The Diameter of Bronchial Resection Margin is Associated With Postoperative Lung Metastasis and Long-term Survival

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Abstract

Background

To investigate the significance of the diameter of bronchial resection margin (DBRM) on the postoperative lung metastasis and long -term survival of patients with primary lung cancer.

Methods

We retrospectively analyzed the data of 1844 patients with primary lung cancer between January 2006 and December 2010 after surgery. Patients were divided into DBRM≤1 cm group (826 patients) and DBRM>1 cm group (1018 patients). Propensity score matching was used to reduce grouping selection bias. Furthermore, we divide the 974 patients who had definite first metastasis site into lung metastasis group (283 patients) and other metastasis group (691 patients), and analyzed related risk factors and prognosis of metastasis. Disease-free survival and overall survival were the study end points.

Results

The DBRM≤1 cm group had a significantly better prognosis than DBTM>1 cm group (5-year DFS, 36.5% vs 25.7%; $P < 0.001$; 5-year OS, 45.4% vs 34.1%; $P < 0.001$). After multivariate survival analysis, DBRM remained the independent favorable effect on DFS (HR, 1.198; 95% CI, 1,071 to 1.340; $P = 0.002$) and OS (HR, 1.186; 95% CI, 1.060 to1.327; $P = 0.003$). PSM further confirmed that DBRM≤1 cm group had a better DFS ($P = 0.032$) and OS ($P = 0.026$) than the DBRM>1 cm group. It revealed that the DBRM was an independent risk factor for postoperative lung metastasis, and postoperative adjuvant therapy could improve the OS of lung metastases.

Conclusions

The DBRM was an independent risk factor for postoperative lung metastasis and adjuvant therapy could improve long-term survival.

Introduction

It is important to obtain a cancer-free bronchotomy margin during lung cancer surgery, and the availability of a "safe margin" could improve postoperative survival (1). Tumor spread through air spaces (STAS) was reported as a novel poor prognostic factor in the latest World Health Organization (WHO) classification (2). In recent studies, STAS in patients with lung cancer was shown to be associated with high recurrence rates and poor survival after surgical resection (3, 4). We consider that the size of DBRM may affects STAS, which in turn affects the prognosis. So far, there were no reports on how to control DBRM during surgery and no studies confirmed the effects of DBRM on STAS and prognosis. The aim of our study was to investigate the effect of DBRM on postoperative lung metastasis and long-term survival of patients with primary lung cancer.

Patients And Methods

Patients

Clinical and survival follow-up data of 1916 patients who underwent surgery of lung cancer in Tianjin Medical University Cancer Hospital from January 2006 to December 2010 were collected. Sex, age, smoking history, tumor location, tumor area, surgical treatment, surgical time, surgical blood loss, DBRM, pT stage, pN stage, pTNM stage, pathological type, the station of resected lymph nodes, adjuvant chemotherapy and radiotherapy were included in clinical data. The follow-up data included DFS, OS and the first metastasis site after surgery. The pathological types were based on WHO classification (5). Tumor stage was performed according to the eighth edition of staging standards of International Lung Cancer Research Association (IASLC) (6). We excluded some cases with the circumstances as follows, patients with metastasis before surgery, patients who underwent partial resection or segmentectomy without lymph node resection, patients with bronchial resection margin positive and patients with radiotherapy and chemotherapy before surgery. Finally, 1844 patients were enrolled in our study (Fig. 1).

Follow-Up

The patients were followed up to death or until December 31, 2019 by regular outpatient review, letter visit, telephone call, etc. Postoperative routine examination included tumor markers of lung cancer, chest X-ray, chest CT, brain CT, brain MRI, abdominal CT, bone scan, abdominal ultrasound, etc. The DFS was calculated from the date of surgery to recurrence or metastasis and the OS was calculated from the date of surgery to death or the end point date. The DFS and OS were calculated by month. By the end of follow-up, 91 patients in the DBRM ≤ 1 cm group and 111 patients in the DBRM > 1 cm group lost contact after surgery. We compared the 202 lost contact ones with 1642 ones who had complete follow-up information on basic clinical characteristics. The result showed that there was no statistically difference between the two groups ($P > 0.05$, Table S1).

Study Design

The primary outcome was DFS and OS. The DBRM was divided into DBTM ≤ 1 cm group and DBTM > 1 cm group. In order to obtain the cutoff value, the DBRM was grouped according to the minimum grouping influencing factors and the method of calculating the minimum survival *P*-value (7).

Statistical Analysis

SPSS (IBM, SPSS statistics version 26.0) software and GraphPad Prism (version 8.0.2) were used for data processing and figure formatting. x^2 test was used for categorical variables, and *t* test was used for continuous variables. Multivariate analysis was used the logistic regression model to analyze the relation between lung metastasis and risk factors. Survival rate was calculated by Kaplan-Meier method. Univariate and Multivariate prognosis analysis was performed using Cox regression model. In all analyses, two-tailed $P < 0.05$ was considered statistically significant.

Propensity score matching (PSM)

PSM was performed using through 1:1 nearest-neighbor matching with a math tolerance value of 0.02 for reducing selection bias between DBTM ≤ 1 cm group and DBTM > 1 cm group (8). PSM for patients were calculated by using a multiple logistic regression with the following characteristics: sex, age, smoking history, tumor location, tumor area, surgical treatment, surgical time, surgical blood loss, pT stage, pN stage, pTNM stage, pathological type, the station of resected lymph nodes, adjuvant chemotherapy and radiotherapy. In order to ensure the continuity and randomness of the statistical data, we did not exclude the lost contact patients because these cases still have basic clinical and pathological information. Furthermore, the SPSS statistical software automatically excludes the ones without survival follow-up information data during survival analysis.

Results

1. Basic Clinical Characteristics Before and After PSM

A total of 1844 patients were enrolled. There were 1180 (64.0%) males and 664 (36.0%) females. The mean age was 59.7 ± 9.5 years, the minimum age was 23 years, and the maximum age was 89 years. The mean DBRM was 1.36 ± 0.56 cm (0.3 cm to 6 cm).

Table 1 shows the basic characteristics of the enrolled patients (n = 1844) grouped by DBRM before and after PSM. In the study cohort, 826 (44.8%) patients were enrolled in the DBRM ≤ 1 cm group and 1018 (55.2%) were enrolled in the DBRM > 1 cm group. Before PSM, there were differences in sex, smoking history, tumor area, surgical treatment, tumor size, pT stage, pN stage, pTNM stage and pathological type (*P*-values were < 0.001, < 0.001, < 0.001, < 0.001, < 0.001, 0.001, 0.012, 0.002, and < 0.001, respectively) between the two groups. However, there were no significant differences between the two groups after PSM (*P* > 0.05).

Table 1
Patients Baseline Data Grouped by DBRM Before and After PSM

Characteristic	Study Cohort (N = 1844)			After PSM (N = 1424)		
	DBRM ≤ 1 cm (826)	DBRM > 1 cm (1018)	*P*	DBRM ≤ 1 cm (712)	DBRM > 1 cm (712)	*P*
Sex			< 0.001			0.546
Male	444 (53.8)	736 (72.3)		444 (62.4)	455 (63.9)	
Female	382 (46.2)	282 (27.7)		268 (37.6)	257 (36.1)	
Age, years			0.989			0.502
< 65	558 (67.6)	688 (67.6)		476 (66.9)	464 (65.2)	
≥ 65	268 (32.4)	330 (32.4)		236 (33.1)	248 (34.8)	
Smoking history			< 0.001			0.911
No	338 (40.9)	289 (28.4)		246 (34.6)	244 (34.3)	
Yes	488 (59.1)	729 (71.6)		466 (65.4)	468 (65.7)	
Tumor location			0.164			0.632
Left lung	378 (45.8)	499 (49.0)		319 (44.8)	328 (46.1)	
Right lung	448 (54.2)	519 (51.0)		393 (55.2)	384 (53.9)	
Tumor area			< 0.001			0.957
Central	303 (36.7)	511 (50.2)		288 (40.4)	289 (40.6)	
Peripheral	523 (63.3)	507 (49.8)		424 (59.6)	423 (59.4)	
Surgical treatment			< 0.001			0.987
Lobectomy	799 (96.7)	851 (83.6)		685 (96.2)	688 (96.6)	
Pneumonectomy	27 (3.3)	167 (16.4)		27 (3.8)	24 (3.4)	
Surgical time, min			0.832			0.396
≤ 120	430 (52.1)	535 (52.6)		370 (52.0)	386 (54.2)	
> 120	396 (47.9)	483 (47.4)		342 (48.0)	326 (45.8)	
Surgical blood loss, ml			0.648			0.306
< 150	485 (58.7)	587 (57.7)		412 (57.9)	431 (60.5)	

Characteristic	Study Cohort (N = 1844)			After PSM (N = 1424)		
	DBRM ≤ 1 cm (826)	DBRM > 1 cm (1018)	*P*	DBRM ≤ 1 cm (712)	DBRM > 1 cm (712)	*P*
≥150	341 (41.3)	431 (42.3)		300 (42.1)	281 (39.5)	
Tumor size, cm (mean ± SD)	3.7 ± 2.0	4.1 ± 2.2	< 0.001	3.8 ± 2.1	4.0 ± 2.1	0.308
pT stage			0.001			0.061
T1a	43 (5.2)	40 (3.9)		29 (4.1)	35 (4.9)	
T1b	172 (20.8)	145 (14.2)		147 (20.6)	113 (15.9)	
T1c	197 (23.8)	241 (23.7)		172 (24.2)	162 (22.8)	
T2a	173 (20.9)	224 (22.0)		142 (19.9)	164 (23.0)	
T2b	107 (13.1)	138 (13.6)		98 (13.8)	90 (12.6)	
T3	87 (10.5)	160 (15.7)		79 (11.1)	108 (15.2)	
T4	47 (5.7)	70 (6.9)		45 (6.3)	40 (5.6)	
pN stage			0.012			0.160
N0	441 (53.4)	496 (48.7)		362 (50.8)	368 (51.7)	
N1	139 (16.8)	152 (14.9)		122 (17.1)	97 (13.6)	
N2	246 (29.8)	370 (36.4)		228 (32.1)	247 (34.7)	
pTNM stage			0.002			0.750
I	318 (38.5)	318 (31.2)		250 (35.1)	242 (34.0)	
II	212 (25.7)	262 (25.7)		188 (26.4)	182 (25.6)	
III	296 (35.8)	438 (43.1)		274 (38.5)	288 (40.4)	
Pathological type			< 0.001			0.376
ADC	389 (47.1)	358 (35.2)		311 (43.6)	292 (41.0)	
SQ	271 (32.8)	490 (48.1)		256 (36.0)	288 (40.4)	
SCC	28 (3.4)	37 (3.6)		27 (3.8)	24 (3.4)	
Others	138 (16.7)	133 (13.1)		118 (16.6)	108 (15.2)	
SRLNs			0.084			0.477
<6	331 (40.1)	368 (36.1)		273 (38.3)	260 (36.5)	

Characteristic	Study Cohort (N = 1844)			After PSM (N = 1424)		
	DBRM ≤ 1 cm (826)	DBRM > 1 cm (1018)	*P*	DBRM ≤ 1 cm (712)	DBRM > 1 cm (712)	*P*
≥6	495 (59.9)	650 (63.9)		439 (61.7)	452 (63.5)	
Chemotherapy			0.271			0.432
No	292 (35.4)	335 (32.9)		245 (34.4)	231 (32.4)	
Yes	534 (64.6)	683 (67.1)		467 (65.6)	481 (67.6)	
Radiotherapy			0.168			0.792
No	669 (81.0)	798 (78.4)		566 (79.5)	570 (80.1)	
Yes	157 (19.0)	220 (21.6)		146 (20.5)	142 (19.9)	

NOTE: Data presented as No. (%) unless otherwise noted. Abbreviations: DBRM, the diameter of bronchial resection margin; PSM, propensity score matching (1:1, Match Tolerance Value = 0.02); ADC, adenocarcinoma; SQ, squamous cell carcinoma; SCC, small cell carcinoma; SRLNs, station of resected lymph nodes.

2. Patients Grouped by DBRM Survival Before and After PSM

In our study, the 5-year DFS rates were 36.5% in the DBRM ≤ 1 cm group and 25.7% in the DBRM > 1 cm group (median, 39 vs 27 months). The 5-year OS rates were 45.4% in the DBRM ≤ 1 cm group and 34.1% in the DBRM > 1 cm group (median, 53 vs 42 months). It showed significant differences in DFS (*P*-values; <0.001 and 0.032, respectively) and OS (*P*-values; <0.001 and 0.026, respectively) between the two groups before and after PSM. The DFS and OS in the DBRM ≤ 1 cm group were better than those in the DBRM > 1 cm group (Fig. 2).

3. Analysis of Survival Factors

Univariate analysis showed that age, tumor area, surgical treatment, DBRM, pT stage, pN stage, pTNM stage, pathological type, SRLNs, postoperative chemotherapy and radiotherapy were associated with the DFS (*P*-values: <0.001, < 0.001, < 0.001, < 0.001, 0.028, < 0.001, < 0.001, 0.001, 0.001, 0.001 and < 0.001, respectively); age, tumor area, surgical treatment, DBRM, pT stage, pN stage, pTNM stage, pathological type, SRLNs, postoperative chemotherapy and radiotherapy were associated with the OS (*P*-values: <0.001, < 0.001, < 0.001, < 0.001, 0.024, < 0.001, < 0.001, 0.001, 0.002, 0.001 and < 0.001, respectively). Additional multivariate analysis showed that DBRM were independent factors for DFS (HR, 1.198; 95% CI, 1.071 to 1.340; *P* = 0.002) and OS (HR, 1.186; 95% CI, 1.060 to 1.327; *P* = 0.003), together with age, tumor area, pN stage, pTNM stage, SRLNs and postoperative radiotherapy (Table 2).

Table 2
Univariate and Multivariate Cox Regression Analysis of Prognostic Factors in Primary Lung Cancer

	Univariate Analysis				Multivariate Analysis			
Predictor	DFS		OS		DFS		OS	
	P	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)
Sex	0.424	0.954 (0.850 to 1.071)	0.343	0.946 (0.842 to 1.061)				
Age	< 0.001	1.839 (1.637 to 2.066)	< 0.001	2.003 (1.782 to 2.250)	< 0.001	1.044 (1.038 to 1.051)	< 0.001	2.172 (1.937 to 2.434)
Smoking history	0.310	1.063 (0.945 to 1.196)	0.106	1.102 (0.979 to 1.240)				
Tumor location	0.486	0.961 (0.871 to 1.079)	0.648	0.975 (0.876 to 1.086)				
Tumor area	< 0.001	0.749 (0.673 to 0.834)	< 0.001	0.731 (0.656 to 0.814)	0.029	0.879 (0.783 to 0.987)	0.002	0.831 (0.741 to 0.933)
Surgical treatment	< 0.001	1.356 (1.143 to 1.608)	< 0.001	1.356 (1.143 to 1.608)	0.058	1.193 (0.994 to 1.432)	0.050	1.201 (1.000 to 1.442)
Surgical time	0.274	0.942 (0.846 to 1.048)	0.461	0.960 (0.863 to 1.069)				
Blood loss	0.394	1.048 (0.941 to 1.168)	0.280	1.061 (0.953 to 1.182)				
DBRM	< 0.001	1.303 (1.169 to 1.452)	< 0.001	1.305 (1.171 to 1.455)	0.002	1.198 (1.071 to 1.340)	0.003	1.186 (1.060 to 1.327)
pT stage	0.028	1.030 (1.003 to 1.058)	0.024	1.031 (1.004 to 1.058)	0.511	0.990 (0.962 to 1.019)	0.598	0.992 (0.964 to 1.021)

	Univariate Analysis			Multivariate Analysis			
pN stage	< 0.001	1.490 (1.403 to 1.582)	< 0.001	1.475 (1.390 to 1.567)	0.006	1.169 (1.046 to 1.306)	0.019	1.142 (1.022 to 1.277)
pTNM	< 0.001	1.588 (1.488 to 1.695)	< 0.001	1.588 (1.488 to 1.694)	< 0.001	1.396 (1.236 to 1.577)	< 0.001	1.450 (1.283 to 1.639)
Pathological type	0.001	0.790 (0.570 to 1.094)	0.001	0.754 (0.543 to 1.048)	0.125	1.043 (0.988 to 1.102)	0.077	1.050 (0.995 to 1.109)
SRLNs	0.001	0.828 (0.741 to 0.924)	0.002	0.839 (0.752 to 0.937)	< 0.001	0.735 (0.657 to 0.822)	< 0.001	0.767 (0.686 to 0.857)
Chemotherapy	0.001	1.317 (1.173 to 1.479)	0.001	1.239 (1.104 to 1.391)	0.881	1.009 (0.893 to 1.142)	0.305	0.937 (0.829 to 1.061)
Radiotherapy	< 0.001	1.398 (1.231 to 1.589)	< 0.001	1.303 (1.146 to 1.481)	0.002	1.240 (1.083 to 1.418)	0.042	1.143 (1.000 to 1.308)

NOTE: HR, hazard ratio; DBRM, the diameter of bronchial resection margin; SRLNs, station of resected lymph nodes.

4. Metastasis Rate After Surgery

We analyzed the 974 patients who had definite first metastasis site. According to this data, we concluded that patients with DBRM > 1 cm had a larger proportion (181 cases, 64.0%) in 283 cases of lung metastasis (Fig. 3A). When quantitatively analyzed the DBRM of different metastatic sites, we found that lung metastasis owned the largest DBRM compared with the other sites (Fig. 3B).

5. The DBRM is An Independent Risk Factor for Lung Metastasis

Table 3 shows that Lung metastasis after surgery was significantly correlated with age, tumor area and the DBRM (*P*-values: 0.016, 0.014 and 0.013, respectively). These factors were further analyzed by multivariate logistic analysis, and the result revealed that the DBRM was an independent risk factor of lung metastasis (OR, 1.417; 95% CI, 1.062 to 1.890; $P = 0.018$).

Table 3
Univariate and Multivariate Analysis of Lung Metastasis and Other Metastasis Cohort

	Univariate Analysis						
		Metastasis Site No. (%)			Multivariate Analysis		
Variable	No.	Lung	Other	*P*	OR	95% CI	*P*
No.	974	283	691				
Sex				0.086			
Male	610	189 (31.0)	421 (69.0)				
Female	364	94 (25.4)	270 (74.6)				
Age, years				0.016	1.444	1.083 to 1.926	0.012
< 65	634	168 (26.5)	466 (73.5)				
≥ 65	340	115 (33.8)	225 (66.2)				
Smoking history							
No	329	95 (28.9)	234 (71.1)				
Yes	645	188 (29.1)	457 (70.9)				
Tumor location				0.544			
Left lung	443	133 (30.0)	310 (70.0)				
Right lung	531	150 (28.2)	381 (71.8)				
Tumor area				0.014	0.726	0.548 to 0.961	0.025
Central	470	154 (32.8)	316 (67.2)				
Peripheral	504	129 (25.6)	375 (74.4)				
Tumor size, cm (mean ± SD)		3.9 ± 2.0	4.0 ± 2.2	0.328			

	Univariate Analysis			
pT stage				0.817
T1	435	130 (29.9)	305 (70.1)	
T2	342	100 (29.2)	242 (70.8)	
T3	131	37 (28.2)	94 (71.8)	
T4	66	16 (24.2)	50 (75.8)	
pN stage				0.848
N0	461	138 (29.9)	323 (70.1)	
N1	128	36 (28.1)	92 (71.9)	
N2	385	109 (28.3)	276 (71.7)	
pTNM stage				0.814
I	309	94 (30.4)	215 (69.6)	
II	217	62 (28.6)	155 (71.4)	
III	448	127 (28.3)	321 (71.7)	
Pathological type				0.342
ADC	388	114 (29.4)	274 (70.6)	
SQ	403	124 (30.8)	279 (69.2)	
SCC	43	8 (18.6)	35 (81.4)	
Others	140	37 (26.4)	103 (73.6)	
SRLNs				0.319
<6	362	112 (30.9)	250 (69.1)	
≥6	612	171 (27.9)	441 (72.1)	

	Univariate Analysis						
DBRM				0.013	1.417	1.062 to 1.890	0.018
≤1 cm	411	102 (24.8)	309 (75.2)				
> 1 cm	563	181 (32.1)	382 (67.9)				
NOTE: Data presented as No. (%) unless otherwise noted. Abbreviations: OR, odds ratio; DBRM, the diameter of bronchial resection margin; ADC, adenocarcinoma; SQ, squamous cell carcinoma; SCC, small cell carcinoma; SRLNs, station of resected lymph nodes.							

6. Lung Metastasis and the Other M etastasis Survival Analysis

We compared lung metastasis with the other metastasis for survival and concluded that lung metastasis had a worse OS than the other metastasis (5-year OS, 27.7% vs 30.7%; $P = 0.0042$; median, 33 vs 40 months) (Fig. 4A). Lung metastasis patients had a worse OS ($P < 0.001$) than the other metastasis according to the patients without postoperative chemotherapy (Fig. 4B). However, there had no significant difference ($P = 0.785$) in the patients with postoperative chemotherapy (Fig. 4C). Similarly, OS ($P = 0.014$) for patients without postoperative radiotherapy showed that lung metastasis had a worse prognosis than the other metastasis (Fig. 4D), but there had no significant difference ($P = 0.947$) in the patients with postoperative radiotherapy (Fig. 4E).

Discussion

Metastasis of lung cancer is the leading cause of death in clinical patients (9). For early stage lung cancer, surgery is still the preferred treatment. Surgical methods and adjuvant chemoradiotherapy (10, 11, 12) have been considered as prognostic factors for lung cancer. Therefore, reasonable surgical methods and appropriate adjuvant treatment are of great significance for postoperative long-term survival of patients with lung cancer.

Postoperative bronchial resection margin of lung cancer patients is positive or negative reflecting whether the tumor is completely resected. It has always been considered an important reason for the patient's recurrence. A positive resection margin indicates a poor prognosis (13). Studies have shown that the recurrence and metastasis of cancer patients are closely related to the positive rate of resection margins (14, 15). Therefore, ensuring no cancer resection margins during lung cancer surgery is essential for postoperative recurrence and metastasis and long-term survival.

Our retrospective analysis showed that DBRM is an independent prognostic factor for postoperative recurrence and metastasis and long-term survival. We further analyzed that DBRM is an independent risk factor for postoperative lung metastasis and recurrence, which can be used as a reference guide for

surgery and prognosis. Current studies have shown that lung cancer radiotherapy and chemotherapy can increase the negative rate of surgical margins, thereby improving postoperative survival (16). We concluded that the postoperative lung metastasis rate and the poor prognosis are high when the DBRM is large. This may be caused by the following reasons: firstly, when the DBRM is large, the margin is also larger, and the possibility of cancer cell survival will increase, although the later pathological results showed negative, but ordinary optical microscopes could not completely diagnose the remaining cancer cells (17); when the margin is large, the surrounding alveolar tissue is more (18), the adjacent alveolar tissue is destroyed more, and the lung tissue containing tumor cells is exposed the area and space are relatively large, so it is easier for tumor cells to spread through the alveolar space to metastasize (19, 20); at the same time, intraoperative operations may cause tumors to spread through the alveolar space or increase exfoliated cells, which will increase the postoperative lung metastasis rate; secondly, the analysis results showed that older patients (≥ 65 years) with central lung cancer are also independent risk factors for postoperative lung metastasis (21), this may be due to the declining of lung function in patients with older age or anatomical factors related, which need to explore furtherly.

By comparing the data of lung metastasis and other sites, the results showed that postoperative lung metastasis had a worse prognosis than other sites. There is no significant difference in the prognosis of the receiving adjuvant therapy between the two groups, but the non-receiving groups had a significant difference, which showed that postoperative adjuvant therapy can indeed further improve the survival rate (22). These results maybe provide a reference for the treatment of patients with large postoperative DBRM.

Limitations

There are some limitations in our study. Firstly, this is a single-center retrospective study, even though propensity score matching was used to control the confounding factors on the outcomes. Secondly, not all patients can be followed up to the site of the first metastasis, so postoperative lung metastasis may be affected by more factors. Last, for patients with metastases after surgery, we only studied whether they had received adjuvant therapy, but did not conduct research on specific chemotherapy or radiotherapy regimens, and did not indicate the selectivity of adjuvant therapy regimens. Consequently, long-term effects remain to be studied with larger sample and confirmed with multicenter randomized clinical trial.

Conclusions

In conclusion, the DBRM was an independent risk factor for postoperative lung metastasis and adjuvant therapy could improve long-term survival.

Abbreviations

DBRM, the diameter of bronchial resection margin; PSM, propensity score matching; OS, overall survival; DFS, disease-free survival; STAS, tumor spread through air spaces; IASLC, International Lung Cancer Research Association; SRLNs, station of resected lymph nodes; ADC, adenocarcinoma; SQ, squamous cell carcinoma; SCC, small cell carcinoma; HR, hazard ratio; OR, odds ratio.

Declarations

Ethical approval and consent to participate

This study complied with the requirements of the Ethics Committee of Tianjin Medical University Cancer Institute and Hospital and adhered to the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

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Availability of data and materials

The datasets of this study available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Zengtuan Xiao, Mengzhe Zhang and Xiaofei Wang contributed equally to this study and share first authorship. Zengtuan Xiao, conceptualization, data collection, data analysis, writing-original draft. Mengzhe Zhang, data collection, data analysis, writing-original draft. Xiaofei Wang, data collection, data analysis, writing-original draft. Jialin Gong, data collection. Zuo Liu, data collection. Zhenfa Zhang, conceptualization, project administration, data analysis, supervision, writing-review. All authors read and approved the final manuscript.

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References

1. Rami-Porta R, Mateu-Navarro M, Freixinet J, et al. Type of resection and prognosis in lung cancer. Experience of a multicentre study. Eur J Cardiothorac Surg. 2005;28(4):622-628.
2. Marx A, Chan JK, Coindre JM, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. J Thorac Oncol. 2015;10(10):1383-1395.
3. Jia M, Yu S, Gao H, Sun PL. Spread Through Air Spaces (STAS) in Lung Cancer: A Multiple-Perspective and Update Review. Cancer Manag Res. 2020;12:2743-2752.
4. Yokoyama S, Murakami T, Tao H, et al. Tumor Spread Through Air Spaces Identifies a Distinct Subgroup With Poor Prognosis in Surgically Resected Lung Pleomorphic Carcinoma. Chest. 2018;154(4):838-847.
5. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015;10(9):1243-1260.
6. Detterbeck FC, Chansky K, Groome P, et al. The IASLC Lung Cancer Staging Project: Methodology and Validation Used in the Development of Proposals for Revision of the Stage Classification of NSCLC in the Forthcoming (Eighth) Edition of the TNM Classification of Lung Cancer. J Thorac Oncol. 2016;11(9):1433-1446.
7. Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. J Natl Cancer Inst. 1994;86(11):829-835.
8. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. Stat Med. 2006;25(12):2084-2106.
9. Hung JJ, Yeh YC, Jeng WJ, et al. Prognostic Factors of Survival after Recurrence in Patients with Resected Lung Adenocarcinoma. J Thorac Oncol. 2015;10(9):1328-1336.
10. Kozower BD, Sheng S, O'Brien SM, et al. STS database risk models: predictors of mortality and major morbidity for lung cancer resection. Ann Thorac Surg. 2010;90(3):875-883.
11. Shi W, Zhang W, Sun H, Shao Y. Sleeve lobectomy versus pneumonectomy for non-small cell lung cancer: a meta-analysis. World J Surg Oncol. 2012;10:265.
12. Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non

small-cell lung cancer guideline. J Clin Oncol. 2007;25(34):5506-5518.

13. Gunluoglu MZ, Kocaturk CI, Demir A, Urer HN, Dincer SI, Bedirhan MA. Bronchial Stump Recurrence after Complete Resection of Lung Cancer: Effect of the Distance between the Tumor and Bronchial Resection Margin. Thorac Cardiovasc Surg. 2018;66(2):156-163.
14. Jo JK, Hong SK, Byun SS, Zargar H, Autorino R, Lee SE. Positive surgical margin in robot-assisted radical prostatectomy: correlation with pathology findings and risk of biochemical recurrence. Minerva Urol Nefrol. 2017;69(5):493-500.
15. Tatsugami K, Yoshioka K, Shiroki R, et al. Reality of nerve sparing and surgical margins in surgeons' early experience with robot-assisted radical prostatectomy in Japan. Int J Urol. 2017;24(3):191-196.
16. Sato H, Toyooka S, Soh J, et al. Advantage of Induction Chemoradiotherapy for Lung Cancer in Securing Cancer-Free Bronchial Margin. Ann Thorac Surg. 2017;104(3):971-978.
17. Lv T, Zou J, Liu H, et al. Detection of oncogenic mutations in resected bronchial margins by next-generation sequencing indicates early relapse in stage IA lung adenocarcinoma patients. Oncotarget. 2017;8(25):40643-40653.
18. Onozato ML, Kovach AE, Yeap BY, et al. Tumor islands in resected early-stage lung adenocarcinomas are associated with unique clinicopathologic and molecular characteristics and worse prognosis. Am J Surg Pathol. 2013;37(2):287-294.
19. Dai C, Xie H, Su H, et al. Tumor Spread through Air Spaces Affects the Recurrence and Overall Survival in Patients with Lung Adenocarcinoma >2 to 3 cm. J Thorac Oncol. 2017;12(7):1052-1060.
20. Kadota K, Kushida Y, Katsuki N, et al. Tumor Spread Through Air Spaces Is an Independent Predictor of Recurrence-free Survival in Patients With Resected Lung Squamous Cell Carcinoma. Am J Surg Pathol. 2017;41(8):1077-1086.
21. Kim D, Kim HK, Choi YS, Kim K, Kim J, Shim YM. Central Lung Cancer Management: Impact of Bronchial Resection Margin Length. Thorac Cardiovasc Surg. 2015;63(7):583-588.
22. Mishra MV, Louie AV, Gondi V, Slotman B. The evolving role of radiotherapy in the management of small cell lung cancer. J Thorac Dis. 2018;10(Suppl 21):S2545-S2554.

Figures

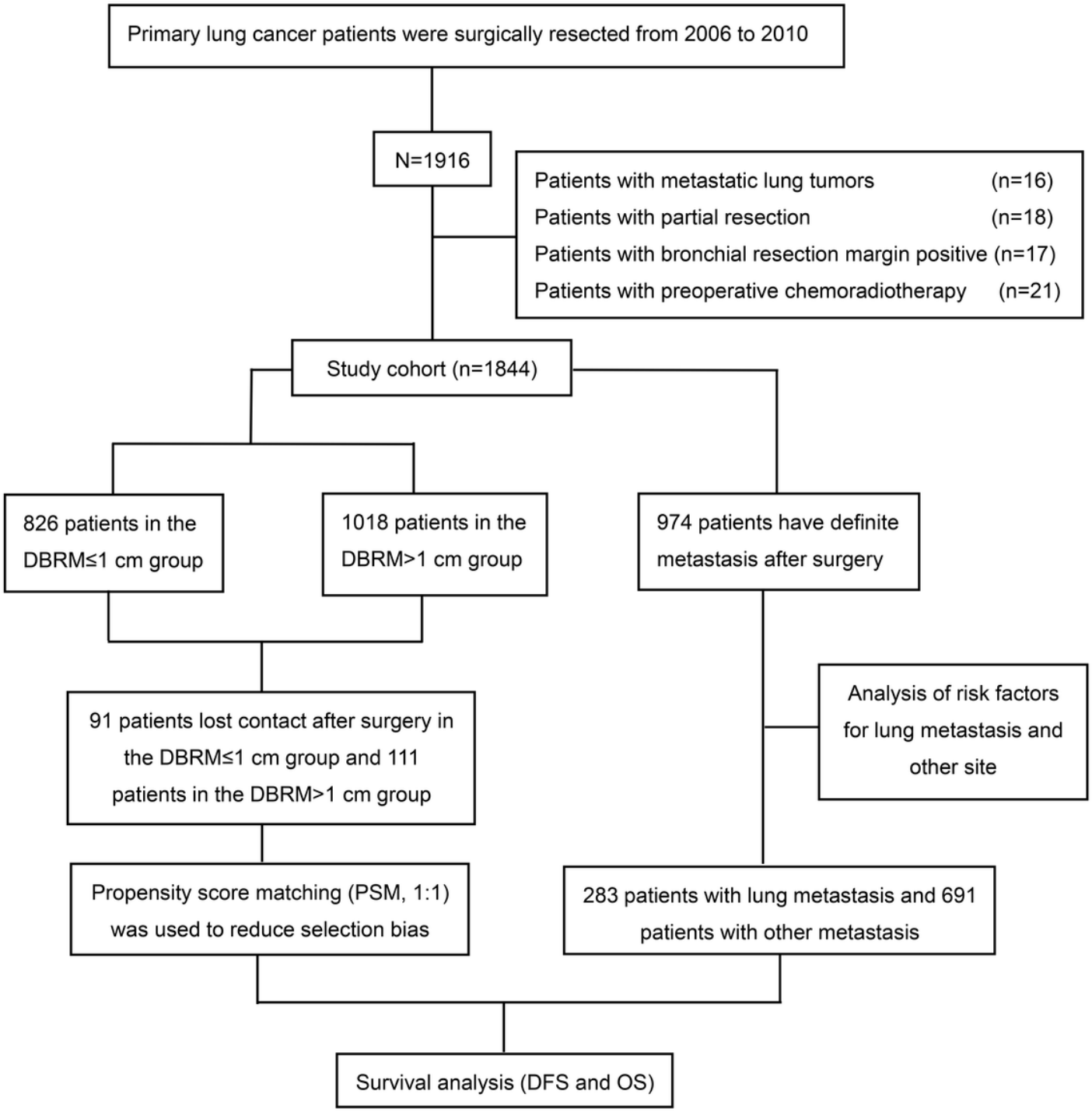
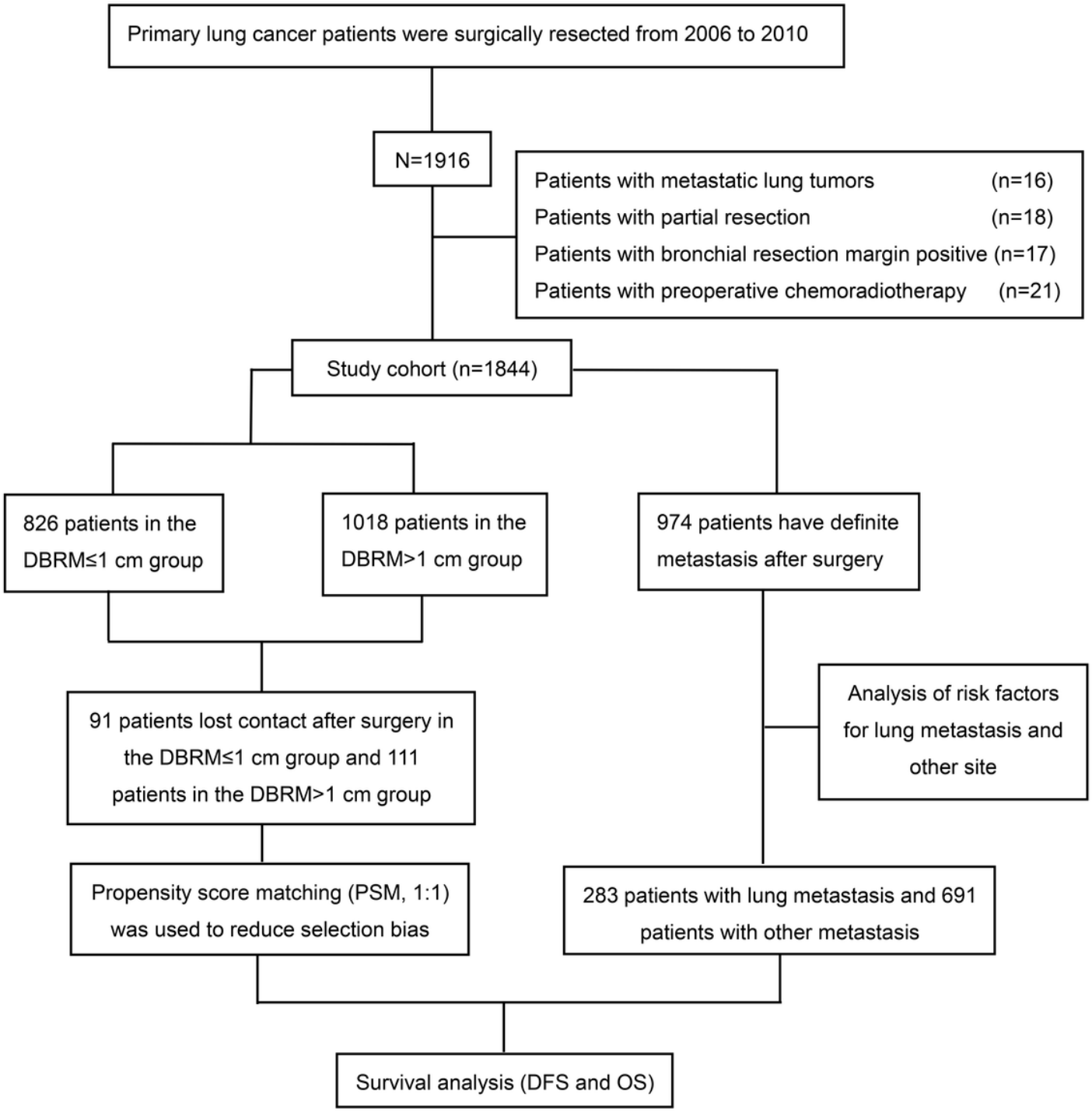


Figure 1

Patients flow diagram. DBRM, the diameter of bronchial resection margin; PSM, propensity score matching; OS, overall survival; DFS, disease-free survival.



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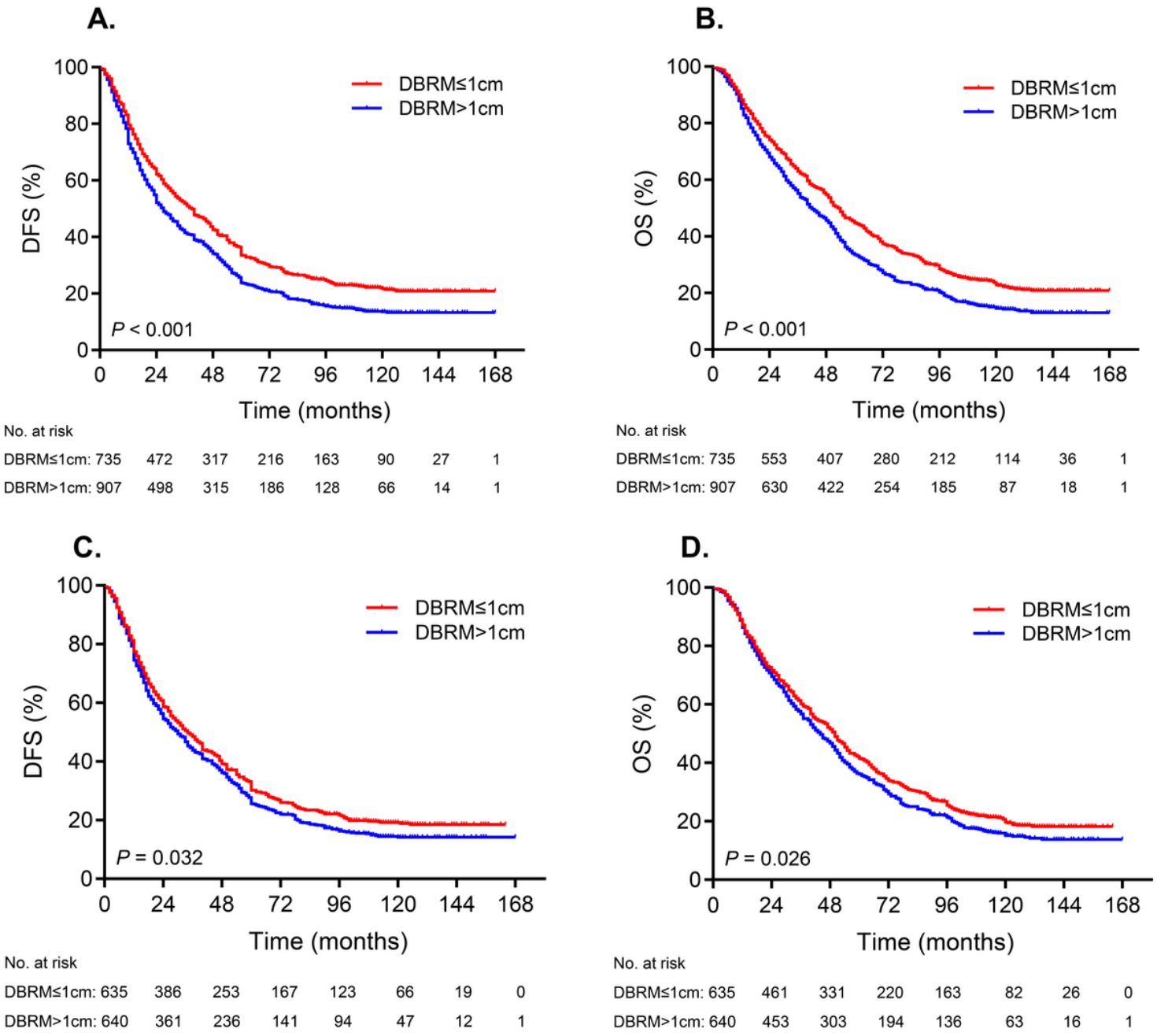
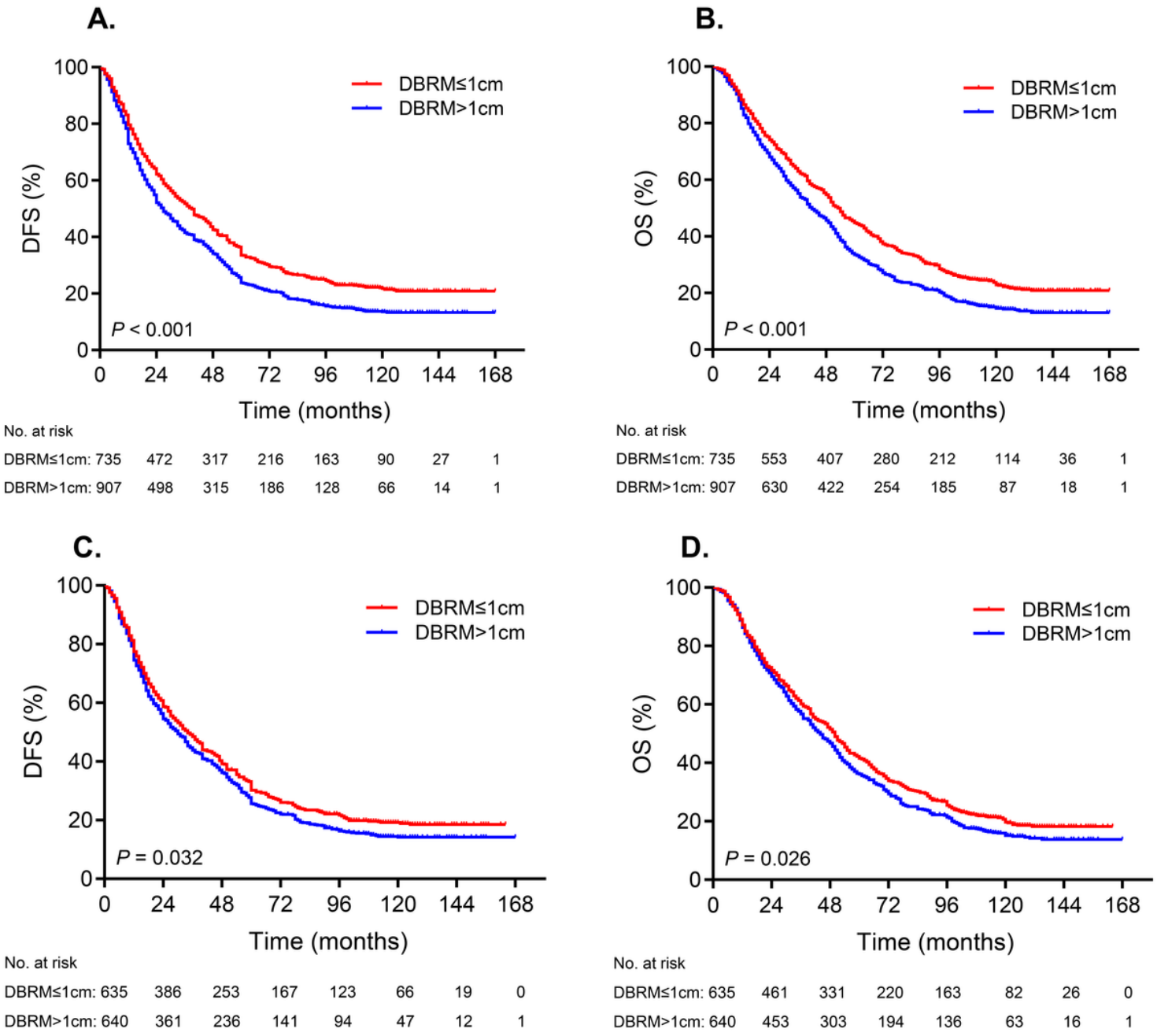


Figure 2

DBRM Kaplan-Meier curves for (A) DFS before PSM; (B) OS before PSM; (C) DFS after PSM; (D) OS after PSM. DBRM, the diameter of bronchial resection margin; PSM, propensity score matching; OS, overall survival; DFS, disease-free survival.



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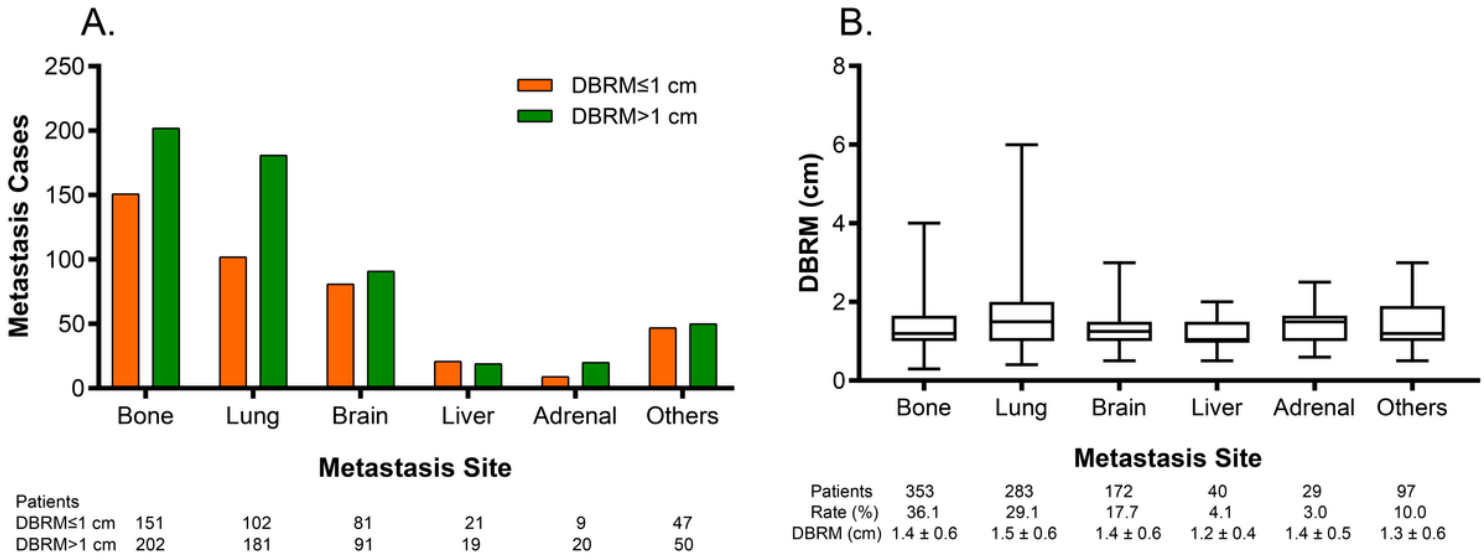

Figure 3

(A). Metastasis case in different site grouped by the DBRM; (B). Different metastasis site with a DBRM size expressed by mean ± SD. DBRM, the diameter of bronchial resection margin; SD, standard deviation.

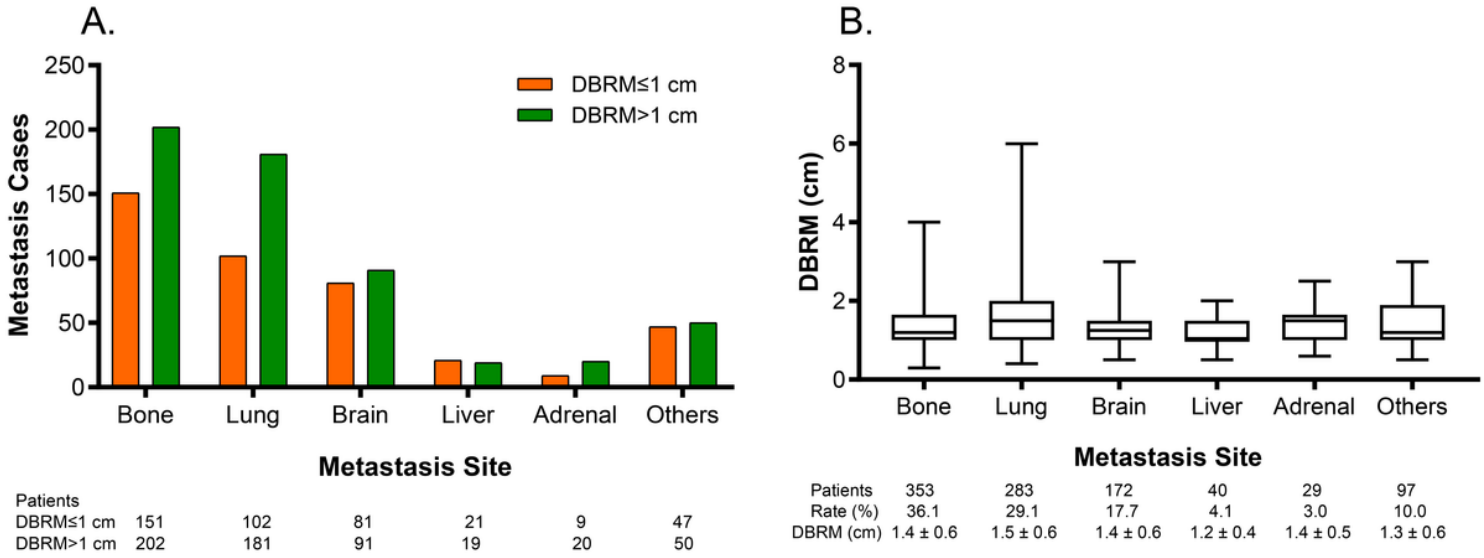

Figure 3

(A). Metastasis case in different site grouped by the DBRM; (B). Different metastasis site with a DBRM size expressed by mean ± SD. DBRM, the diameter of bronchial resection margin; SD, standard deviation.

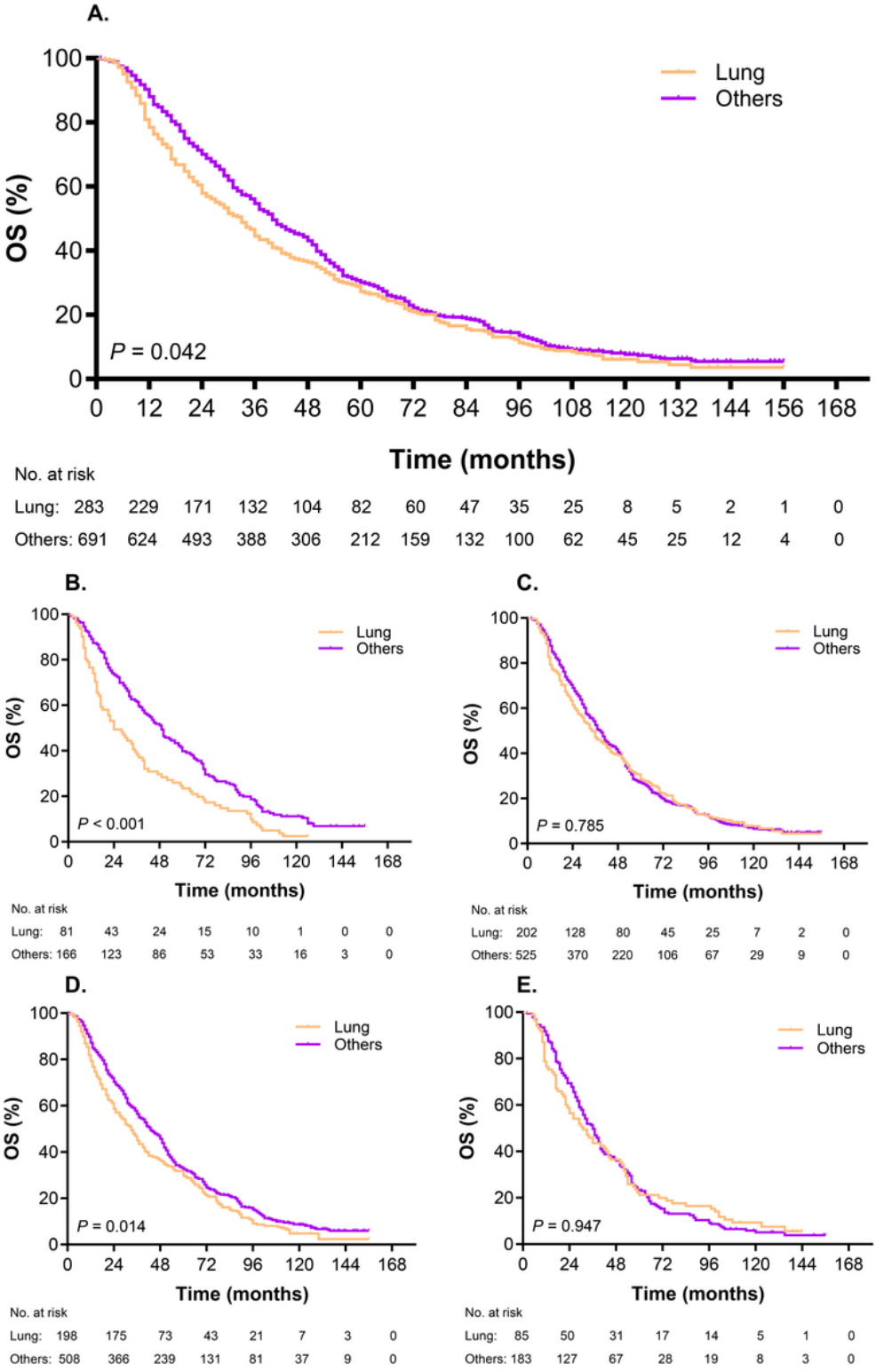

Figure 4

Kaplan-Meier curves for (A): OS for patients with lung and all other metastasis; (B) and (C): OS for patients without and with postoperative chemotherapy; (D) and (E): OS for patients without and with postoperative radiotherapy. OS, overall survival.

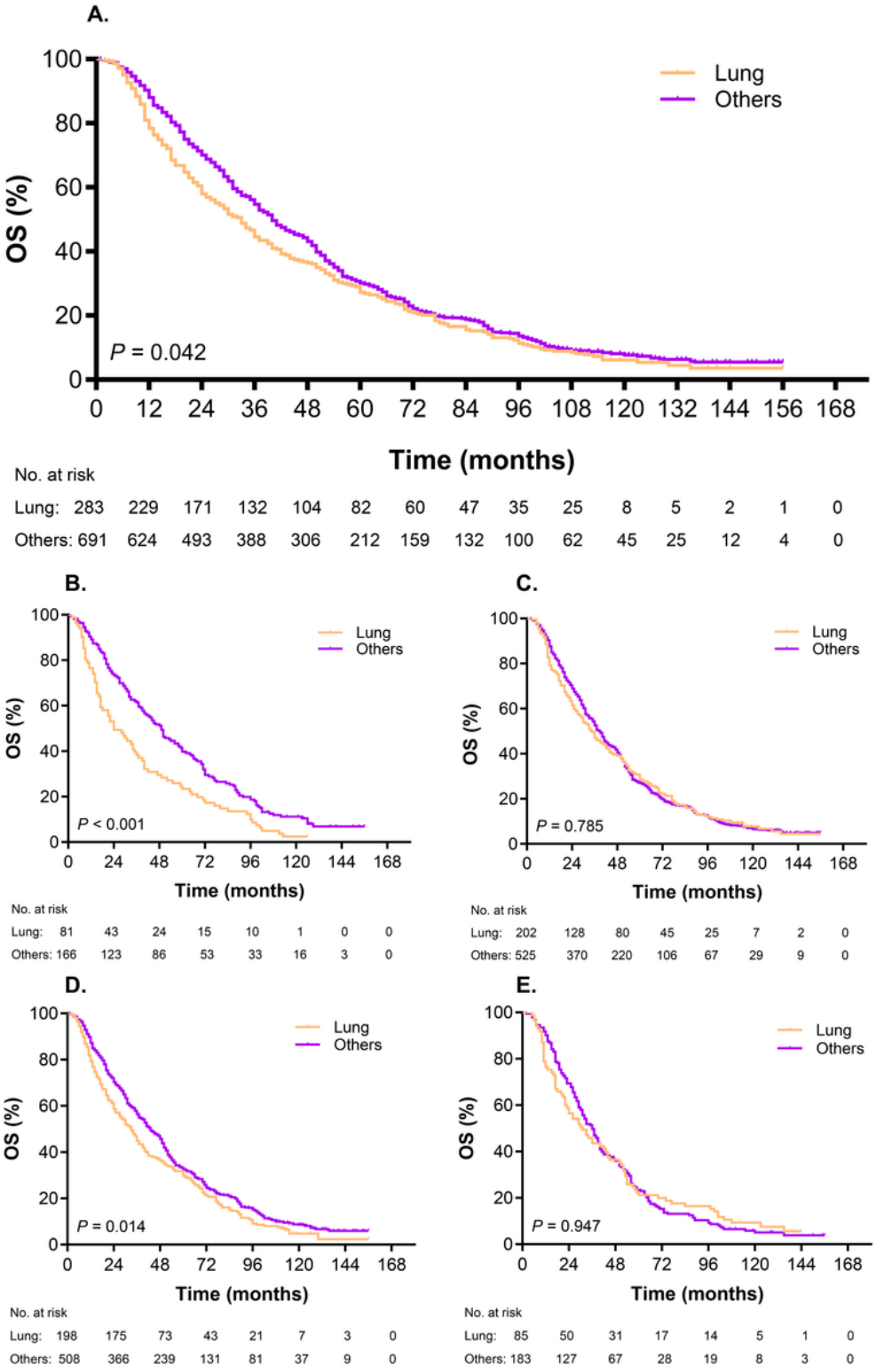

Figure 4

Kaplan-Meier curves for (A): OS for patients with lung and all other metastasis; (B) and (C): OS for patients without and with postoperative chemotherapy; (D) and (E): OS for patients without and with postoperative radiotherapy. OS, overall survival.

Supplementary Files

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