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Impact of previous extra-pulmonary malignancies on surgical outcomes of sequential primary non-small cell lung cancer

Chenxi Zhang [a,b,1], Xiyang Tang [a,1], Wenhao Liu [b], Kaifu Zheng [a], Xiaofei Li [c], Nan Ma [d,**], Jinbo Zhao [a,*]

[a] Department of Thoracic Surgery, Tangdu Hospital, Air Force Medical University. No.569, Xinsi Road, Xi'an, Shaanxi, 710038, China
[b] Department of Cardio-thoracic Surgery, 900 Hospital of PLA, Fuzhou, Fujian, 350001, China
[c] Department of Thoracic Surgery, Chest Hospital, Xi'an International Medical Center, No.777, Xitai Road, Xi'an, Shaanxi, 710100, China
[d] Department of Ophthalmology, Tangdu Hospital, Air Force Medical University, No.569, Xinsi Road, Xi'an, Shaanxi, 710038, China

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ABSTRACT

Reduced cancer deaths have led to an increase in the number of cancer survivors and the risk of the second primary tumor. This study explored the surgical outcomes of patients with non-small cell lung cancer as the second primary tumor and the impact of previous extra-pulmonary malignancies. Patients' data were obtained from Surveillance, Epidemiology and End Results database. The patients were divided into lung surgery and non-surgery groups. Propensity-score matching was used to balance potential confounders. Kaplan-Meier curves were generated to test the overall survival and lung-cancer-specific survival. Cox regression analysis was performed to calculate death risk. In total 3054 lung surgery and 1094 non-surgery patients with stage I-II non-small cell lung cancer as the second primary tumor were included. The surgery group showed longer overall survival (68 vs. 22 months) and lung cancer-specific survival (not reached vs. 37 months) than those of non-surgery groups (both $P < 0.001$). Patients with previous hormone-dependent malignancies had similar survival rates (overall survival: 22 vs. 20 months, $P = 0.666$; lung cancer-specific survival: 38 vs. 37 months, $P = 0.292$) as those with non-hormone dependent malignancies in the non-surgery group. Significantly longer overall survival (90 vs. 60 months, $P = 0.001$) was observed in patients with hormone-dependent malignancies in the surgery group; however, there was no difference in lung cancer-specific survival ($P = 0.225$). Competing risk analysis showed that for patients undergoing lung surgery, there was higher previous malignancy-induced mortality in patients with non-hormone dependent malignancies than in patients with hormone-dependent malignancies. However, there was no difference in lung cancer-induced mortality between the two groups. Patients who underwent lobectomy showed longer survival than those who underwent pneumonectomy and other resection types (89, 27.5 and 65 months, $P < 0.001$). In summary, lung surgery is beneficial for patients with stage I-II non-small cell lung cancer as the second primary tumor after hormone-dependent malignancy resection.

Abbreviations: NSCLC, non-small cell lung cancer; NSCLC-2, non-small cell lung cancer as the second lung cancer; PSM, propensity-score matching; OS, overall survival; LCSS, lung cancer specific survival; AJCC, American Joint Committee on Cancer.

* Corresponding author.
** Corresponding author.
E-mail addresses: nan_ma@163.com (N. Ma), zhaojinbo@aliyun.com (J. Zhao).

[1] These authors contributed equally to this manuscript.

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1. Introduction

The cancer death rate has declined by approximately 31% from its peak in 1991–2018, resulting in an increasing number of cancer survivors at high risk of the second primary tumor [1,2]. Lung cancer accounts for one-third of the second primary tumors [3], and non-small cell lung cancer (NSCLC) is the predominant histological type [4]. However, there is still no consensus on the indication for surgery in patients with a history of extra-pulmonary malignancy followed by NSCLC as the second primary tumor (NSCLC-2).

A series of retrospective studies have demonstrated the effectiveness of surgery on patients with early-stage NSCLC-2 [5–9]. Nonetheless, most of these studies were single-center analyses with small sample sizes or only one specific previous malignancy. The universality and generalizability of these benefits in patients with different previous malignancies should be verified.

To explore the surgical outcomes and the impact of previous extra-pulmonary malignancies on the prognosis of patients with early-stage NSCLC-2, the Surveillance, Epidemiology and End Results (SEER) database [10] was used to extract data from cases of NSCLC-2 following ten extra-pulmonary malignancies with highest incidence globally in both male and female, respectively [11].

2. Materials and methods

Informed consent and ethical approval for this study was waived by the ethics committee of Tangdu Hospital owing to the public access and unidentified patient information in the SEER database.

2.1. Participants

The SEER-9, SEER-13, and SEER-18 registries were used to retrieve eligible candidates according to the international classification of disease for oncology, third edition (ICO-D-3). Patients meeting the following criteria were included: (I) age >18 years at the time that the first or the second malignancy was diagnosed; (II) histologically confirmed malignancy regardless of the first or the second malignancy; (III) non-small cell lung cancer diagnosed as a second malignancy; (IV) surgically treated extra-pulmonary malignancies before NSCLC-2; and (V) stage I and II NSCLC-2 according to the 8th edition of American Joint Committee on Cancer (AJCC) staging. Patients were excluded if they had more than two primary tumors other than NSCLC and one previous extra-pulmonary malignancy. Additionally, we excluded any duplicated patient data as shown by repeated patient ID numbers.

2.2. Identification of second primary non-small cell lung cancer

Because of the restricted enrollment criteria of the SEER database in multiple primary cancers, the labels “Patients ID” and “Sequence number” in the SEER database were used to identify cases of NSCLC-2 and the corresponding previous malignancies. Patients diagnosed with the following malignancies, which were labeled as the first primary tumor of the two malignancies, were retrieved from the year of establishment of SEER database to 2015. These malignancies included bladder, breast, cervical uteri, corpus uteri, colon, esophagus, kidney, liver, ovary, prostate, rectum, non-melanoma of the skin, stomach, and thyroid tumor. Data from patients with NSCLC-2 patients were extracted as follows: patients diagnosed with non-small cell lung cancer were labeled as the second primary of two or more malignancies from 2004 to 2015.

The “Patients ID” matched NSCLC-2 to its corresponding previous malignancy.

2.3. Data collection

The following variables of NSCLC-2 were collected: demographics (age, sex, race, year of diagnosis, household income, and rural-urban residence), tumor characteristics of (histology, differentiation, tumor laterality, tumor extension, tumor size, N-stage, and M-stage), treatment strategy (with or without surgery), and survival data (survival month from diagnosis of NSCLC and survival status). All stages of patients were re-classified according to the 8th edition of the AJCC System.

The following information on previous extra-pulmonary malignancies was also extracted: cancer type (bladder/breast/cervical uteri/corpus uteri/colon/esophagus/kidney/liver/ovary/prostate/rectum/non-melanoma of skin/stomach and thyroid), stage (in situ/localized/regional/distant), surgery performed or not, and survival data (survival month from diagnosis of first malignancy, and death of first malignancy or not).

The diagnostic interval between the two primary cancers was calculated as the survival months of the first malignancy minus that of NSCLC-2. Survival time was calculated from the time of diagnosis of NSCLC-2.

2.4. Endpoints

The primary and the secondary endpoints were overall survival (OS) and lung-cancer-specific survival (LCSS), respectively.

2.5. Propensity-score matching

Propensity-score matching (PSM) was performed to adjust for potential confounders that might be associated with survival between the surgery and non-surgery groups (including age at lung cancer diagnosis, race, sex, year of lung cancer diagnosis, histology,

tumor grade, tumor laterality, type of previous malignancy, diagnosis interval time, previous malignancy stage, lung cancer stage, house incomes and residence). Patients were matched by a 1:1 ratio using the nearest-neighbor method, and the caliper was restricted to 0.01 [12].

2.6. Statistical analysis

Category data were presented as n (%) and measured by chi-square or Fisher exact test. Survival curves were developed by Kaplan-Meier method and compared by log-rank test. A Cox regression model was established to estimate hazard ratios (HR) and 95% confidence intervals (CI). Competing risk analysis was conducted to calculate cancer-specific survival differences with adjusted competing events of previous malignancy [13,14]. A p-value below 0.05 was considered statistical difference.

Excel 2010 (Microsoft Inc., Redmond, WA, USA) and the "VLOOKUP" function were used for the "patient ID" matching of NSCLC-2 and its previous malignancy. All statistical analyses were performed by R software (version 4.0.5, r-project, http://www.r-project.org, RRID: SCR_001905).

3. Results

3.1. Clinical characteristics

In total, 600,866 patients with extra-pulmonary malignancies developed a second tumor, and 12,201 NSCLC-2 patients were

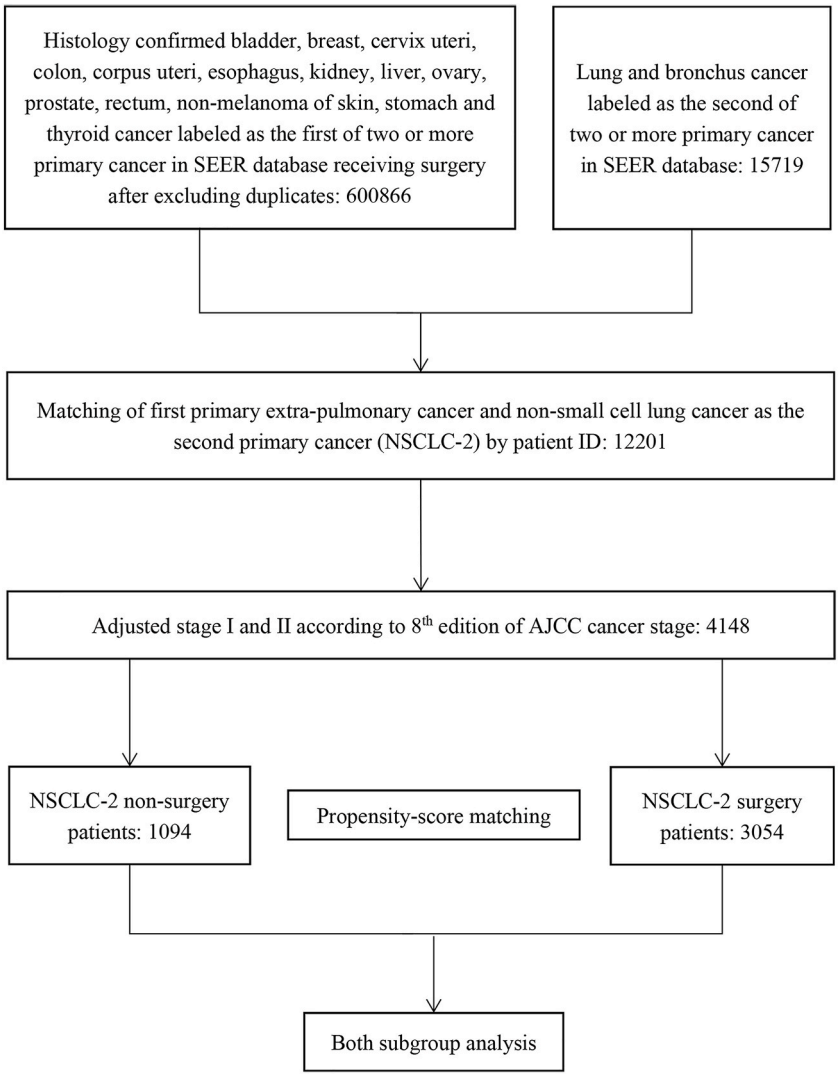

Fig. 1. Flowchart of patient selection.

identified in the database by patient ID matching, of which 4148 were stage I and II NSCLC-2. Among these, 3054 patients received lung surgery and 1094 did not (Fig. 1).

Regarding the proportion of previous malignancies, the breast (36.04%), colon (19.73%) and prostate (18.14%) were the most common locations in the entire NSCLC-2 cohort. Among male patients, those with previous prostate (45.28%), colon (27.00%) and rectum (9.26%) malignancies were the most common. Those with previous breast (59.45%), colon (14.87%) and corpus uteri (8.72%) malignancies were the most abundant among female patients (Fig. 2A). Median interval times from diagnosis of previous malignancy to NSCLC were as follows (months): esophagus (18), liver (22), stomach (22), colon (40), rectum (42), skin (44.5), kidney (49), thyroid (47), corpus uteri (55), breast (63), bladder (67), ovary (64.5), prostate (87.5) and cervix uteri (175) (Fig. 2B). Previous malignancies were categorized as hormone-dependent (bladder, thyroid, corpus uteri, ovary, breast, prostate and cervix uteri) or non-hormone-dependent (liver, stomach, esophagus, colon, rectum, kidney and skin) malignancies.

The detailed clinical characteristics of the patients divided into the lung surgery and non-surgery groups are presented in Supplementary Table 1.

3.2. Prognostic factors of NSCLC-2

Multivariate Cox regression analysis showed that lung surgery was a favorable prognostic factor for OS with an HR of 0.366 (95% CI: 0.332–0.404, $P < 0.001$) for survival. Patients with previous hormone-dependent malignancies had significantly better survival rates than those with non-hormone-dependent malignancies (HR: 0.862, 95%CI: 0.787–0.943). Age, sex, race, year of lung cancer diagnosis, histology, tumor grade, lung cancer stage, previous malignancy stage and residence were all independent prognostic factors for OS (all $P < 0.05$). For LCSS, lung surgery still showed benefits with an HR of 0.323 (95% CI: 0.283–0.368). Age, sex, year of lung cancer diagnosis, tumor grade, lung cancer stage, and residence were independent prognostic factors (all $P < 0.05$). Lung cancer histology and type of previous malignancy did not affect LCSS (both $P > 0.05$) (Supplementary Table 2).

3.3. Effectiveness of lung surgery

The median OS of lung surgery and non-surgery patients were 90 and 22 months ($P < 0.001$), respectively. The median LCSS in these two groups were not reached and 38 months ($P < 0.001$), respectively. The estimated 1-, 2-, 3-, 5-, and 10-year OS rates in the lung surgery group were 90.3%, 81.3%, 71.4%, 63.4% and 38.8%, respectively. The corresponding LCSS in the lung surgery group were 94.7%, 88.1%, 82.1%, 75.2% and 65.9%, respectively. The estimated 1-, 2-, 3-, 5-, and 10-year OS rates in the non-surgery group were 69.8%, 47.1%, 34.3%, 19.6% and 4.7%, respectively. The corresponding LCSS in the non-surgery group were 80.4%, 64.1%, 51.7%, 38.6% and 23.3%, respectively (Fig. 3A-B).

When patients were further stratified according to the lung cancer stage, lung surgery prolonged both OS (93 vs. 26 months, $P < 0.001$) and LCSS (not reached vs. 45 months, $P < 0.001$) in the stage I subgroup. Similar results were also observed in the stage II subgroup (OS: 43 vs. 14 months, $P < 0.001$; LCSS: 91 vs. 19 months, $P < 0.001$) (Supplementary Figs. 1A–1B).

To balance the potential confounders, a PSM was performed on 721 patients in each group (Supplementary Table 3). The median

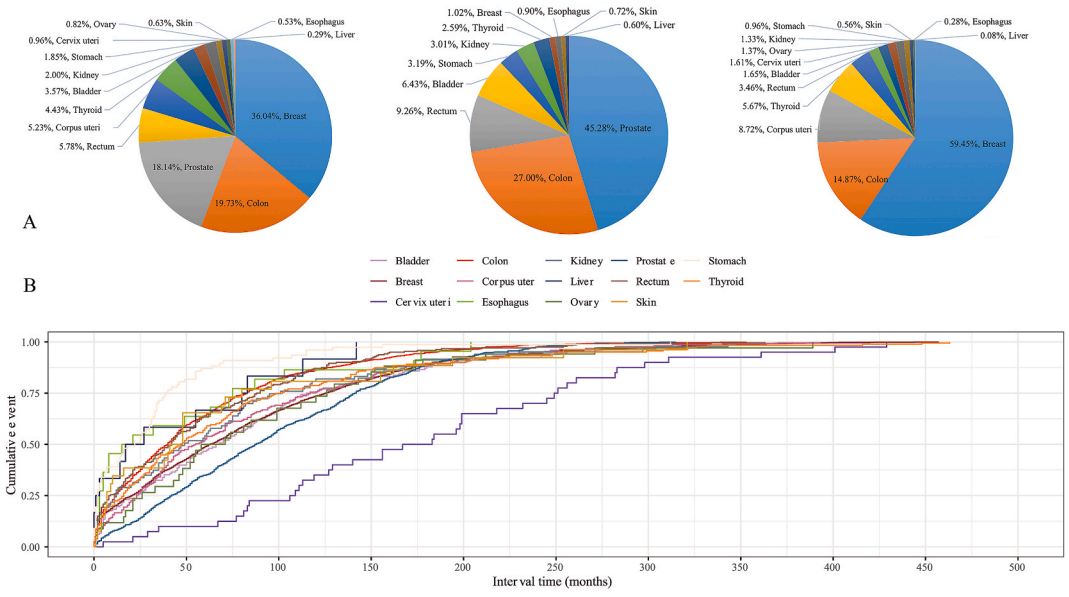

Fig. 2. Clinical information of patients with NSCLC-2. A: proportion of patients with different previous malignancies; B: time interval between previous malignancies and NSCLC-2. NSCLC-2: non-small cell lung cancer as the second primary tumor.

OS of lung surgery and non-surgery patients after PSM were 68 and 22 months, respectively ($P < 0.001$). The median LCSS of these two groups were not reached and 37 months ($P < 0.001$) (Fig. 4A-B).

In patients with previous hormone-dependent cancers, the median OS (90 vs. 22 months, $P < 0.001$) and median LCSS (not reached vs. 38 months, $P < 0.001$) were both prolonged in the lung surgery group. For patients with previous non-hormone-dependent cancer, lung surgery also showed benefits in terms of OS (60 vs. 20 months, $P < 0.001$) and LCSS (not reached vs. 37 months, $P < 0.001$) (Supplementary Figs. 2A–2D).

The median OS of patients with previous hormone-dependent and non-hormone-dependent malignancies in the lung surgery group were 22 and 20 months, respectively. After adjusting for confounders, there was no survival difference between the two cohorts (HR = 0.967, 95% CI: 0.831–1.125, $P = 0.666$). The median LCSS of these two cohorts were 38 and 37 months, respectively. No significant difference was found when after adjusting for confounders (HR: 0.900, 95% CI: 0.739–1.095, $P = 0.292$) (Fig. 5A-C).

In the non-surgery group, the median OS of patients with previous hormone-dependent and non-hormone-dependent malignancies were 90 and 60 months, respectively. Patients with previous hormone-dependent malignancies still showed significantly better survival rates than those with non-hormone-dependent malignancies (HR = 0.827, 95% CI: 0.737–0.927, $P = 0.001$). The LCSS of these two cohorts were both not reached and not statistically different after adjusting for confounders (HR: 0.902, 95% CI: 0.763–1.066, $P = 0.225$) (Fig. 5B-D).

A competing risk analysis was performed between patients with previous hormone-dependent and non-hormone-dependent malignancies in both the lung surgery and non-surgery groups. In the non-surgery group, there was no difference in lung-cancer-induced mortality ($P = 0.292$) or previous-malignancies-induced mortality ($P = 0.687$) between these two cohorts. In the lung surgery group, there was still no difference in lung-cancer-induced mortality between the two groups ($P = 0.225$). However, previous-malignancies-induced mortality in the non-hormone-dependent cohort was significantly higher than that in the hormone-dependent cohort ($P < 0.001$) (Supplementary Figs. 3A–3B).

Regarding the lung resection type, the median OS of lobectomy, pneumonectomy and other resection types were 89, 27.5 and 65 months, respectively ($P < 0.001$). The median LCSS of pneumonectomy was 97 months, but this were not reached for lobectomy and other resection types (Fig. 6A-B).

4. Discussion

This study is not the first to explore the characteristics and surgical outcomes of NSCLC-2 following previous extra-pulmonary

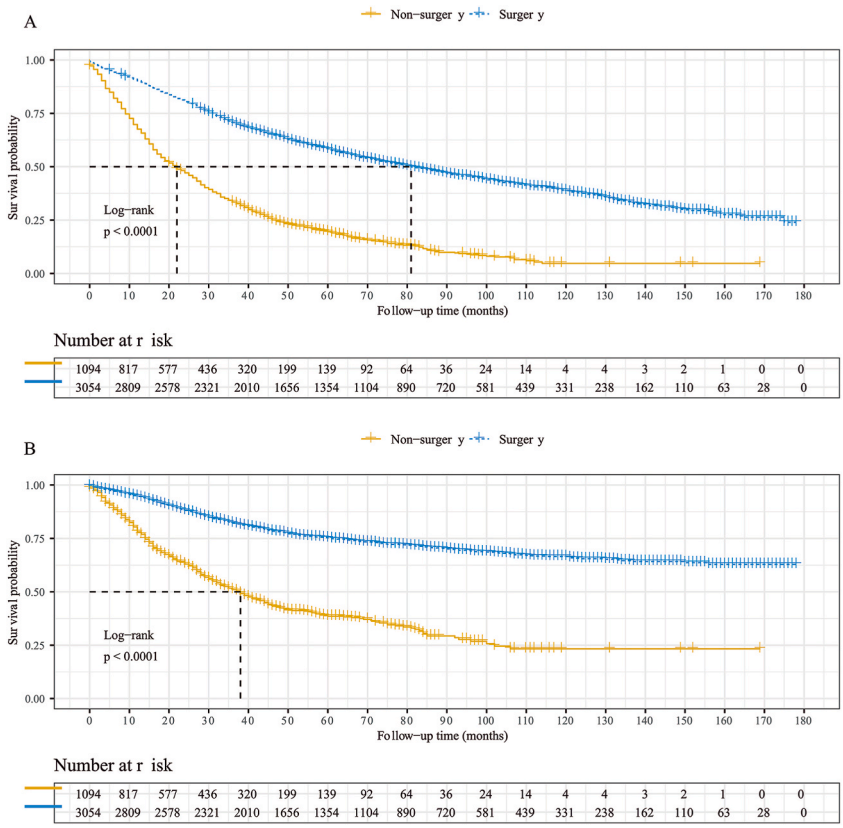

Fig. 3. Kaplan-Meier curve of all patients stratified by surgery and non-surgery. A: overall survival; B: lung cancer specific survival.

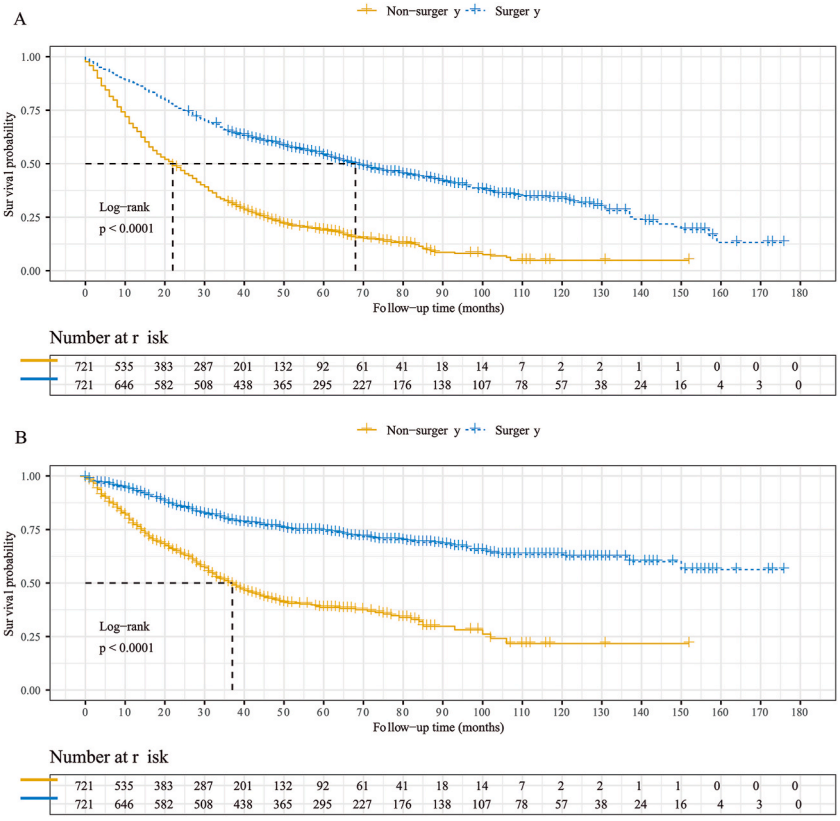

Fig. 4. Kaplan-Meier curve of patients with NSCLC-2 after propensity-score matching. A: overall survival; B: lung-cancer-specific survival.

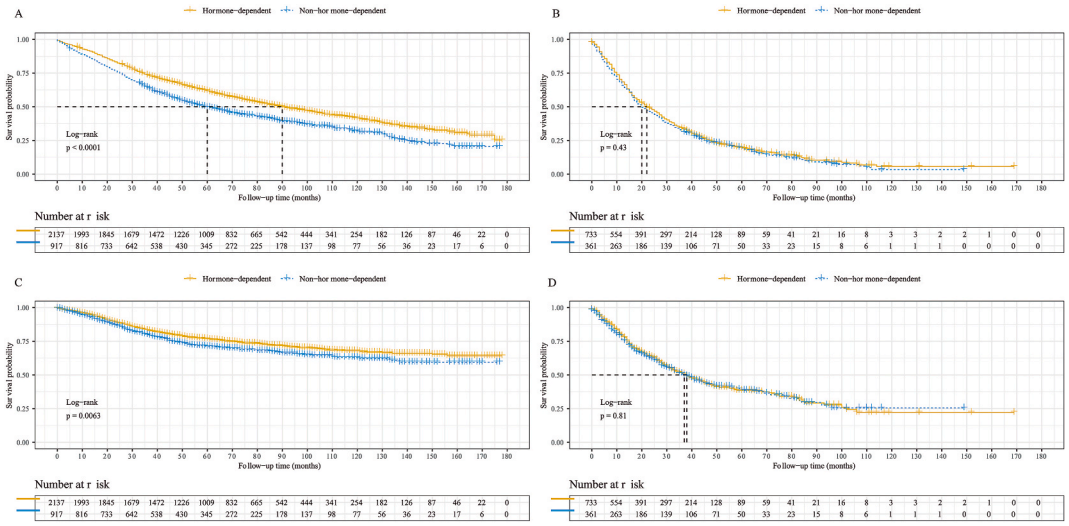

Fig. 5. Kaplan-Meier curve of patients with NSCLC-2 stratified by hormone-dependent and non-hormone-dependent malignancies. A: OS of patients with lung surgery; B: OS of patients without lung surgery; C: LCSS of patients with lung surgery; D: LCSS of patients without lung surgery. OS: overall survival; LCSS: lung-cancer-specific survival.

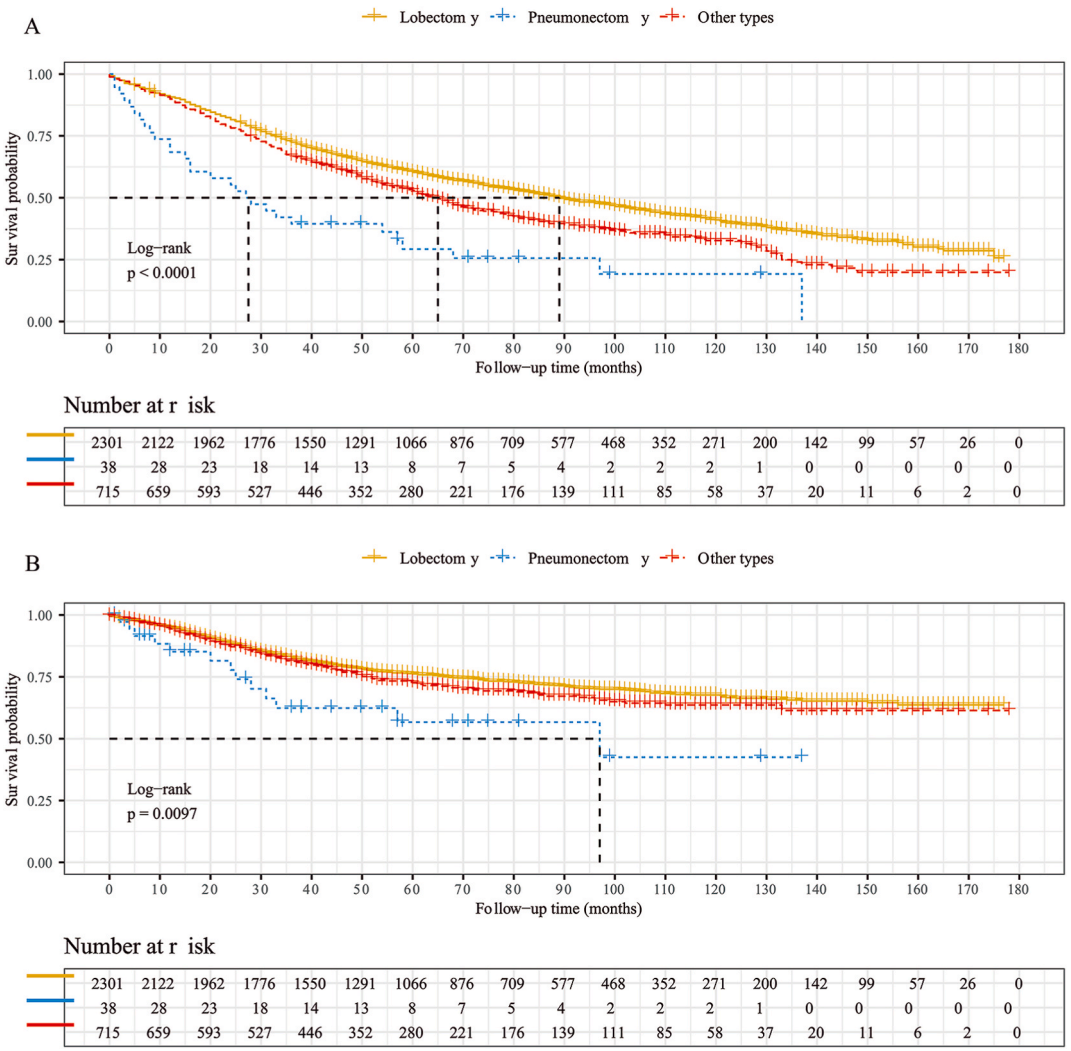

Fig. 6. Kaplan-Meier curve of patients with NSCLC-2 receiving different lung resection type. A: overall survival; B: lung cancer specific survival. NSCLC-2: non-small cell lung cancer as the second primary tumor.

malignancies. However, it further verified the effectiveness of surgery on NSCLC-2 by enrolling a series of cancer types based on a large population. It was also worth noting that previous cancer types played an essential role in the prognosis of NSCLC-2. Among patients who underwent lung surgery, those with previous hormone-dependent malignancies had significantly more favorable survival than those with non-hormone-dependent malignancies. Thus, patients with NSCLC-2 after extra-pulmonary malignancy resection are still eligible for lung surgery, and a standard treatment strategy for these patients should be established. However, it should be noted that patients with previous head and neck cancer were not included in the present analysis because of its relatively lower incidence, though it is reported to be more likely to develop a second lung cancer [15,16].

The incidence of lung cancer has decreased in recent years [17]. However, this analysis showed that the absolute number of patients with NSCLC-2 increased, which might be due to the consistent increase in extra-pulmonary malignancy survivors after the improved therapeutic treatment [18], and the widely conducted lung cancer screening plan [19–21]. This finding highlights the importance of establishing a surveillance strategy for NSCLC-2.

Based on the increasing occurrence of NSCLC-2, screening for patients with lung cancer with previous malignancy history should be considered. About 5.6%–7.7% patients would develop NSCLC-2 even ten years after resection of precancerous lesions [22]. General lung screening for people with high lung cancer-related risks (including tobacco smoking, previous lung cancer and radiation) has been recommended in several guidelines [23]. However, only the National Comprehensive Cancer Network (NCCN) has recommended screening for patients with a history of extra-pulmonary cancer [24]. In this study, breast, prostate and colon cancers were the most common malignancies with sequential NSCLC, which was similar to a previous study [25]. Thus, routine follow-up chest CT should be considered for survivors of these malignancies.

Our findings confirmed the survival advantage of lung surgery for NSCLC-2. Louie et al. analyzed 616 patients with early-stage

NSCLC-2 following treatment of head and neck, and found significant reductions in death risk in patients who underwent lung surgery compared with patients who underwent radiotherapy or palliative treatment ($P < 0.001$) [6]. In another study conducted by Hofmann et al., 59 patients with NSCLC-2 receiving curative treatment, including surgery, obtained a median OS of 31 months, which was significantly longer than those of palliative (6.9 months) and best supportive care (1.6 months) treatment (both $P < 0.001$). In addition, a series of studies have explored the survival of NSCLC-2 in patients who receiving lung surgery compared with that of patients with NSCLC diagnosed as the only primary tumor [4,26–28]. Although the NSCLC-2 showed inconsistent surgical outcomes when compared with primary NSCLC only, previous malignancy history is still not considered a contradiction for sequential lung resection [8]. In this study, we conducted a PSM analysis to balance the potential confounding biases that might influence survival, and the benefits of surgery for NSCLC-2.

Surgical outcomes for NSCLC-2 were based on the AJCC staging system. In previous single-center studies, early cancer stage showed more favorable survival than advanced-stage cancer but failed to achieve statistical significance [29,30]. Milano et al. conducted a study based on the SEER database, enrolling 3529 female patients with NSCLC-2 following previously treated breast cancer. A significantly longer OS was found in patients with localized stage NSCLC-2 compared with the regional and the distant stage (5.1 years vs. 1.9 years vs. 4.6 months) [31]. In our study, stage I patients showed significantly better survival than stage II patients, whereas patients with stage III and IV NSCLC-2 were excluded because of their heterogeneity and nonstandard surgery indications. Nonetheless, it was confirmed that the survival of patients with early-stage NSCLC-2 was similar to that of patients with NSCLC alone.

The most important finding of this study was the significantly favorable survival of patients with previous hormone-dependent malignancies. The effect of previous malignant types on the survival for NSCLC-2 remains unclear. Massard et al. conducted a study of NSCLC-2 with various extra-pulmonary malignancies and divided these previous malignancies into tobacco-induced, hormone-independent and miscellaneous cancers. However, no survival differences were found among these groups [29]. Ko et al. found that patients with previous breast and thyroid malignancies had significantly longer OS than those with gastrointestinal and genitourinary tract malignancies [32]. Pages et al. found that patients with NSCLC-2 with previous breast and uteri malignancies owe the highest OS, followed by those with skin, kidney, colon, rectum, prostate and bladder malignancies [28]. Similarly, a classification of hormone-dependent and non-hormone-dependent malignancies was generated in this study. A significantly higher OS was found in the hormone-dependent cohort after lung resection while adjusting for confounders. Moreover, competing risk analysis revealed that the patients in both cohorts had equivalent lung-cancer-induced mortality. In contrast, significantly more patients in the non-hormone-dependent cohort died of their first cancer. The inherently favorable prognosis of hormone-independent malignancies might explain the better overall survival in this cohort [1]. It has been suggested that the survival of NSCLC-2 was mainly dominated by lung cancer existing. This means regardless of the previous malignancy, lung surgery is beneficial for survival. If both lesions were moved, survival of these patients is determined by previous malignancies. Nevertheless, the hypothesis needs to be verified.

Regarding the type of resection, lobectomy is the best choice compared with other resection types. In clinical practice, lobectomy and segmentectomy are the most common anatomical resection methods with curative intent, with the most favorable outcomes in patients with NSCLC alone [33,34]. The selection of surgery type mainly depends on thoracic stage or tumor size of lung cancer [35,36]. Nevertheless, in patients with NSCLC-2, the prognosis of resection type remains unclear. Louie et al. found that both pneumonectomy and sublobar resection had similar survival rates compared with lobectomy among patients with NSCLC-2 with previous head and neck cancers [6]. Nakao et al. found that limited lung resection did not affect the survival of patients with NSCLC-2 [27]. But in another study by Page et al. significantly worse survival was observed in patients who underwent pneumonectomy [28]. In our study, patients who underwent lobectomy had better survival compared with those who underwent sub-lobectomy, and those who received pneumonectomy had the worst survival. Thus, the selection of surgery type for NSCLC-2 should also refer to primary NSCLC alone.

There are also several limitations in this study. Firstly, this was a retrospective analysis, with unavoidable biases. Secondly, the identification of the second primary NSCLC was based on the records of SEER database, which might be a misclassification of metastatic cancer, especially in patients with lung lesions diagnosed within six months of the first malignancy. Patients with the same histology and short diagnostic intervals were excluded from previous studies to eliminate the probability of incorrect classification. However, the SEER program constructed rigorous criteria to diminish the possibility to the maximum extent, and excluding the aforementioned patients may also induce selection biases. Thirdly, owing to the lack of baseline information and multi-modality treatment data, such as smoking habits, family cancer history, comorbidities, pulmonary function, radiation dose/sequence, completeness of resection and systemic therapy, it was difficult to further analyze these critical prognostic factors without causing uncontrollable balances between the surgery and non-surgery groups. For this, we performed a PSM analysis and further Cox regression to diminish the confounders, which might induce over-estimated effects of surgery on survival. Fourthly, only patients with previous malignancy resection were enrolled. The survival of those without surgery for their first malignancy should be explored in the future. Besides, we could not appropriately and briefly classify the surgery methods under the condition of 14 cancer types. Fifthly, patients with invasion of the diaphragm are labeled as code 600, which is as same as the pancoast, the invasion of phrenic nerve, and invasion of pericardium. Thus, a few T4 patients under the 8th TNM stage were enrolled. However, there were only 81 patients labeled with 600 extension code based on our results, which could be a minor confounder of the results. Sixthly, only 14 cancer types with sequential NSCLC-2 were included in this analysis, and the multi-disciplinary treatment strategies for previous malignancies were unknown. Thus, all results of the present study should be interpreted cautiously, and patients with more sites of previous malignancy and detailed therapeutic information should be explored in the future.

In conclusion, lung surgery is still recommended for patients with NSCLC-2 after previous malignancy resection. Of these, patients with early-stage lung cancer and those with previous hormone-dependent malignancies would obtain more favorable outcomes.

Ethics statement

The requirement for informed consent and ethical approval for this study was waived by the ethics committee of Tangdu Hospital owing to public access and unidentified patient information in the SEER database.

Author contribution statement

Chenxi Zhang; Xiyang Tang: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Wenhao Liu; Kaifu Zheng: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xiaofei Li; Nan Ma; Jinbo Zhao: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at URL:https://pan.baidu.com/s/1hvEecgFqumKCQJcFkAoWhw, access number: 1231.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17898.

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