The prognostic value of PET/CT in clinical stage I lung cancer patients: A propensity-match analysis.

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Research article

Keywords: positron emission tomography/computed tomography, prognosis, lung cancer

Posted Date: September 6th, 2019

DOI: https://doi.org/10.21203/rs.2.14002/v1

Abstract

Introduction The application of PET/CT directly improved treatment choice and management in 25% of non-small cell lung cancer patients and 29% of small cell lung cancer patients. However, the long-term outcome of altering the management of these patients remains unclear. The aim of this study was to compare the 5-year overall survival rates of two groups of clinical stage I lung cancer patients: those who received PET/CT and those who did not.

Methods Data were obtained from the Taiwan Society of Cancer Registry. There were 6,587 clinical stage I lung cancer patients analyzed between 2009 and 2014 in this retrospective study. We performed propensity matching to reduce the bias; it resulted in both groups having 2,649 patients. We measured the 1, 3, and 5-year survival rates of all clinical stage I lung cancer patients and the survival rates of pathological I, II and III lung cancer patients and compared the survival rates between clinical stage I lung cancer patients with PET/CT scans and patients without PET/CT scans.

Results The 1, 3, and 5-year survival rates of all clinical stage I lung cancer patients are 97.2%, 88.2% and 79.0%, respectively. The 1, 3, and 5-year survival rates are 97.0%, 88.2% and 79.8% in the PET/CT group and 97.5%, 88.1% and 78.2% in the no PET/CT group; there was no statistical difference (p= 0.6528).

Conclusion Although stage I lung cancer patients who received PET/CT had their management strategies modified and avoided any unnecessary thoracotomies, our data showed that there was no 5-year survival benefit for these patients.

Background

Lung cancer is identified as the leading cause of cancer death worldwide.[1] Around three-quarters of lung cancer cases were diagnosed at a late stage and less than 20% of lung cancer cases were diagnosed at stage I.[2] Through the popularity of screening nowadays, we increasingly detect earlier stage nodules and the algorithms grow more complex. Both planning and prognosis are dependent on the precise staging. The pretreatment evaluation of stage I lung cancer includes pulmonary function tests, a bronchoscopy, mediastinal lymph node evaluation, brain MRI with contrast, and positron emission tomography/computed tomography (PET/CT).[3]

Computed tomography (CT) with contrast provides excellent tumor information. However, it is hard to differentiate between benign and malignant lesions.[4] The combination of PET and CT scanners was introduced into clinical practice in 1998.[5] Previous studies showed PET/CT has high sensitivity (96.8%) and intermediate specificity (77.8%) for malignancy.[6] The application of PET/CT directly improved treatment choice and management in 25% of non-small cell lung cancer patients and 29% of small cell lung cancer patients.[7, 8] Furthermore, PET/CT helps to differentiate between benign and malignant pulmonary nodules.[9] Though there are so many benefits after PET/CT evaluation, the long-term survival rates remained unclear.

For this study, we obtained data from the Taiwan Society of Cancer Registry (TSCR) over a 5-year period. We aimed to analyze if the introduction of PET/CT can provide better survival rate to clinical stage I lung cancer patients.

Methods

Database

This study was approved in our hospital's institutional review board. The population data was obtained from the TSCR. This data includes the entire population of 23 million people in Taiwan. This database includes registration files and original claims data for each patient. All the patients were strictly confirmed by tissue diagnosis. The following items were included in the study: age, gender, smoking status, cell type, operative method, clinical stage, pathologic stage and treatment.

Study Sample

This study searched data from the TSCR between January 2009 and December 2014. We identified patients who were diagnosed with lung cancer by the diagnostic codes C34.0, C34.1, C34.2, C34.3, C34.8, and C34.9. We identified a total of 64,918 patients with malignant lung neoplasm who received surgical treatment. (Fig 1.) There were 8,566 patients who were diagnosed at clinical stage I.

A total of 1,979 patients were excluded from the study. Among these, 1,210 patients had a missing follow-up 3 months post-operation; 625 had a missing pathological stage; 47 patients had a missing smoking status; 9 patients had a missing tumor size and 88 patients had missing lymph node data. Therefore, a total of 6,587 patients were enrolled into the study. There were 2,727 patients who received PET/CT, and the other 3,860 patients did not receive PET/CT. In order to reduce the bias, we used propensity matching of age, gender, smoking status, cell type and clinical stage. There were 2,649 patients in both groups after the propensity match.

Statistical Analysis

We used SAS software (SAS System for Windows, version 9.2; SAS Institute, Cary, NC) to perform the statistical analysis for this study.

The outcome measures for our study were 1, 3, and 5-year survival rates of all clinical stage I lung cancer patients; and survival rates of pathological I, II and III lung cancer patients who was diagnosed as clinical stage I and received surgery. We compared the survival rates between clinical stage I lung cancer patients with PET/CT scans and patients without PET/CT scans.

Survival curves were plotted by the Kaplan–Meier method, and the difference in survival was calculated by the log-rank test. Univariate and multivariate analyses were performed with the Cox proportional hazards model using SAS software. Statistical analysis with a p value less than 0.05 was considered statistically significant.

Results

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Discussion

Our study was a retrospective study investigating the prognosis of clinical stage I lung cancer patients in Taiwan after receiving PET/CT. Previous studies showed lots of prognostic factors in lung cancer such as age, gender, stage, performance status, tumor differentiation and lactate dehydrogenase.[10, 11] Our study revealed that older age, male gender, current smoking status, SqCC cell type, clinical stage Ib and advanced pathological stage were independent factors of a poor 5-year survival rate. However, PET/CT was not independent factors.

Focusing on PET/CT, it is widely used in the evaluation of stage I lung cancer. There were several advantages reported of the application to ung cancer patients. First, PET/CT provides high accuracy in cancer evaluation. Minamimoto et al. analyzed 854 lung cancer screening patients and showed that PET/CT had higher accuracy than PET only (100.0% vs. 63.2%).[12] Another study reported that the sensitivity and specificity of malignant solitary pulmonary nodules were 82% and 66% for CT, 88% and 71% for PET, and 88% and 77% for PET/CT.[13] Both studies indicated that the combination of PET and CT was effective for lung cancer screening. Therefore, PET/CT is commonly suggested after a CT examination. Not only does PET/CT have high sensitivity and specificity, but the positive predictive value and negative predictive value are even high in a series of studies. Chao et al. reviewed several studies and declared that PET/CT had high accuracy in nodal staging of lung cancer patients. The average positive predictive value and negative predictive value were 71% and 90%, respectively.[14]

Second, the usage of PET/CT reduces futile treatments and the associated morbidity and thus reduces costs. Several previous studies claimed that there were economic benefits of PET/CT in the management of patients with lung cancer.[15–18] Schreyogg et al. concluded that the incremental cost-effectiveness ratio (ICER) was $3,508 per non-small cell lung cancer (NSCLC) patient when comparing PET/CT to CT alone.[17] Similarly, Sogaard et al. performed a randomized clinical trial of 189 NSCLC patients and showed that the ICER was estimated at $3,927 when patients received PET/CT.[18] It is suggested that PET/CT is highly preferred for pretreatment evaluation of stage I lung cancer. However, due to PET/CT being much more expensive than other pretreatment evaluations in Taiwan, our study showed only 41.4% (2,727/6,587) of patients received PET/CT. Most of our patients did not receive PET/CT because of economic problems and their health insurance policies.

Third, there were several studies indicating that the application of PET/CT resulted in stage migration of lung cancer patients. Gregory et al. analyzed 168 NSCLC patients who received PET/CT and showed that there was stage migration in 50.6% (41.1% upstaged, 9.5% down-staged) of them.[19] On the other hand, there was 12% to 44% stage migration after receiving PET/CT in small cell lung cancer (SCLC) patients.[20, 21] Furthermore, most restaging after receiving PET/CT resulted in the altering of management and prognosis. The difference of stage migration rates between NSCLC and SCLC patients after PET/CT remained unknown. We assumed that PET/CT had better diagnostic value in NSCLC due to the tumor characteristics. The absorption of 18F-FDG is different in these different tumors, which resulted in a variance in image accuracy.

Lastly, the management strategies were also changed after PET/CT. Taus et al. reported that 34.6% of NSCLC patients receiving PET/CT contributed to 24.4% of treatment modifications and the avoidance of 5.2% of futile thoracotomy cases.[22] Kubota et al. even showed that PET/CT could contribute to 71.6% of the modifications of management strategies in lung cancer patients.[23] Our data indicated that clinical stage I lung cancer patients who received PET/CT had a higher lobectomy rate and a lower wedge resection rate. Moreover, patients were more likely to receive chemotherapy after receiving PET/CT. We assumed that most people in our study were upstaged after receiving a PET/CT scan and that the management strategies altered as well.

In the past, we merely used history taking and CT with contrast to determine the clinical stage. While PET/CT was introduced for pretreatment evaluation, a high proportion of patients receiving PET/CT had stage migration. Theoretically, PET/CT could lead to better prognosis of these patients. However, our data showed that a higher 5-year survival rate is not a benefit. There were few studies reporting the effects of PET/CT on the prognosis of lung cancer patients. Although management strategies were altered after lung cancer patients received PET/CT, their pathological stage did not change. We only varied the clinical stage and considered the different managements of the disease, but the 5-year survival rate did not change even when management strategies altered after PET/CT. Previous studies only mentioned that PET/CT lead to a more accurate clinical stage and changed the management. Our study pointed out that PET/CT did not alter the prognosis of stage I lung cancer patients. Further prospective study is needed to confirm this result.

There are some limitations of our study. First, this is a retrospective study. Although there was a huge amount of data, a prospective study is more convincing. Second, there might be a selection bias due to PET/CT scans being expensive in Taiwan. Patients who could afford the cost of a PET/CT scan might be able to afford other precise medication and have a better outcome.

Conclusions

Although stage I lung cancer patients receiving PET/CT resulted in the modification of management strategies and the avoidance of unnecessary thoracotomy, our data showed that there was no 5-year survival benefit for these patients.

Clinical Practice Points

Previous studies claims that PET/CT has high sensitivity (96.8%) and intermediate specificity (77.8%) for malignancy. In non-small cell lung cancer patients, it improved treatment choice in 25%. However, in our study the application of PET/CT provides no 5-year survival benefit in clinical stage I lung cancer patients.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and material: The datasets used and/or analyzed during the current

study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: The authors declare that they have no funding for this study.

Authors' contributions:

Overall conception and design: YF and BY. Technical design and analysis of data: WH, JY and HC. Contribution to acquisition of clinical data and interpretation and analysis of clinical data: CH and SH.

All authors critically reviewed the manuscript and revised it. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgment:

A special gratitude I give to the chairman of our department, Mr. Cheng, whose stimulating suggestions and encouragement helped me to coordinate my project, especially when writing this report.

References

1.Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30.

2.Walters S, Maringe C, Coleman MP, et al. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. Thorax. 2013;68(6):551–564.

3.Wood DE, Kazerooni EA, Baum SL, et al. Lung Cancer Screening, Version 3.2018, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2018;16(4):412–441.

4.Steinert HC. PET and PET-CT of lung cancer. Methods Mol Biol. 2011;727:33–51.

5.De Wever W, Stroobants S, Coolen J, et al. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. Eur Respir J. 2009;33(1):201–212.

6.Hashimoto Y, Tsujikawa T, Kondo C, et al. Accuracy of PET for diagnosis of solid pulmonary lesions with 18F-FDG uptake below the standardized uptake value of 2.5. J Nucl Med. 2006;47(3):426–431.

7.Kamel EM, Zwahlen D, Wyss MT, et al. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. J Nucl Med. 2003;44(12):1911–1917.

8.Herder GJ, Van Tinteren H, Comans EF, et al. Prospective use of serial questionnaires to evaluate the therapeutic efficacy of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in suspected lung cancer. Thorax. 2003;58(1):47–51.

9.Gould MK, Maclean CC, Kuschner WG, et al. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA. 2001;285(7):914–924.

10.Lyons G, Quadrelli S, Silva C, et al. Analysis of survival in 400 surgically resected non-small cell lung carcinomas: towards a redefinition of the T factor. J Thorac Oncol. 2008;3(9):989–993.

11.Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. Chest. 2002;122(3):1037–1057.

12.Minamimoto R, Senda M, Jinnouchi S, et al. Detection of lung cancer by FDG-PET cancer screening program: a nationwide Japanese survey. Anticancer Res. 2014;34(1):183–189.

13.Jeong SY, Lee KS, Shin KM, et al. Efficacy of PET/CT in the characterization of solid or partly solid solitary pulmonary nodules. Lung Cancer. 2008;61(2):186–194.

14.Chao F, Zhang H. PET/CT in the staging of the non-small-cell lung cancer. J Biomed Biotechnol. 2012;2012:783739.

15.Cao JQ, Rodrigues GB, Louie AV, et al. Systematic review of the cost-effectiveness of positron-emission tomography in staging of non—small-cell lung cancer and management of solitary pulmonary nodules. Clin Lung Cancer. 2012;13(3):161–170.

16.Ruben JD, Ball DL. The efficacy of PET staging for small-cell lung cancer: a systematic review and cost analysis in the Australian setting. J Thorac Oncol. 2012;7(6):1015–1020.

17.Schreyogg J, Weller J, Stargardt T, et al. Cost-effectiveness of hybrid PET/CT for staging of non-small cell lung cancer. J Nucl Med. 2010;51(11):1668–1675.

18.Sogaard R, Fischer BM, Mortensen J, et al. Preoperative staging of lung cancer with PET/CT: cost-effectiveness evaluation alongside a randomized controlled trial. Eur J Nucl Med Mol Imaging. 2011;38(5):802–809.

19.Gregory DL, Hicks RJ, Hogg A, et al. Effect of PET/CT on management of patients with non-small cell lung cancer: results of a prospective study with 5-year survival data. J Nucl Med. 2012;53(7):1007–1015.

20.Brink I, Schumacher T, Mix M, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging. 2004;31(12):1614–1620.

21.Arslan N, Tuncel M, Kuzhan O, et al. Evaluation of outcome prediction and disease extension by quantitative 2-deoxy–2-[18F] fluoro-D-glucose with positron emission tomography in patients with small cell lung cancer. Ann Nucl Med. 2011;25(6):406–413.

22.Taus A, Aguilo R, Curull V, et al. Impact of 18F-FDG PET/CT in the treatment of patients with non-small cell lung cancer. Arch Bronconeumol. 2014;50(3):99–104.

23.Kubota K, Matsuno S, Morioka N, et al. Impact of FDG-PET findings on decisions regarding patient management strategies: a multicenter trial in patients with lung cancer and other types of cancer. Ann Nucl Med. 2015;29(5):431–441.

Tables

Table:

Table 1. Clinical demographic data of patients with clinical stage I lung cancer

	All patients			Propensity-matched patients		
Characteristics	With PET/CT	Without	*P*	With PET/CT	Without	*P*
Numbers	2,727	3,860		2,649	2,649	
Age (years)	63.63±11.12	62.10±11.08	<.0001	63.55±11.12	63.24±11.04	0.9668
<50	302(11.07%)	485(12.56%)		291(10.99%)	302(11.4%)	
50-59	655(24.02%)	1,083(28.06%)		647(24.42%)	647(24.42%)	
60-69	885(32.45%)	1,231(31.89%)		862(32.54%)	852(32.16%)	
>=70	885(32.45%)	1,061(27.49%)		849(32.05%)	848(32.01%)	
Gender			0.2058			0.3929
Male	1,234(45.25%)	1,686(43.68%)		1,206(45.53%)	1,237(46.70%)	
Female	1,493(54.75%)	2,174(56.32%)		1,443(54.47%)	1,412(53.3%)	
Smoking status			<.0001			0.6295
Never	1,303(47.78%)	2,113(54.74%)		1,274(48.09%)	1,246(47.04%)	
Current	255(9.35%)	350(9.07%)		249(9.4%)	266(10.04%)	
Quit	1,169(42.87%)	515(13.34%)		1,126(42.51%)	1,137(42.92%)	
Cell type			<.0001			0.9990
SqCC	263(9.64%)	318(8.24%)		258(9.74%)	258(9.74%)	
AD	2,191(80.34%)	3,027(78.42%)		2,120(80.03%)	2,121(80.07%)	
Others	273(10.01%)	515(13.34%)		271(10.23%)	270(10.19%)	
Treatment			<.0001			
Lobectomy	2,035(74.62%)	2,571(66.61%)				
Wedge	307(11.26%)	778(20.16%)				
Others	385(14.12%)	511(13.24%)				
Clinical stage			<.0001			0.3924
Ia	1,684(61.75%)	2,786(72.18%)		1,663(62.78%)	1,693(63.91%)	
Ib	1,043(38.25%)	1,074(27.82%)		986(37.22%)	956(36.09%)	
Pathologic stage			<.0001			
I	2,229(81.74%)	3,407(88.26%)				
II	285(10.45%)	259(6.71%)				
III	213(7.81%)	194(5.03%)				
Survival rate						
1 year	0.9691	0.9789	0.0703	0.9699	0.9745	0.7243

3 years	0.8778	0.8951	0.0460	0.8819	0.8814	0.9145
5 years	0.7921	0.8020	0.1247	0.7976	0.7822	0.6528

SqCC: squamous cell carcinoma; AD: adenocarcinoma

Table 2. Univariate analysis of mortality risk

Variables	HR	95% Confidence Interval	P value
Age			
<50 (ref)	1		
50-59	1.115	(0.757-1.641)	0.5815
60-69	1.936	(1.353-2.769)	0.0003
>=70	3.715	(2.629-5.247)	<.0001
Gender			
Female (ref)	1		
Male	2.341	(1.983-2.763)	<.0001
Smoking status			
Never (ref)	1		
Current	3.045	(2.253-4.114)	<.0001
Quit	1.959	(1.585-2.422)	<.0001
Cell type			
Adenocarcinoma (ref)	1		
SqCC	3.217	(2.645-3.911)	<.0001
Others	1.702	(1.338-2.165)	<.0001
Treatment			
Lobectomy (ref)	1		
Wedge resection	1.497	(1.206-1.858)	0.0003
Others	1.192	(0.957-1.483)	0.1164
Clinical stage			
Ia (ref)	1		
Ib	2.353	(2.006-2.759)	<.0001
Pathologic stage			
I (ref)	1		
II	2.954	(2.390-3.650)	<.0001
III	3.510	(2.812-4.381)	<.0001
PET			
No (ref)	1		
Yes	1.142	(0.974-1.340)	0.1023

HR = hazard ratio

Table 3. Multivariate analysis of mortality risk

Variables	HR	95% Confidence Interval	P value
Age			
<50 (ref)	1		
50-59	1.004	(0.680-1.481)	0.9852
60-69	1.511	(1.053-2.168)	0.0252
>=70	2.195	(1.534-3.141)	<.0001
Gender			
Female (ref)	1		
Male	1.436	(1.187-1.737)	0.0002
Smoking status			
Never (ref)	1		
Current	1.600	(1.158-2.210)	0.0044
Quit	1.357	(1.083-1.700)	0.008
Cell type			
Adenocarcinoma (ref)	1		
SqCC	1.381	(1.107-1.723)	0.0042
Others	1.238	(0.964-1.589)	0.095
Treatment			
Lobectomy (ref)	1		
Wedge resection	1.599	(1.275-2.004)	<.0001
Others	1.080	(0.865-1.349)	0.4972
Clinical stage			
Ia (ref)	1		
Ib	1.235	(1.009-1.512)	0.041
Pathologic stage			
I (ref)	1		
II	1.900	(1.301-2.775)	0.0009
III	2.333	(1.424-3.821)	0.0008
PET			
No (ref)	1		
Yes	0.991	(0.844-1.164)	0.9105

HR = hazard ratio

Figures

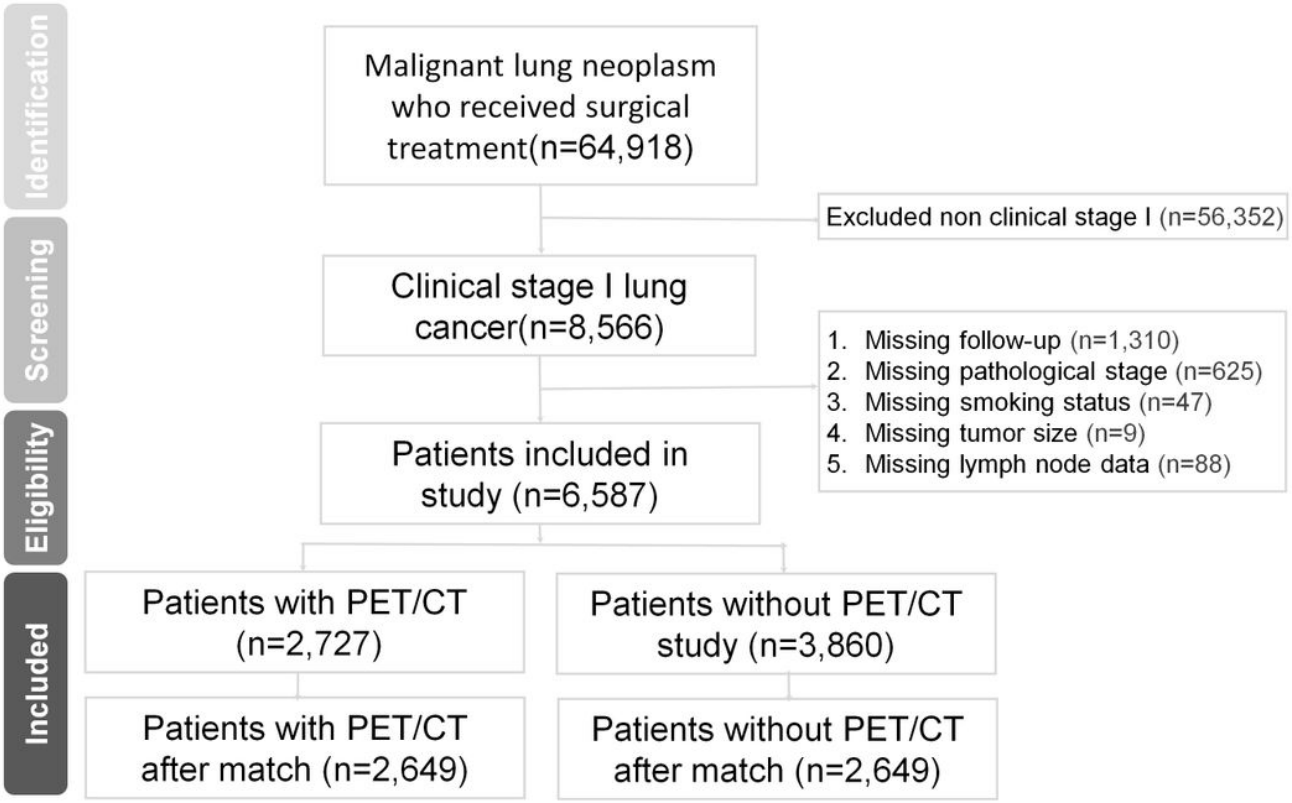

Figure 1

Flow chart of patients through study

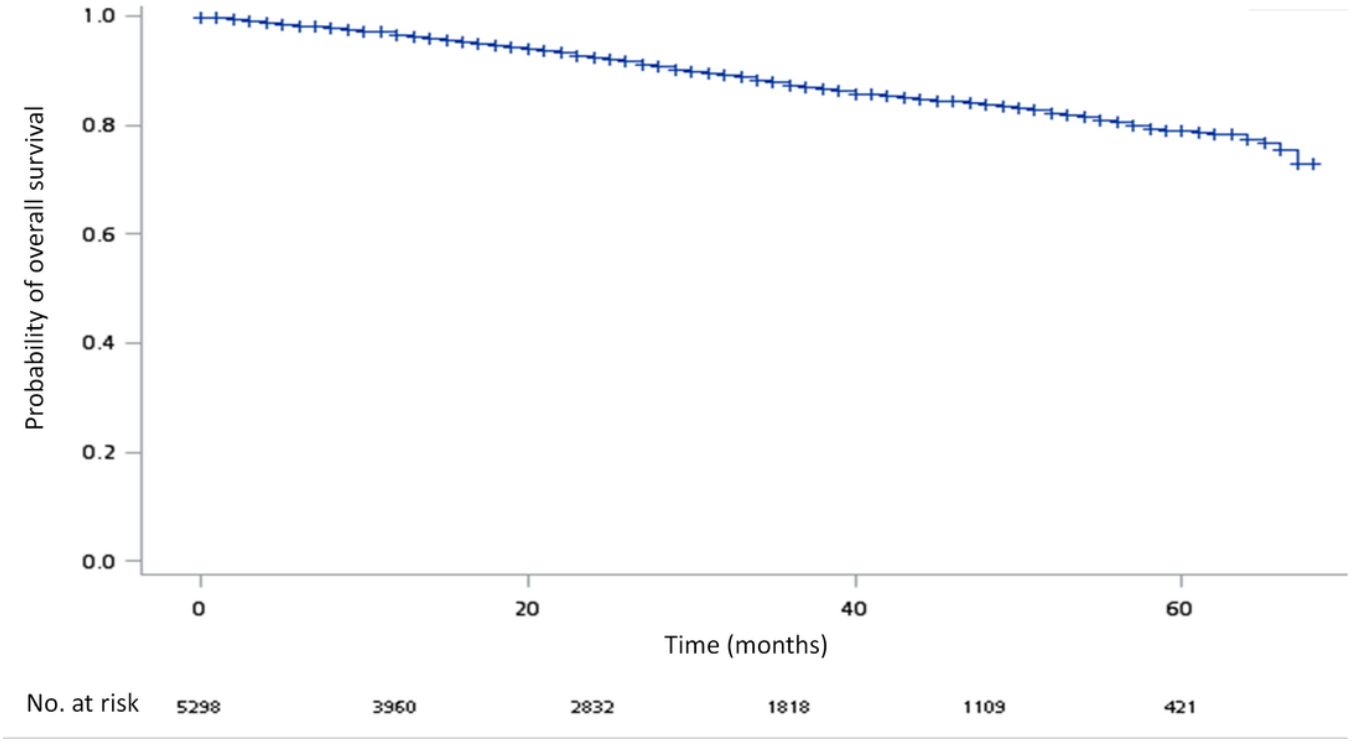

Figure 2

The survival rates of clinical stage I lung cancer patients

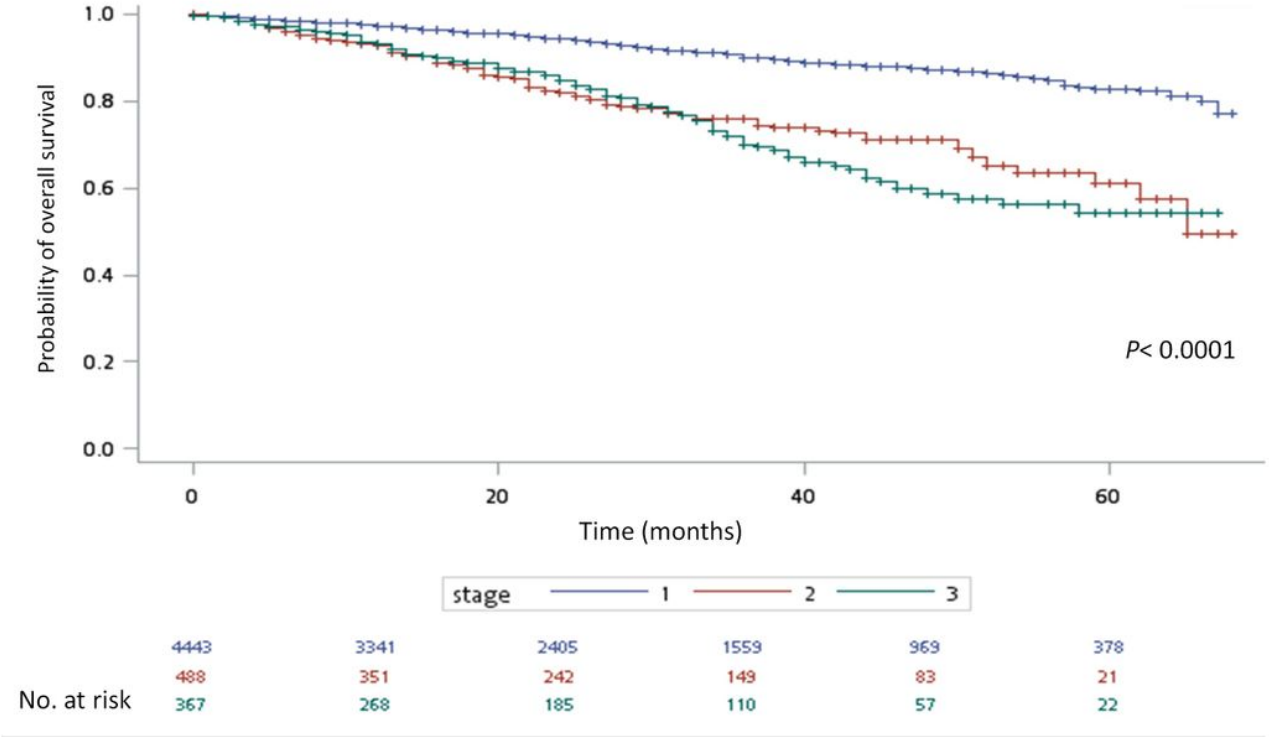

Figure 3

The survival rates of pathologic stage I, II and III lung cancer patients who was diagnosed as clinical stage I and received surgery

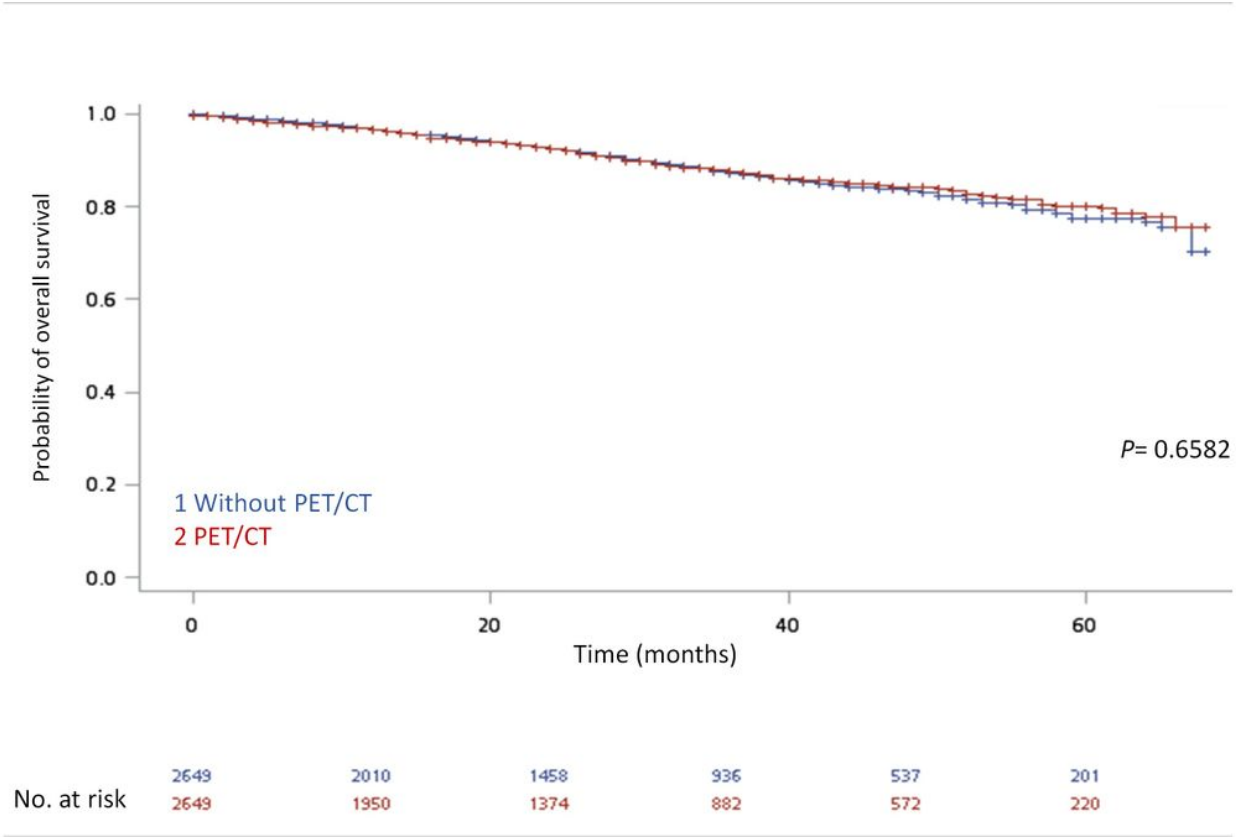

Figure 4

The survival rates of clinical stage I lung cancer patients divided into the PET/CT group and the no PET/CT group after propensity matching