRF vs DM on the survival rate is shown in Figure 1. A statistically significant difference could be seen in survival between the two groups. The RR between LRF and DM groups was 0.68 (95% CI=0.60-0.78, p<0.00001) for 5-year OS.

VPI vs non-visceral pleural invasion (NVPI) in locoregional recurrence

We next analyzed the association between VPI and OS in NSCLC patients. The effect of VPI vs NVPI on the survival rates is shown in Figure 2 and concerns 5 eligible studies [14,22,24,26,27] involving a total of 3102 patients. For the VPI risk factor, the pooled RR estimate was 1.25 (95%CI=1.09-1.42, p=0.0009) with no significant heterogeneity (Q =15.8; I^2=75%, p=0.003). These results suggest that VPI is a poor prognostic indicator of tumor recurrence.

LVI versus non-lymphovascular invasion (NLVI) in locoregional recurrence

We also studied the risk of recurrence and death in NSCLC patients with LVI. The main characteristics of the included patients are described in Table 2. The effect of LVI vs NLVI on the survival rate is shown in Figure 3. As shown, 6 eligible studies with a total of 1735 patients were included in the analysis. For the LVI group, the RR estimates for OS were 1.16 (95%CI: 1.04-1.30; p=0.009). Significant heterogeneity was found (Q=3.9; I^2=0%, p=0.42). In the analysis of OS, LVI

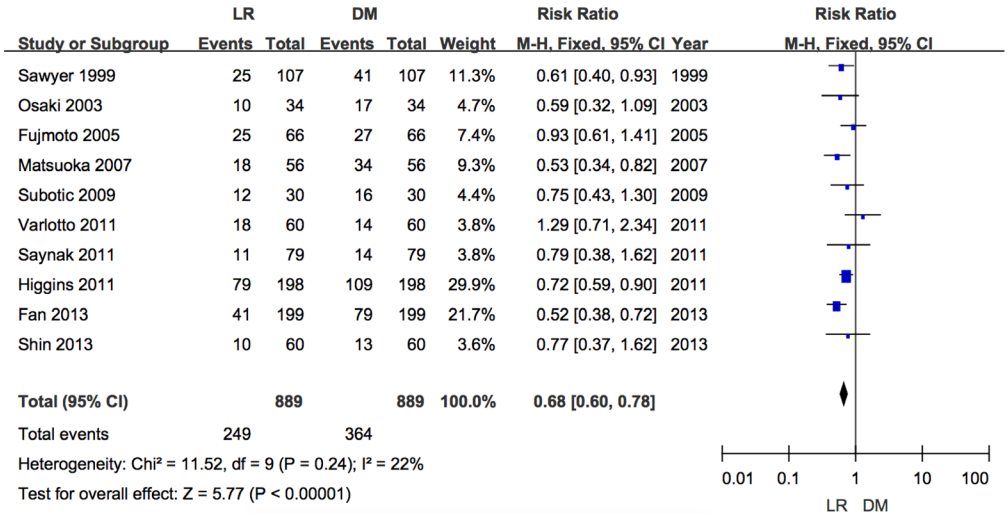

Figure 1. Overall survival in the LRF group compared with the DM group (Forest Plot). The RR of 1-year overall survival was 0.68 (95%CI 0.60-0.78; p<0.00001)

Table 2. Characteristics of risk factors in the eligible studies of the lymphovascular invasion group

First author [Ref]	*Year*	*LVI N*	*VPI N*	*LRR (5-year)*	*Tumor stage*	*Other risk factors for LRR*
Kelsey [27]	2009	210	201	25	I-III	Cell histology/sublobar resections
Higgins [24]	2011	79	63	40	II-III	VATS approach/number of positive N1 lymph nodes
Saynak [22]	2011	72	38	37	I-IV	Tumor size
Varlotto [23]	2011	20	U	46	II-III	Chemotherapy
Guerra [14]	2013	U	267	3	I-III	Surgical procedure/tumor size/ pathologic N1 stage
Fan [26]	2013	18	117	20.6	II-III	Smokers/positive lymph nodes at station 10/ IMD

LVI: lymphovascular invasion, VPI: visceral pleural invasion, LRR: locoregional recurrence, VATS: video-assisted thoracoscopic surgery, U: unknown, IMD: incomplete mediastinal lymph node dissection or examination

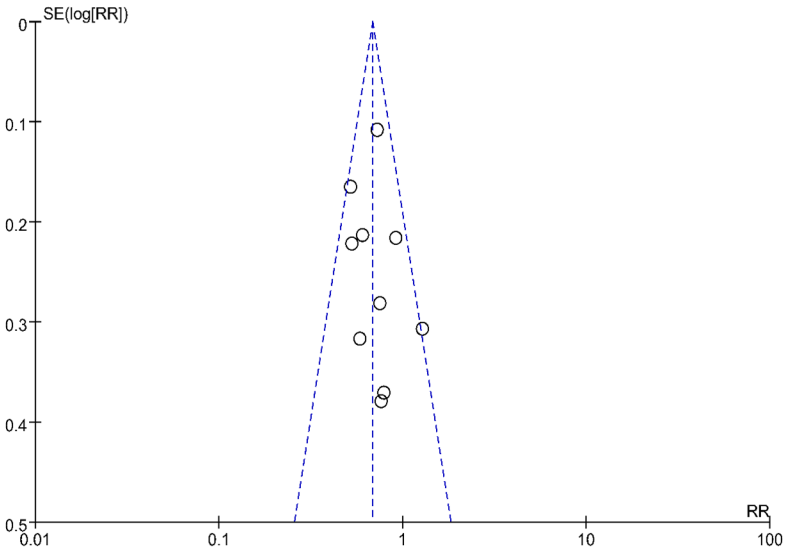

Figure 2. Funnel plot of overall survival for the LRF group compared with the DM group. The middle vertical line represents the extension cord of merger measurement. Each of the rectangles represents one of the included randomized clinical trials (RCTs). The symmetric inclined line laid on both ends of the vertical line indicates that there is no publication bias between the RCTs included in the study.

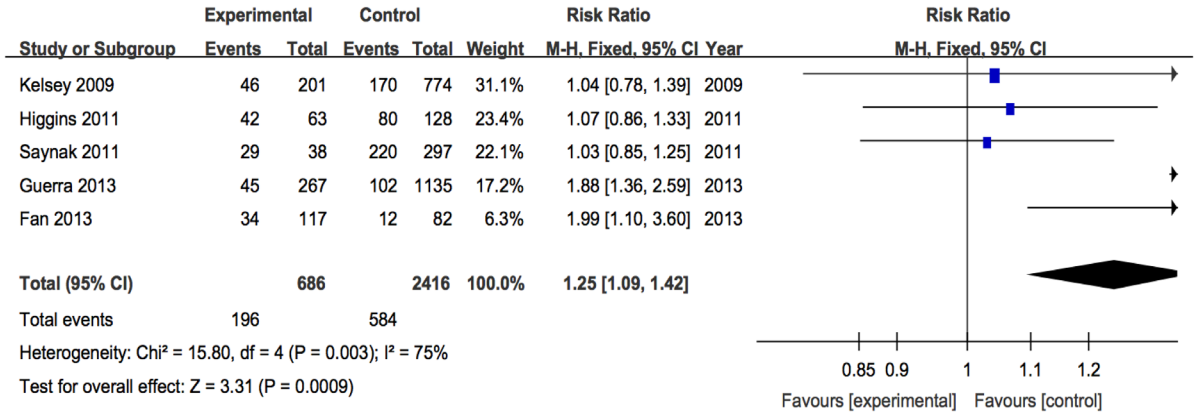

Figure 3. Overall survival in the VPI group compared with the non VPI group (Forest Plot). The RR of 5-year overall survival was 1.25 (95%CI 1.09-1.42; p=0.0009).

appeared to significantly increase the risk for death in stage I patients. In these analyses, there was no evidence of statistical heterogeneity. These results suggest that LVI is a poor prognostic indicator and is independent of the tumor stage and histological type.

Publication bias assessment

Publication and reporting bias was considered and calculated because the required data were usually available only in full publications. We did not include unpublished papers, reviews or abstracts. The symmetry of the funnel plot (Figure 2) indicated that there was no publication bias and the data of the included studies could be combined with safety. Then, the Egger's test was used to provide statistical evidence of the funnel plot symmetry. The results still did not suggest any evidence of publication bias.

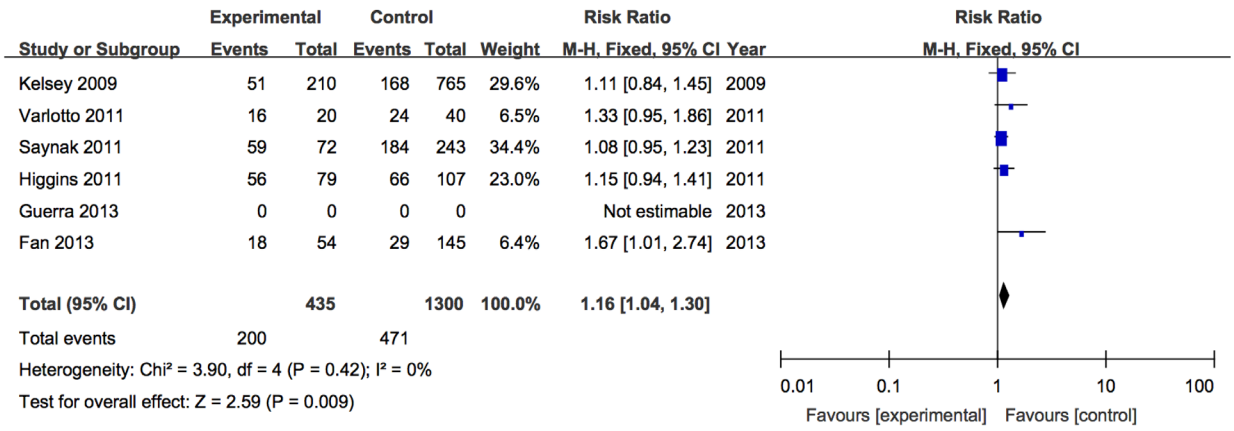

Figure 4. Overall survival in the LVI group compared with the non LVI group (Forest Plot). The RR of 5-year overall survival was 1.16 (95%CI 1.04-1.30; p=0.009).

Discussion

This study evaluated the rate of LRF/DM and risk factors in patients with resected N1 NSCLC. The type of lymphadenectomy in the present study was complete removal of all palpable and visible lymph nodes. The 7th edition of TNM classification of lung cancer provided a revision of T descriptor, which divided T1 into T1a and T1b and T2 into T2a and T2b, according to new tumor size cut-offs [28]. In contrast, the N descriptor has remained unchanged [29]. The IASLC staging committee developed a revised lymph node map which grouped lymph node stations into "zones", for instance, peripheral or hilar for N1 [15]. A few previous studies have assessed the prognostic significance of direct extension to N1 lymph nodes. Marra et al. [30] studied T1-4N1M0 disease and reported that the prognosis of patients with direct extension to N1 lymph nodes was significantly better than that of patients with metastases to hilar, interlobar or both hilar and interlobar lymph nodes. Mayer et al. [31] reported that postoperative RT significantly reduced local recurrence, but there was no significant improvement in OS and disease-free survival (DFS). The risk of local recurrence after surgery for resected NSCLC has not been well defined and with the improvement of systemic therapy [32,33] local control will likely be achieved finally. Baldini et al. [34] reported a retrospective study in stage II patients (T1N1 and T2N1), with a 3-year OS of 56% and 43% in patients with postoperative RT vs those with surgery alone, respectively.

Cancer progression and metastasis are complex and multistep processes. Locoregional invasion begins with microscopic metastasis by tumor cells into the host stroma within or surrounding the primary tumor. The cancer cells can spread to the lung and other sites through LVI and the regional lymph nodes, thoracic duct, superior vena cava, and pulmonary artery. VPI and LVI appear to be a fundamental step in cancer locoregional recurrence. When tumor cells penetrate a blood vessel or a peripheral lymphatic, they can detach, disseminate and arrest in the microvasculature through the circulation, leading to poor prognosis for patients with NSCLC. LVI is defined by the identification of tumor cells in the lumen of lymphatic vessels, which are often covered by endothelial cells and contain few lymphocytes. VPI of the primary tumor has been shown in multiple studies to be a poor prognostic factor for both recurrence-free and OS [36-38] and is recognized by the present TNM staging system. Sublobar resections are a well-recognized risk factor for local recurrence [39]. For lack of sufficient data, our meta-analysis only focused on the effect of tumor VPI and LVI on the survival of recurrent N1 NSCLC patients. Higgins et al. found that, with increasing numbers of positive N1 lymph nodes (p=0.02), and VPI (p=0.04), the risk of local failure in resected N1 NSCLC patients was significantly increased [26]. In our study, in patients with resected N1 NSCLC, the 5-year rate of LRF was 40.6%. By comparison, the 5-year rate of distant failure was 59.4%. Furthermore, certain patholog-

ic features can place patients at particularly high risk of LRF, such as LVI and VPI. All these may indicate further consideration for administration of adjuvant local therapy.

Postoperative RT has been used to prevent local failure and possibly to increase long-term survival for decades. However, the role of postoperative RT in NSCLC still remains controversial. The addition of RT may exert a deleterious effect by virtue of the acute or delayed radiation effects, such as radiation pneumonitis or cardiotoxicity, however, it is likely that the lungs of most of the patients are already damaged by surgery and smoking. By convincing evidence from the analysis, no increase of RT-related deaths was observed. In the Adjuvant Navelbine International Trialist Association (ANITA) randomized study [12] postoperative RT compared with chemotherapy was found to be associated with detrimental survival in N1 disease patients, however, even if the ANITA trial was a randomized study, the patients that were recommended for postoperative RT were selected by the researchers, so patient selection bias may have influenced the results. For the cause of death, a great number of trials do not provide detailed information, and there is lack of evidence that adjuvant RT could result in death when compared to cancer itself.

The results of this meta-analysis indicated that adjuvant RT is likely to be beneficial for patients with high risk factors of local recurrence, and the deleterious effect was likely to be small and easily outweighed on survival. It is necessary to emphasize the outdated irradiation techniques such as conventional RT, hypofractionated treatments, opposed lateral portals, and excessive radiation volumes [13,40]. With the advent of modern technology, Trodella et al. [41] found that for patients with resected N0 NSCLC, adjuvant RT achieved significantly higher rates of local control, OS, and DFS. Kelsey et al. [42] reported that in a retrospective study with mediastinal lymphadenopathy recurrence, half of the patients were treated with RT alone, median survival was 17 months and 2-year OS was 38%, which is similar to what was reported in the aforementioned trials. This finding suggests that in selected patients with LRF, RT is a valuable salvage modality and should be considered. An accurate assessment of patterns of failure after surgery is helpful to guide postoperative therapy. Given the recognized risk of local recurrence, even in patients with early-stage disease, a reanalysis of postoperative RT appears prudent.

The limitations of our study need attention and include (a) potential biases, (b) the fact that most of the disease recurrence determination was based on radiographic imaging, (c) significant heterogeneity, and (d) unsatisfactory statistical power. We have to understand the inherent risk of bias of these studies. Patients started on palliative treatments often had local recurrence and a poorer prognosis compared with patients without recurrence. For patients who had already local recurrence, further progression is likely to continue, eventually resulting in death. Subgroup analysis for different tumor stages was not provided in our study because we lacked the related survival data in the corresponding clinical trials.

In conclusion, the high local failure rates in the mediastinum may suggest the need for additional consolidation treatment, such as adjuvant RT. With improvements in radiation technology, the rate of related complications is relatively low and can be tolerated. Further information from randomized trials is needed to explore different adjuvant approaches based on histology and lymph node status that not only improve disease control and survival but also minimize the adverse effects of treatment.

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