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ARTICLE

Postoperative UFT-/Tegafur-based Chemotherapy Versus Postoperative Radiotherapy for Early-stage Non-small Cell Lung Cancer: A Systematic Review and Network Meta-analysis

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ABSTRACT

Background: Both of UFT-/Tegafur-based postoperative chemotherapy and postoperative radiotherapy have made large progress in treatment of early-stage non-small cell lung cancer. While it is unclear that, whether UFT-/Tegafur-based postoperative chemotherapy is superior to postoperative radiotherapy for early-stage non-small cell lung cancer with no direct evidence. **Methods:** Electronic databases (Pubmed, embase, cochrane library and clinicaltrials.gov) were searched to obtain relevant studies. This systematic review and meta-analysis is reported in accordance with the Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (number **CRD42018095979**). Sensitive analysis was conducted by excluding overweight studies. Funnel plot and egger's test were performed to conduct publication bias. **Results:** Twenty-one randomized control trials were included. Our results suggested UFT-/Tegafur-based postoperative chemotherapy could improve overall survival over postoperative radiotherapy [HR=0.69 (0.59-0.80), p=0.000]. But subgroup analysis about stage showed there was no significant difference between them, no matter of stage I, II and III. As to chemotherapy regime, both UFT-/Tegafur + platinum+vinca alkaloid [HR=0.68 (0.56-0.82), p=0.000] and UFT-/Tegafur only [HR=0.66 (0.54-0.79), p=0.000] were superior to radiotherapy. Subgroup analysis about radiotherapy delivery method and dose showed, significant improvement of chemotherapy over radiotherapy for Cobalt-60 only [HR=0.54 (0.39-0.75), p=0.000], Cobalt-60 and linac [HR=0.69 (0.59-0.81), p=0.000] and ≥45 Gy [HR=0.64 (0.54-0.75), p=0.000], but not for linac only [HR=0.78 (0.60-1.03), p=0.081] and ≥ 45 Gy [HR=0.86 (0.67-1.11), p=0.241]. **Conclusion:** UFT-/Tegafur-based postoperative chemotherapy was superior to postoperative radiotherapy for improving overall survival of early-stage non-small cell lung cancer, but it is not always so under certain circumstance, such as RT delivery method and radiation dose. Of course, it is imperative to further explore differences in specific stage, such as I A and I B.

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1. Introduction

Non-small cell lung cancer (NSCLC) is a malignant tumor with high mortality, accounting for about 85% of lung cancer. [1] Because of the high invasiveness and rapid progress, it is very important to carry out effective treatment of NSCLC in the early stage. Although surgical resection is currently the standard treatment for early NSCLC, long-term postoperative survival is unsatisfactory. [2-3] Therefore, many studies have explored the efficacy of postoperative UFT/Tegafur-based adjuvant chemotherapy and radiotherapy.

Through systematic retrieval, we have found that most studies have shown that UFT/Tegafur based adjuvant chemotherapy improves overall survival, [4-6] but postoperative radiotherapy seems not. [7-8] In addition, most clinicians also think that postoperative UFT/Tegafur-based adjuvant chemotherapy is better than postoperative radiotherapy, but there is no direct evidence. Moreover, new studies have found that postoperative radiotherapy may also improve survival rates in early non-small cell lung cancer patients. [9-10] Therefore, the difference of UFT/Tegafur-based postoperative adjuvant chemotherapy and postoperative radiotherapy in the treatment of early non-small cell lung cancer is puzzling. In recent years, network meta-analysis, a method of obtaining evidence from evidence-based medicine, has been paid much attention to. Indirect comparison, as a special type of meta-analysis with reliabie results, [11-12] is also widely used. [13-14] Given no report of direct comparison between UFT/Tegafur based postoperative adjuvant chemotherapy and radiotherapy in treatment of early-stage non-small cell lung cancer, we performed this systematic review and network meta-analysis, expecting to provide assistance for clinic.

2. Methods

2.1 Search Strategy

Relevant published or unpublished RCT studies were selected by searching Pubmed, Embase, Cochrane library and ClinicalTrials.gov. We used MESH terms “chemotherapy”, “radiotherapy”, “surgery” and “Carcinoma, non-small cell lung”, and the retrieval strategy of Pubmed as follow: surgery[Title/Abstract] OR “General Surgery” [Mesh] AND Therapy, Drug [Title/Abstract] OR Drug Therapies [Title/Abstract] OR Therapies, Drug [Title/Abstract] OR Chemotherapy [Title/Abstract] OR Chemotherapies Pharmacotherapy [Title/Abstract] OR Pharmacotherapies [Title/Abstract] OR “Drug Therapy” [Mesh] AND placebo [Title/Abstract] OR “Controlled Clinical Trial” [Publication Type] OR “Randomized Controlled Trial” [Publication Type] AND Carcinoma, Non Small Cell Lung [Title/Abstract] OR Carcinomas, Non-Small-Cell Lung [Title/Abstract] OR Lung Carcinoma, Non-Small-Cell [Title/Abstract] OR Lung Carcinomas, Non-Small-Cell [Title/Abstract] OR Non-Small-Cell Lung Carcinomas [Title/Abstract] OR Nonsmall Cell Lung Cancer [Title/Abstract] OR Non-Small-Cell Lung Carcinoma [Title/Abstract] OR Non Small Cell Lung Carcinoma [Title/Abstract] OR Carcinoma, Non-Small Cell Lung [Title/Abstract] OR Non-Small Cell Lung Cancer [Title/Abstract] OR “Carcinoma, Non-Small-Cell Lung” [Mesh] OR radiation therap* [Title/Abstract] OR PORT [Title/Abstract] OR Radiother* [Title/Abstract] OR “Radiotherapy” [Mesh] AND surgery [Title/Abstract] OR “General Surgery” [Mesh] AND Carcinoma, Non Small Cell Lung [Title/Abstract] OR Carcinomas, Non-Small-Cell Lung [Title/Abstract] OR Lung Carcinoma, Non-Small-Cell [Title/Abstract] OR Lung Carcinomas, Non-Small-Cell [Title/Abstract] OR Non-Small-Cell Lung Carcinomas [Title/Abstract] OR Nonsmall Cell Lung Cancer [Title/Abstract] OR Non-Small-Cell Lung Carcinoma [Title/Abstract] OR Non Small Cell Lung Carcinoma [Title/Abstract] OR Carcinoma, Non-Small Cell Lung [Title/Abstract] OR Non-Small Cell Lung Cancer [Title/Abstract] OR “Carcinoma, Non-Small-Cell Lung” [Mesh] AND placebo [Title/Abstract]) OR “Controlled Clinical Trial” [Publication Type] OR “Randomized Controlled Trial” [Publication Type]. Additional new studies were identified by reading included studies and relevant reviews. All of the postoperative chemotherapy regime was UTF/Tegarfur-based. This systematic review and meta-analysis is reported in accordance with the Preferred Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (number CRD42018095979). Randomized control trials were included if they met following criteria: (1) postoperative chemotherapy vs surgery alone; (2) postoperative radiotherapy vs surgery alone; (3) early-stage non-small cell lung cancer; (4) providing estimates of overall survival.

2.2 Data Extraction

Two authors (LX Yu and M Song) independently extracted the original data. Disagreement was resolved by discussion. The extracted data were consisted of the follow items: the first author’s name, publication year, methods, study design, matching criteria, total number of cases and controls, stage and therapy regime.

2.3 Statistical Analysis

Review manager 5.3 and Stata 14.0 were performed to conduct this meta-analysis. Taking low heterogeneity into

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account, we use fixed effect model to pool estimates. In addition, we excluded the researches with overweight to conduct sensitive analysis and implement subgroup analysis to explore the differences of postoperative chemotherapy and postoperative radiotherapy of non-small cell lung stage and therapy regime. Publication bias was tested by funnel plot and egger's test, and P value of egger's test < 0.05 is considered significant. Hazard ratio with 95%CI and odds ratio with 95%CI were used to assess estimates of survival.

3. Results

3.1 Eligible Studies

As shown in Figure 1, total twenty-one randomized control trials [15-35] were identified finally, eleven about postoperative UFT/Tegafur-based chemotherapy [15-25] and ten about postoperative radiotherapy. [26-35] Two studies were from Study Group for Adjuvant Chemotherapy for Lung Cancer (SGACLC ACTLC), and one study was from Lung Cancer Study Group (LCSG). Especially, one study obtained from the reference is an unpublished data. Characteristics of included studies were shown in Table 1. The range of size was from 58 to 999, and chemotherapy regime mainly contained UFT/Tegarfur + platinum + vinca alkaloid and UFT/Tegarfur only. Characteristics of included studies were shown in Table 1. Methodological quality graph and summary were in Figure 2 and Figure 3.

Table 1. Characteristics of included studies

Study, year	Methods	Size (n)	Intervention	Stage	Therapy regime
SGACLC ACTLC, 1992	RCT:1982 to 1985	306	Postoperative CT	NK	Cisplatin,mitomycin,tegafur
SGACLC ACTLC, 1995	RCT:1985 to 1987	332	Postoperative CT	Ⅰ，Ⅱ，Ⅲ	Cisplatin,doxorubicin,UFT
Wada H, 1996	RCT:1985 to 1988	208	Postoperative CT	Ⅰ，Ⅱ，Ⅲ	Tegarfur,uracil
	RCT:1985 to 1988	323	Postoperative CT	Ⅰ，Ⅱ，Ⅲ	Cisplatin,vindesine,UFT
Wada H, 1999	RCT:1988 to 1989	225	Postoperative CT	Ⅰ，Ⅱ	Cisplatin,vindesine,mitomycin,tegarfur,uracil
Xu G, 1998	RCT:1989 to 1992	70	Postoperative CT	Ⅰ，Ⅱ，Ⅲ	Cisplatin,vindesine,doxorubicin,cyclophosphamide
Imaizumi M, 2005	RCT:1982 to 1988	104	Postoperative CT	Ⅰ	Cisplatin,vindesine,tegarfur,uracil
	RCT:1992 to 1995	104	Postoperative CT	Ⅰ	Tegarfur,uracil
Nakagawa M, 2005	RCT:1991 to 1994	367	Postoperative CT	Ⅰ，Ⅱ	Tegarfur,uracil
Nakagawa K, 2006	RCT:1992 to 1994	172	Postoperative CT	Ⅰ	Tegarfur,uracil
	RCT:1992 to 1994	95	Postoperative CT	Ⅱ，Ⅲ	Cisplatin,vindesine,tegarfur,uracil
Sawamura K, 1988	RCT:1982 to 1987	321	Postoperative CT	Ⅰ	Tegarfur
	RCT:1982 to 1986	83	Postoperative CT	Ⅱ，Ⅲ	Doxorubicin,mitomycin,tegarfur
	RCT:1982 to 1987	28	Postoperative CT	Ⅱ	Cisplatin,tegarfur
Endo C, 2003	RCT:1992 to 1994	219	Postoperative CT	Ⅰ，Ⅱ	Tegarfur,uracil
Kato H, 2004	RCT:1994 to 1997	999	Postoperative CT	Ⅰ	Tegarfur,uracil
Chang Y,2015	Pooled analysis of RCT	58	Postoperative RT	Ⅰ	54 Gy in three 18 Gy fractions/ 50 Gy in four 12.5 Gy fractions within 5 days
					54 Gy in three 18 Gy fractions over 5-8 days/ 60 Gy in four 12 Gy fractions over 10-14 days
Park JH, 2007	RCT:1989 to 1998	111	Postoperative RT	Ⅱ，Ⅲ	50.4 to 55.8 Gy in 1.8 to 2 Gy fractions, 5 times a week
EORTC 0886, 2000	RCT:1986 to 1990	106	Postoperative RT	Ⅱ，Ⅲ	56 Gy in 28 fractions in 5.5 weeks
van Houtte P, 1980	RCT:1966 to 1977	224	Postoperative RT	Ⅰ，Ⅱ，Ⅲ	60 Gy in 30 fractions in 6 weeks
Feng QF, 2000	RCT:1981 to 1995	317	Postoperative RT	Ⅱ，Ⅲ	60 Gy in 30 fractions in 6 weeks
Dautzenberg B, 1999	RCT:1986 to 1994	189	Postoperative RT	Ⅰ，Ⅱ，Ⅲ	60 Gy in 24 to 30 fractions in 6 weeks
	RCT:1988 to 1994	539	Postoperative RT	Ⅰ，Ⅱ，Ⅲ	60 Gy in 24 to 30 fractions in 6 weeks
LCSG, 1986	RCT:1978 to 1985	230	Postoperative RT	Ⅱ，Ⅲ	50 Gy in 25 to 27.5 fractions in 5 to 5.5 weeks
Stephens RJ, 1996	RCT:1986 to 1993	308	Postoperative RT	Ⅱ，Ⅲ	40 Gy in 15 fractions in 3 weeks
Lafitle JJ, 1996	RCT:1985 to 1991	163	Postoperative RT	Ⅰ	45 to 60 Gy in 22.5 to 30 fractions in 6weeks
Trodella L, 2002	RCT:1989 to 1997	104	Postoperative RT	Ⅰ	50.4 Gy in 1.8 Gy/d in 5 weeks and 3 days

NK, not known; RCT, randomised controlled trial; CT, chemotherapy; RT, radiotherapy; Gy-Gray,unit of radiotherapy dose; UFT, Uracil/tegafur

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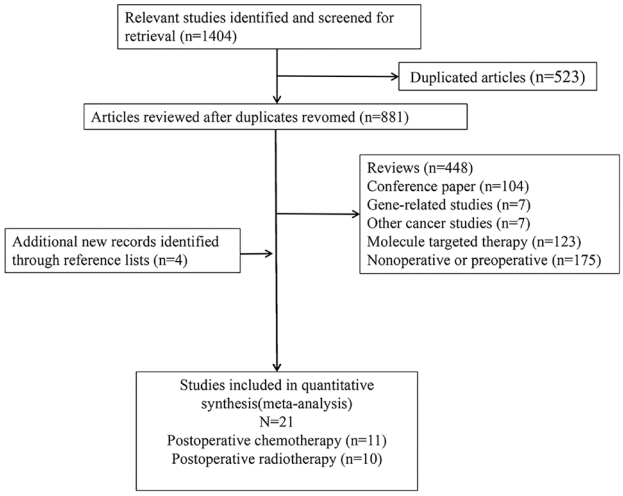

Figure 1. Quality of reporting of meta-analyses flow diagram.

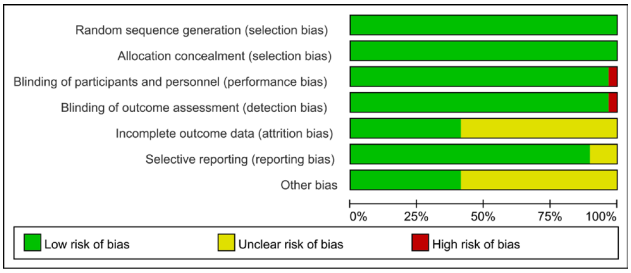

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

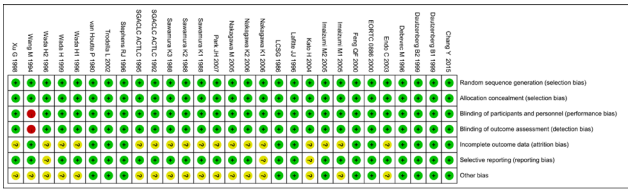

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

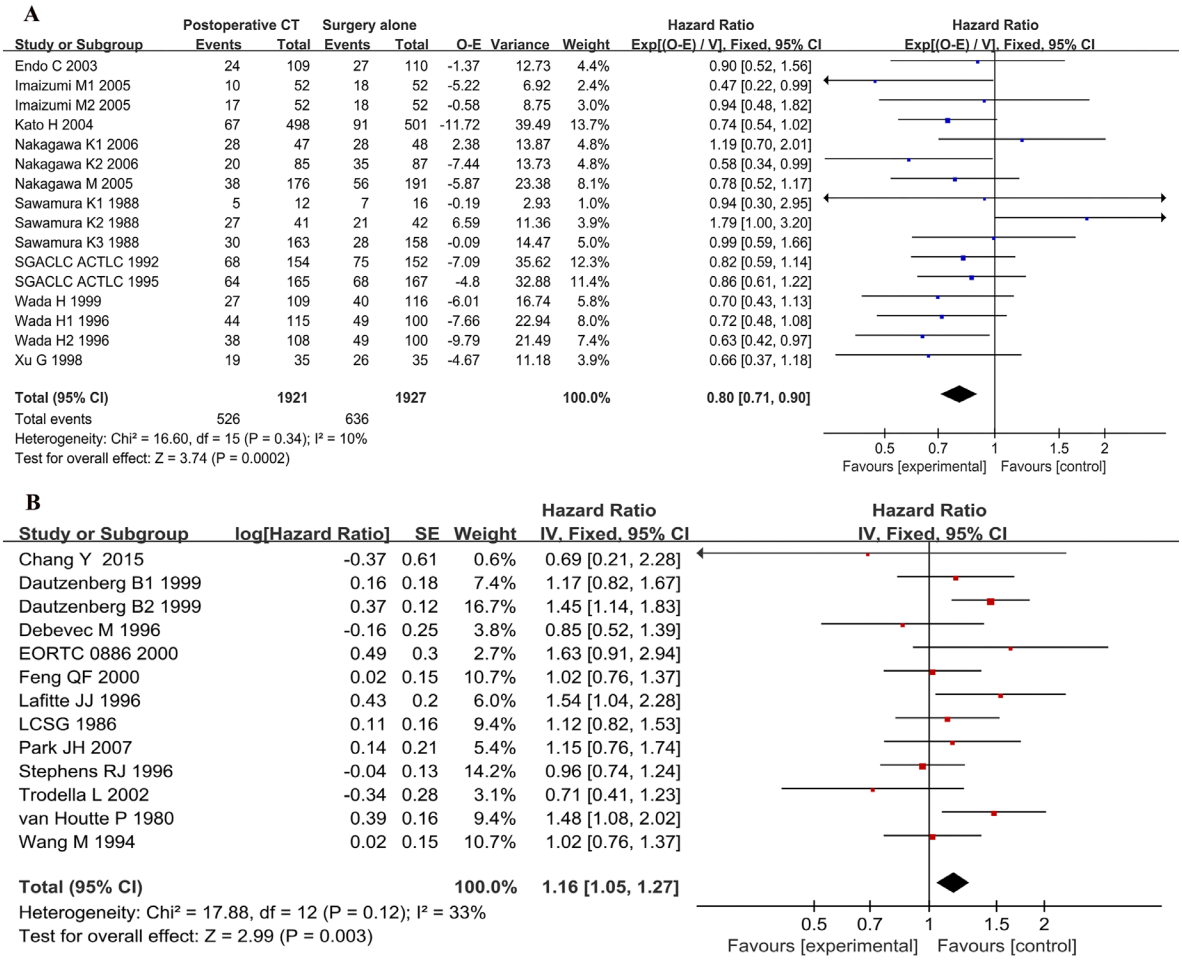

Figure 4. Forest plots of postoperative chemotherapy vs surgery alone group (A) and postoperative radiotherapy vs surgery alone group (B)

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3.2 Overall Survival

For overall survival, the pooled Hazard Ratios of death were 0.80 (0.71-0.90, p=0.0002) and 1.16 (1.06-1.27, p=0.003) in postoperative UFT/Tegarfur-based chemotherapy vs surgery alone group and postoperative radiotherapy vs surgery alone group, respectively. Network indirect comparison suggested that postoperative UFT/Tegarfur-based chemotherapy could improve overall survival over postoperative radiotherapy [HR=0.69 (0.59-0.80), p=0.000], which was shown in Table 2.

3.3 Subgroup Analysis

To explore potential influential factors, subgroups analysis about non-small cell lung cancer stage and therapy regime were performed. For stage, there no evidence of important statistical significance between postoperative chemotherapy and postoperative radiotherapy [stage Ⅰ HR=0.80 (0.64-1.00), p=0.051, stage Ⅱ HR=0.79 (0.50-1.26), p=0.324, stage Ⅲ HR=0.88 (0.58-1.36), p=0.574]. For chemotherapy regime, both UFT/Tegarfur+platinum+vinca alkaloid and UFT/Tegarfur only could improve overall survival over radiotherapy [HR=0.68 (0.56-0.82), p=0.000, 0.66 (0.54-0.79), p=0.000]. In terms of RT delivery method, postoperative chemotherapy is superior to postoperative radiotherapy in Cobalt-60 only [HR=0.54 (0.39-0.75), p=0.000] and Cobalt-60 and linac [HR=0.69 (0.59-0.81), p=0.000], but not in linac only[HR=0.78 (0.60-1.03), p=0.081]. Similarly, with ≥45 Gy radiation dose, there existed significant difference between postoperative chemotherapy and postoperative radiotherapy [OR=0.64 (0.54-0.75), p=0.000], while not with ＜ 45 Gy radiation dose [OR=0.86 (0.67-1.11), p=0.241]. The main results were shown in Table 2.

Table 2. Summary effect of survival index

Outcome/Subgroup	No. Of patients	Statistical method	Effect size (relative value)	P value
Overall survival	3956/2349	Hazard Ratio (Fixed, 95%CI)	**0.69 (0.59-0.80)**	**0.000**
Subgroup (stage)				
Stage I	2574/572	Hazard Ratio (Fixed, 95%CI)	0.80 (0.64-1.00)	0.051
Stage II	190/817	Hazard Ratio (Fixed, 95%CI)	0.79 (0.50-1.26)	0.324
Stage III	178/746	Hazard Ratio (Fixed, 95%CI)	0.88 (0.58-1.36)	0.574
Subgroup (chemotherapy regime)				
UFT/Tegafur+P+VA	1375/2349	Hazard Ratio (Fixed, 95%CI)	**0.68 (0.56-0.82)**	**0.000**
UFT/Tegafur only	2390/2349	Hazard Ratio (Fixed, 95%CI)	**0.66 (0.54-0.79)**	**0.000**
Subgroup (RT delivery method)				
Cobalt-60 only	3956/202	Hazard Ratio (Fixed, 95%CI)	**0.54 (0.39-0.75)**	**0.000**
Cobalt-60 and linac	3956/2063	Hazard Ratio (Fixed, 95%CI)	**0.69 (0.59-0.81)**	**0.000**
Linac only	3956/395	Hazard Ratio (Fixed, 95%CI)	0.78 (0.60-1.03)	0.081
Subgroup (radiation dose)				
≥45 Gy	3956/2019	Odds Ratio (Fixed, 95%CI)	**0.64 (0.54-0.75)**	**0.000**
＜ 45 Gy	3956/382	Odds Ratio (Fixed, 95%CI)	0.86 (0.67-1.11)	0.241
No. Of patients, postoperative chemotherapy/postoperative radiotherapy P+VA, platinum+vinca alkaloid				

3.4 Sensitive Analysis and Publication Bias

We excluded overweight studies, such as Kato et al, SGACLC ACTLC and Dautzenberg2 et al, to conduct sensitive analysis, and final result was not changed [HR=0.69 (0.57-0.84), p=0.000]. Funnel plots were shown in Figure 4. Egger's test suggested that there was no publication bias in postoperative UFT/Tegarfur-based chemotherapy group (p=0.637) and postoperative radiotherapy group (p=0.417).

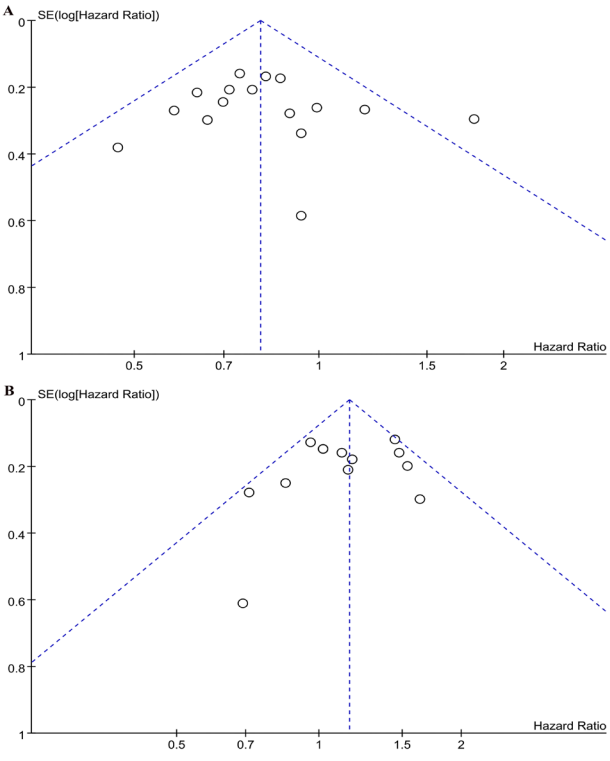

Figure 5. Funnel plots of postoperative chemotherapy vs surgery alone group (A) and postoperative radiotherapy vs surgery alone group (B)

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4. Discussion

Surgical resection is the recommended method for the treatment of non-small cell lung cancer, but the postoperative survival rate is always unsatisfactory, even in the early stage, the 5-year survival rate is only 45.1%, [36] so the choice of postoperative adjuvant treatment is very important. Recent years, many scholars have studied the effects of postoperative UFT/Tegarfur-based adjuvant chemotherapy and adjuvant radiotherapy in the treatment of early-stage non-small cell lung cancer. The results showed that UFT/Tegarfur-based adjuvant chemotherapy seemed to be superior to postoperative adjuvant radiotherapy, but there was no definitive comparative evidence. Therefore, we wonder much that UFT / Tegarfur based adjuvant chemotherapy is really better than postoperative adjuvant radiotherapy? If so, is it true for every aspect, such as specific stage? Based on that, we conducted the network meta-analysis. Our results showed that UFT/Tegarfur based adjuvant chemotherapy could significantly improve the overall survival rate of patients [HR=0.69 (0.59-0.80) p=0.000] compared with postoperative adjuvant radiotherapy, but it also changed with different stages and radiotherapy methods.

UFT is an oral fluorouracil preparation that combines tegafur, a prodrug of 5-fluorouracil, with uracil, which inhibits dihydropyrimidine dehydrogenase, the rate-limiting enzyme responsible for 5-fluorouracil catabolism. Tegafur, the major component of UFT, is metabolized to gamma-hydroxybutyric acid and gammabutyrolactone, which inhibit angiogenesis. In recent years, UFT/Tegarfur-based postoperative adjuvant chemotherapy has made great progress in the treatment of early non-small cell lung cancer. Hotta K et al [4] discovered that therapy with tegafur and uracil (UFT; HR, 0.799; 95% CI, 0.668 to 0.957; P =0.015) could yield a significant survival benefit to early-stage NSCLC. In 2005, Hamada C et al [37] showed that postoperative adjuvant chemotherapy with UFT was associated with improved 5- and 7-year survival in a Japanese early-stage NSCLC patient population, whose overall pooled hazard ratio was 0.74 and 95% CI was 0.61 to 0.88 (P =0.001). And in 2009, Hamada C et al [6] reported significant hazard ratio even was 0.62, with much better than before. UFT/Tegarfur based postoperative adjuvant chemotherapy may be promising for early-stage NSCLC.

Most previous studies [7-8] have shown that postoperative radiotherapy couldn't effectively improve the survival rate of early non-small cell lung cancer patients, so the clinical treatment of this program is relatively conservative. But the latest researches have come to the opposite conclusions. Sakib N et al [9] suggested that the addition of PORT significantly improves survival in patients with resectable stage IIIA-N2 NSCLC [HR=0.73（0.58-0.92）,P = 0.008]. Likewise, Patel SH et al [10] reached similar conclusion in III-N2 NSCLC [HR=0.73 （0.58-0.92）,P = 0.008]. In the face of this outcome, we included randomized controlled trials of higher quality, and the results suggested that postoperative radiotherapy might not improve the survival rate of patients with early non-small cell lung cancer [HR = 1.16 (1.06-1.27), P = 0.003]. But this does not necessarily mean that UFT/Tegarfur-based postoperative adjuvant chemotherapy is superior to postoperative radiotherapy in all aspects.

We therefore further compared the effects of UFT/Tegarfur-based postoperative adjuvant chemotherapy with postoperative radiotherapy, and performed a comprehensive analysis of the different stages, chemotherapy regimens, radiotherapy methods and doses of the subgroups Our results suggest that UFT/Tegarfur-based postoperative adjuvant chemotherapy does improve survival in patients with early-stage non-small cell lung cancer [HR = 0.69 (0.59-0.80), P = 0.000], regardless of the chemotherapy regimen（Table 2）. [UFT/Tegafur+P+VA, HR= 0.68 (0.56-0.82), p=0.000; UFT/Tegafur only, HR= 0.66 (0.54-0.79), p=0.000]. However, no significant difference exhibited in stage. [Stage Ⅰ, HR= 0.80 (0.64-1.00), p=0.051; Stage Ⅱ, HR= 0.79 (0.50-1.26), p=0.324; Stage Ⅲ, HR= 0.88 (0.58-1.36), p=0.574] （Table 2）. We may also need sufficient data to further refine staging studies, such as I A, I B, II A, III A. In terms of radiotherapy methods and doses, the results are inconsistent. In the cobalt-60, Cobalt-60 + linac and≥45Gy, the UFT/Tegarfur based postoperative adjuvant chemotherapy could improve early-stage NSCLC overall survival over postoperative radiotherapy [Cobalt-60 only, HR=0.54 (0.39-0.75), p= 0.000; Cobalt-60 and linac, HR= 0.69 (0.59-0.81), p= 0.000; ≥45 Gy, HR= 0.64 (0.54-0.75), p= 0.000]（Table 2）, However, when Linac only and < 45 Gy, there was no significant difference between the two adjuvant regimens. [Linac only, HR= 0.78 (0.60-1.03), p= 0.081; < 45 Gy, HR= 0.86 (0.67-1.11), p= 0.241].（Table 2）.Therefore, UFT/Tegarfur-based postoperative adjuvant chemotherapy isn't always superior to radiotherapy, and the reasons need to be further explored. Sensitivity analysis and publication bias test showed that our results were stable and reliable.

We also need to point out the limitations of our research. First, we do not have enough data for more detailed phased studies, which may be an important reason for the differences in outcomes. Secondly, whether there are differences in the effectiveness of histology is the question we will explore in the future. Finally, we failed to match sample size completely.

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5. Conclusion

Our study suggests that UFT/Tegarfur based postoperative adjuvant chemotherapy may not always be superior to postoperative radiotherapy, and it seems to be closely related to specific treatment methods, especially different radiotherapy interventions. Of course, detailed stage needs to be explored in the future. Our results change our previous understanding that postoperative UFT/Tegarfur-based chemotherapy is always superior to postoperative radiotherapy, which allows us to weigh the options of different methods.

List of abbreviations

Randomized control trials, RCT; Non-small cell lung cancer, NSCLC; Study Group for Adjuvant Chemotherapy for Lung Cancer, SGACLC ACTLC; Lung Cancer Study Group, LCSG; Hazard RatioHR.

Declarations

Ethical Approval and Consent to participate: Non-essential Consent for publication: All authors agree. Availability of data and material: All data and material are Availabile. Competing interests: The authors report no conflicts of interest in this work Funding: None.

Authors' Contributions

LX Yu and M Song conceived and designed the methods, extracted the original data and drafted the manuscript. LX Yu and SF Ji performed statistical analysis. SF Ji interpreted results and revised the manuscript. SF Ji and M Song had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

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