Second lung cancer risk in patients treated for cancer of the cervix: a Population-Based study in the SEER cancer registries

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Research article

Keywords: lung cancer, cervical cancer, second primary cancer, SEER, epidemiology

Posted Date: January 30th, 2020

DOI: https://doi.org/10.21203/rs.2.22306/v1

Abstract

Background: As cervix cancer survival improves, the risk of developing a second cancer has become more important in particular lung cancer. However, the proportion of second primary non-small cell lung cancer after cervix cancer (CC-NSCLC) and associated clinical characteristics are unknown in comparison with first primary non-small cell lung cancer (NSCLC1).

Methods: The Surveillance, Epidemiology and End Results (SEER) cancer registry was used to conduct a large population-based cohort analysis of 16768 patients diagnosed with cervical cancer and 173272 patients diagnosed with NSCLC1 between 1998 and 2010. The analysis included demographic, clinical characteristics, prognostic data and risk factors for CC-NSCLC.

Results: 557 (3.3%) patients developed CC-NSCLC and 451 were eligible for inclusion in the final analyses. The mean age at CC-NSCLC diagnosis was 62.9 years old. In comparison to NSCLC1, patients with CC-NSCLC had a higher rate of squamous cell carcinoma (36.59% vs 19.07%) and were more likely to be diagnosed in young, unmarried and black subgroups. Median survival time was longer for CC-NSCLC than NSCLC-1 before but not propensity score matching. Localized stage, adenocarcinoma, young age, surgical records, no radiotherapy records and well differentiation were associated with better prognosis in CC-NSCLC cohort.

Conclusion: Patients with cervical cancer are at high risk of developing second primary lung cancers. High-risk factors include squamous carcinoma, 50-70years old, black, divorce, history of chemo-radiation therapy and poor differentiation. Prevention in this population as regards the increased risk for second primary cancers is crucial in order to improve the prognosis of patients.

Background

Cervical cancer is the fourth most common cancer worldwide, with an estimated 310 000 annual deaths globally [1–3]. Besides, in low-income countries, cervical cancer is still the leading cause of cancer-related deaths among women. However, improvements in early detection and cancer treatment have led to longer survival among cervical cancer patients. Subsequently, the possibility for patients to develop a subsequent primary cancer becomes a more important consideration [4], with a 14% higher rate of cancer than general population[5]. As a matter of fact, from 1975 to 2001, 756,467 people in the United States have developed a second solid cancer, representing almost 8 percent of the current cancer survivor population. Subsequent malignancies in cancer survivors now constitute 18% of all cancer diagnosis in the US SEER cancer registries [4].

In particular, lung cancer as a second primary malignancy is increasingly common. Indeed, lung cancer is the leading cause of cancer incidence and mortality around the world, with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing 18.4% cancer deaths [1]. Among women, lung cancer constitutes one of the 3 most commonly diagnosed cancers besides breast and colo-rectum

cancers [2]. Notably, lung cancer incidence rates are now higher among young women than among young men in non-Hispanic whites and Hispanics Americans [6].As regards both cervical cancer and lung cancer, approximately 10% of cervical cancer survivors have developed a second malignancy, in which lung cancer accounts for one of the largest numbers [7,8]. However, risk factors of secondary primary lung cancer in cervical cancer patients are not known. Similarly, differences between CC-NSCLC and NSCLC on clinical characteristics and survival have not been studied. Consequently, there is a crucial need to characterize the lung cancer disease in this specific subgroup as regards both their high incidence rates. Thereby, our study aims to focus on clinical differences between CC-NSCLC and NSCLC1 as well as risk factors for secondary primary lung cancer in patients with cervical cancer.

Methods

Ethical Statement

The Research Ethics Committee of Daping Hospital approved the study. Data obtained from SEER database did not require informed patient consent because cancer is a reportable disease in the United States.

Population

We identified cervical cancer cases and NSCLC cases from the SEER program of the National Cancer Institute (http://seer.cancer.gov/). The cohort was composed of adult patients who were pathologically confirmed with cervical cancer or NSCLC from the SEER database from 1998 to 2010. Exclusion criteria were: confirmed by autopsy, unknown age of diagnosis, unknown marriage status, undetermined grade of disease, unknown stage of disease, unknown pathological type. A total of 16768 cervical cancer patients, 173272 NSCLC patients were included in this study. Domestic status was recorded as follows: never married as “unmarried”, married as married or unmarried but having domestic partner; separated, divorced and widowed status were classified as “other”. Except for squamous cell neoplasm and adenocarcinomas, other histology types were recorded as “other”, including NSCLC not otherwise specified.

Statistical analysis

Categorical measurements were described as count and percentage, while continuous measurements were presented as mean□median□and range. The chi-square was used to compare the categorical measurements while the t test was used for continuous ones and for comparing the survival rates between CC-NSCLC and NSCLC1. Survival data were measured from the lung cancer date of diagnosis to the date of all-cause death or the last follow-up. Cumulative survival curves were generated by the Kaplan-Meier method. Differences in survival rates were compared using the log-rank (Mantel-Cox) tests.

Propensity score matching (PSM) analysis was used to balance the difference from baseline characteristics between CC-NSCLC and NSCLC1 groups. According to 1 to 3 matches, 449 CC-NSCLC patients were matched successfully. Covariates entered into the propensity model have included: histology, age at lung cancer diagnosis, race, year of lung cancer diagnosis, stage of lung cancer, marital status, radiotherapy records, chemotherapy records, surgery records and grade. All p values were two-sided, with $p < 0.05$ considered statistically significant. The incidence of second primary lung cancer was compared to the literature. All the analyses were done using SPSS statistical software, version 23 (IBM Corp, Armonk, NY).

Results

Patients Characteristics

A total of 16768 cervical cancer patients and 173272 NSCLC1 patients between 1998 and 2010 were involved. 557 patients (3.3%) were diagnosed with second primary non-small cell lung cancer after cervix cancer (CC-NSCLC) and 451 patients with complete information were eligible for inclusion in the final analyses. The demographic and clinicopathologic features of NSCLC–1 and CC-NSCLC patients are listed in Table 1. There are significant differences in histology, age at diagnosis, race, year at diagnosis, marital and cause of death between CC-NSCLC and NSCLC–1. No significant was detected in stage, radiotherapy records, chemotherapy records, surgery records and grade. The mean time to NSCLC diagnosis was 57 months, with a range of 12–192 months. The mean age of cervical cancer diagnosis was 58.2 years whereas the mean age at subsequent NSCLC diagnosis was 62.9 years. The majority of CC-NSCLC were adenocarcinomas (38.4%) while 36.6% were lung squamous cell carcinoma (LSCC) and 25.1% were other. Of the 173272 NSCLC1 patients in the database, a vast majority was adenocarcinomas (49.05%), and 19.07% of patients were LSCC while 31.89% of patients were other. The proportion of squamous cell carcinoma in CC-NSCLC patients was apparently higher than that in NSCLC1 patients (36.59% vs. 19.07%). The difference in pathologic type distribution between these two cohorts is significant ($p<0.01$).

Clinical features in CC-NSCLC patients

The impact of demographic characteristics and clinical features of cervical cancer on pathological types and clinical stages of lung cancer in CC-NSCLC patients are listed in Table 2. Latency, stage, histology, radiotherapy records, chemotherapy records and grade were associated with pathological types of lung cancer, rather than race, age at cervical cancer diagnosis, year of cervical cancer diagnosis, marital status, surgery records. There was no significant correlation between clinical factors of cervical cancer and stages of lung cancer in CC-NSCLC patients.

The impact of demographic characteristics and clinical features of cervical cancer on the cause of death in CC-NSCLC patients are listed in Table 3. Latency, age at diagnosis, stage, histology, marital status, radiotherapy records, chemotherapy records, surgery records and grade were associated with the causes

of death, rather than race and year of cervical cancer diagnosis. Patients with a latency≤1year were more likely to die of cervical cancer, and those with a latency≥5years were more likely to survive. Married patients with young age, regional stage, treated by radiation or chemotherapy, died more often from cervical cancer. Patients with cervical adenocarcinoma, well or moderately differentiated in terms of histological grade and treated by surgery were more likely to survive. Lung cancer was the most common cause of death（44.8%）.

Risk factors of secondary primary lung cancer in cervical cancer patients

High-risk factors of developing secondary primary lung cancer in cervical cancer patients include: squamous cell carcinomas, age between 50 and 70years old, black race, marital status as divorce or separated or widowed, history of chemo-radiation therapy, poor differentiation. All significant independent factors from Univariate analysis to develop second primary lung cancer are shown in Table 4.

Survival Analysis

The median OS was 16months (range, 1–191 months) vs. 13months (range, 1–227 months) in CC-NSCLC patients and NSCLC1 patients before PSM, whereas 16months vs. 17months after PSM. The difference was significant before PSM ($p < 0.05$) but no significant after PSM (p＞0.05). Figure1 shows the survival curves of CC-NSCLC and NSCLC1 before and after PSM. OS was longer for CC-NSCLC vs. NSCLC–1 before PSM but no significant difference after PSM.

Pathologic type was another important prognostic factor for OS. Unsurprisingly, patients with adenocarcinoma had much longer OS than those with squamous cell carcinomas or other (22.0, 16.0,and 11.0m respectively ($p < 0.01$)). Young patients had superior OS in comparison with patients older than 80. The latter had a median OS of 7 months. Differentiation was also an important prognostic factor. mOS of CC-NSCLC patients with grade I+II, grade III+IV and unknown differentiation were respectively 45, 13 and 10m ($p < 0.01$).Patients who had surgery had a better prognosis（70 vs. 10m, $p < 0.01$, and those who had radiation had a worse prognosis（21 vs. 13m, $p < 0.01$）(Figure2).

Discussion

Over the past three decades, advances in early detection and treatment of cervix cancer have resulted in significant survival improvement among cervical cancer patients. Such survival rates after a cervical cancer diagnosis are higher than they have ever been, due to improvements in cancer therapy and current emerging issues concern long-term events in survivors, with notably the occurrence of second cancer[9]. Patients will develop subsequent primary cancers as a result of shared lifestyle and genetic factors, as well as the first cancer treatment. In particular, lung cancer is one of the most frequent cancers, which is developed among cervical cancer survivors who display a second malignancy. However, risk factors for

secondary primary lung cancer in patients with cervical cancer are poorly known. Similarly, it is unknown if the clinical features of cervical cancer have an impact on the pathological types and stages of secondary lung cancer. Furthermore survival data are lacking as regards differences in terms of prognosis between NSCLC–1 and CC-NSCLC. To the best of our knowledge, our study is the first to focus on CC-NSCLC, with the aim to objective differences between CC-NSCLC and NSCLC1 besides the goal to identify risk factors for secondary primary lung cancer in patients with cervical cancer. Subsequently, our article provides answers to these various issues. First and foremost, CC-NSCLC patients are younger with earlier stages. The proportion of squamous cell carcinoma in CC-NSCLC patients was significantly higher than in NSCLC1 patients (36.59% vs. 19.07%). If CC-NSCLC patients seemed to have a better prognosis, no significant difference was found after PSM. Cervical cancer patients who developed secondary primary lung cancer had several characteristics including a squamous cell carcinomas histologic type, 50–70years old, black race, marital status as divorce or separated or widowed, history of chemo-radiation therapy and poor differentiation.

Concerning epidemiologic data, the incidence of lung cancer differs according to geographical region and over time. In particular, both incidence and mortality from lung cancer continue to increase sharply in China [10,11]. Our results suggest that the incidence of lung cancer among cervical cancer survivors in our cohort (3.3%) was significantly lower in comparison to rates reported in the literature. According to the region-specific incidence Age-Standardized Rates by Sex for Cancers of the Lung in 2018，men in Micronesia/Polynesia have the highest incidence, which is 52.2 per 100,000 whereas female in Northern American have the highest incidence, which is 30.7 per 100,000[1]. However such data concern specifically the incidence of lung cancer, without data concerning cervix cancer. In our cohort, CC-NSCLC patients were younger than NSCLC1 patients, and displayed earlier stages, which may be due to more frequent medical examinations. Squamous cell lung carcinoma was the most common histologic subtype before the 1990s. Currently, adenocarcinoma has become the most common histologic subtype of lung cancer in men and women [12,13]. Although adenocarcinoma（38.36%）remains the most common histologic subtype in CC-NSCLC patients, the proportion of squamous cell carcinoma is significantly higher among NSCLC1 patients（36.59% vs. 19.07%). Squamous cell carcinoma accounts for 19.07% of NSCLC1 patients in our study similarly to data from literature [14]. The high proportion of squamous cell carcinoma in cervical cancer patients may be due to the history of chemo-radiation therapy as well as confounding factors such as unclear primary and cervical cancer metastasis. Besides, it has to be noted that since 2006, the incidence of second primary lung cancer among cervical cancer patients has drastically increased in our study, which cannot be entirely explained by the increase of lung cancer rates. Indeed, more reasons are required to explain the increased incidence of second primary lung cancer in cervical cancer patients. Interestingly, there was no difference in the number of patients undergoing surgery, chemotherapy and radiotherapy between the two groups. The cancer-related death rate of CC-NSCLC patients was significantly lower than in NSCLC1 patients （56.54% vs. 69.39%）, and the survival rate was significantly higher than in NSCLC1 patients（25.50% vs. 10.83%）, with longer OS for CC-NSCLC patients. In addition, CC-NSCLC patients had a delayed diagnosis in comparison to NSCLC1 patients. Subsequently, in our study, patients diagnosed with CC-NSCLC have a favorable lung cancer-specific

survival. However, there was no significant difference in prognosis after PSM between CC-NSCLC and NSCLC1. We infer that the better prognosis of CC-NSCLC before PSM may be due to earlier stages and the young age of the patients. Therefore, for all patients, early diagnosis as well as early treatment is the best way to improve survival. Regular physical examination is necessary. Patients with surgical records, without radiotherapy records had a significant better prognosis. This phenomenon can be partly explained by the fact that more patients in the early stage receive surgical treatment and more patients in the late stage receive radiotherapy.

As regards the impact of cervical cancer patients clinical features on pathological types of lung cancer, our study highlight that the incidence of squamous cell carcinoma is higher in blacks than whites in CC-NSCLC patients（45.0% vs. 36.3%), which is consistent with literature as previous studies have reported that higher incidence of squamous cell carcinoma was observed among Black males and females in comparison to white people[15]. Lung squamous cancer is more common in patients with a longer latency, regional stage and history of cervical squamous cell carcinoma. Thereby, some patients diagnosed with lung squamous cell carcinoma may be metastatic from cervical cancer. In addition, patients with a history of chemo-radiation therapy also have a higher rate of squamous cell carcinoma. A study[16] shows that radiation penetrates epidermis sufficiently to cause irreversible DNA damage in cells located beneath the epidermis causing squamous cell carcinoma. Cervical cancer variables do not affect the stage of CC-NSCLC patients.

Chemotherapy and radiation were proven risk factors for the development of second malignancies among cancer survivors[17]. Traditionally, radiation exposure is considered as one of the most important risk factor for cancer development. Radiation and chemotherapy treatments have a crucial role in the treatment of early cervical cancer, decreasing the risk of cancer recurrence and improving survival, but such treatments are also associated to an increased risk of second malignancies after exposure, especially, in long-term smokers [18–21]. However, no significant high-standardized incidence ratios were observed among the radiation group in a large population-based study using SEER data. The authors explained that a half of the patients were none/unknown status of radiotherapy which could explained such results [17]. In our population-based study using SEER data, significant high incidence ratios were observed in both radiation group and chemotherapy group. With the improvement of radiotherapy technology, the application of Intensity-modulated radiation therapy（IMRT） and 3 dimensional conformal radiation therapy（3D-CRT）has become more and more common [22,23]. Our data cannot assess whether IMRT and 3D-CRT will increase the risk of second primary tumor. No significant SIR was detected in Surgical treatment group.

Finally, our study has several limitations including notably the lack of biological data including PD-L1 status [24–26]. We failed to collect this crucial data as biomarker analysis has not been universalized in clinical practice until very recent years. Consequently, further studies are warranted for targetable driver mutations and PD-L1 in CC-NSCL. Furthermore, our study did not include the interactions of all possible risk factors on cervical cancer patients. Furthermore, the main limitation of the SEER data, like any

retrospective study of treatment effects, is the lack of randomness in treatment regimens, which leads to confounding factors, and result may be biased and interpreted with caution despite the use of PSM to remedy this defect.

Conclusions

Patients with cervical cancer patients are at high risk of developing second primary lung cancers. CC-NSCLC seems to be a distinct entity in female that display a squamous carcinoma, with early-stage at diagnosis and a better prognosis, in comparison to NSCLC1 patients. High-risk factors of developing secondary primary lung cancer in cervical cancer patients include: squamous cell carcinomas, 50–70years old, black race, marital status as divorce, separated or widowed, history of chemo-radiotherapy, poor differentiation, hence the crucial need of prevention in this population as regards the increased risk for second primary cancers, in order to improve the prognosis of patients.

Availability Of Data And Materials

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

Abbreviations

CC-NSCLC: second primary non-small cell lung cancer after cervix cancer

NSCLC1: first primary non-small cell lung cancer

SEER: Surveillance, Epidemiology and End Results cancer registries

OS: Overall Survival

PSM: Propensity score matching

LSCC: lung squamous cell carcinoma

IMRT: Intensity-modulated radiation therapy

3D-CRT: 3 dimensional conformal radiation therapy

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Declarations

Acknowledgments

The SEER program was appreciated for providing free accessible to the database.

Funding

This work was supported by grants from the National Natural Science Foundation

of China (NSFC) No. 81502241

Contributions

Chengyuan Qian and Mingfang Xu designed the study. Chengyuan Qian and Hongliu accessed databases and gathered all variables. Yan Feng, Nan Dai and Yu Pu assumed responsibility for completeness and accuracy of data analysis and interpretation. The manuscript was written by Mingfang Xu. Dongwang was in charge of writing–review and editing. All authors have read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

Data obtained from SEER database did not require informed patient consent because cancer is a reportable disease in the United States.

Consent for publication

Not applicable.

Competing interests

The authors declared that they have no competing interests.

Tables

DIAGNOSIS	Before PSM			After PSM		
	NSCLC	CCNSCLC	P-value	NSCLC	CCNSCLC	P-value
N	173272	451		2245	449	
Histology			<0.001			0.168
AC	84986 (49.05%)	173 (38.36%)		943 (42.00%)	173 (38.53%)	
SCC	33035 (19.07%)	165 (36.59%)		714 (31.80%)	163 (36.30%)	
Other	55251 (31.89%)	113 (25.06%)		588 (26.19%)	113 (25.17%)	
Age at lung cancer diagnosis			<0.001			0.996
25-39	1288 (0.74%)	13 (2.88%)		66 (2.94%)	13 (2.90%)	
40-49	9007 (5.20%)	56 (12.42%)		255 (11.36%)	55 (12.25%)	
50-59	26110 (15.07%)	109 (24.17%)		540 (24.05%)	109 (24.28%)	
60-69	47576 (27.46%)	121 (26.83%)		609 (27.13%)	121 (26.95%)	
70-79	57203 (33.01%)	117 (25.94%)		596 (26.55%)	116 (25.84%)	
≥80	32088 (18.52%)	35 (7.76%)	<0.001	179 (7.97%)	35 (7.80%)	
Race						0.47
White	145404 (83.92%)	338 (74.94%)		1662 (74.03%)	336 (74.83%)	
Black	17839 (10.30%)	80 (17.74%)		379 (16.88%)	80 (17.82%)	
Other	10029 (5.79%)	33 (7.32%)		204 (9.09%)	33 (7.35%)	
Year of lung cancer Diagnosis			<0.001			0.851
1998-2000	24574 (14.18%)	15 (3.33%)		65 (2.90%)	15 (3.34%)	
2001-2005	71076 (41.02%)	107 (23.73%)		520 (23.16%)	106 (23.61%)	
2006-2010	77622 (44.80%)	329 (72.95%)		1660 (73.94%)	328 (73.05%)	
Stage atlung cancer diagnosis			0.11			0.988
localized	39467 (22.78%)	121 (26.83%)		597 (26.59%)	121 (26.95%)	
regional	44937 (25.93%)	115 (25.50%)		578 (25.75%)	115 (25.61%)	
distant	88868 (51.29%)	215 (47.67%)		1070 (47.66%)	213 (47.44%)	
Marital status			<0.001			0.985
never married	18512 (10.68%)	94 (20.84%)		462 (20.58%)	93 (20.71%)	
Married	73728 (42.55%)	185 (41.02%)		930 (41.43%)	184 (40.98%)	
Divorced or Separated or Widowed	81032 (46.77%)	172 (38.14%)		853 (38.00%)	172 (38.31%)	
RADIATION.RECORDS			0.258			0.793
no	104795 (60.48%)	261 (57.87%)		1310 (58.35%)	259 (57.68%)	
yes	68477 (39.52%)	190 (42.13%)		935 (41.65%)	190 (42.32%)	
CHEMOTHERAPY			0.523			0.753
no	104363 (60.23%)	265 (58.76%)		1302 (58.00%)	264 (58.80%)	
yes	68909 (39.77%)	186 (41.24%)		943 (42.00%)	185 (41.20%)	
surgery records			0.117			0.898
no	121139 (69.91%)	300 (66.52%)		1502 (66.90%)	299 (66.59%)	
yes	52133 (30.09%)	151 (33.48%)		743 (33.10%)	150 (33.41%)	
GRADE			0.345			0.94
I-II	41501 (23.95%)	115 (25.50%)		587 (26.15%)	115 (25.61%)	
III-IV	52840 (30.50%)	146 (32.37%)		702 (31.27%)	144 (32.07%)	
unknown	78931 (45.55%)	190 (42.13%)		956 (42.58%)	190 (42.32%)	
CAUSE of death			<0.001			<0.001
lung cancer	120106 (69.32%)	202 (44.79%)		1481 (65.97%)	201 (44.77%)	
cervical cancer	113 (0.07%)	53 (11.75%)		12 (0.53%)	52 (11.58%)	
Alive	18763 (10.83%)	115 (25.50%)		377 (16.79%)	115 (25.61%)	
other	34290 (19.79%)	81 (17.96%)		375 (16.70%)	81 (18.04%)	

Table 1. Demographic and clinicopathological characteristics of patients with CC-NSCLC and NSCLC between 1998 and 2010 in SEER database Demographic before and after PSM

Cervical cancers	Lung cancers				P value	Lung cancers			P value
	Total	AC(%)	SCC(%)	other(%)		Localized(%)	Regional(%)	Distant(%)	
Total	451	173（38.4）	165（36.6）	113（25.1）		121（26.8）	115（25.5）	215（47.7）	
Latency					<0.05				<0.05
≤1year	100	42 (42.0)	31 (31.0)	27 (27.0)		37（37.0）	23（23.0）	40（40.0）	
>1year，≤5years	187	57 (30.5)	69 (36.9)	61 (32.6)		43（23.0）	48（25.7）	96（51.3）	
>5years，≤10years	117	51 (43.6)	47 (40.2)	19 (16.2)		27（23.1）	34（29.0）	56（47.9）	
>10years	47	23 (48.9)	18 (38.3)	6 (12.8)		14（29.8）	10（21.3）	23（48.9）	
Race					>0.05				<0.05
White	338	127 (37.6)	122 (36.1)	89 (26.3)		97（28.7）	84（24.9）	157（46.4）	
Black	80	29 (36.3)	36 (45.0)	15 (18.8)		16（20.0）	23（28.7）	41（51.3）	
Other	33	17 (51.5)	7 (21.2)	9 (27.3)		8（24.2）	8（24.2）	17（51.6）	
Age at cervical cancer diagnosis					>0.05				<0.05
25-39	35	13 (37.1)	15 (42.9)	7 (20.2)		8（22.9）	10（28.6）	17（48.6）	
40-49	77	20 (26.0)	33 (42.9)	24 (31.1)		16（20.8）	19（24.7）	42（54.5）	
50-59	133	61 (45.9)	39 (29.3)	33 (24.8)		32（24.1）	35（26.3）	66（49.6）	
60-69	124	53 (42.7)	43 (34.7)	28 (22.6)		39（31.5）	33（26.6）	52（41.9）	
70-79	68	21 (30.9)	28 (41.2)	19 (27.9)		20（29.4）	17（25.0）	31（45.6）	
≥80	14	5 (35.7)	7 (50.5)	2 (14.3)		6（42.9）	1（7.1）	7（50.0）	
Year of cervical cancer Diagnosis					>0.05				<0.05
1998-2000	112	36 (32.1)	43 (38.4)	33 (29.5)		28（25.0）	30（26.8）	54（48.2）	
2001-2005	216	84 (38.9)	81 (37.5)	51 (23.6)		62（28.7）	51（23.6）	103（47.7）	
2006-2010	123	53 (43.1)	41 (33.3)	29 (23.6)		31（25.2）	34（27.6）	58（47.2）	
Stage at CC cancer diagnosis					<0.001				<0.05
localized	213	103（48.4）	61（28.6）	49（23.0）		60（28.2）	57（26.8）	96（45.0）	
regional	238	70（29.4）	104（43.7）	64（26.9）		61（25.6）	58（24.4）	119（50.0）	
Histology					p<0.001				<0.05
AC	89	49 (55.0)	15 (16.9)	25 (28.1)		20（22.5）	24（27.0）	45（50.5）	
SCC	335	111 (33.1)	146 (43.6)	78 (23.3)		94（28.1）	85（25.4）	156（46.6）	
other	27	13 (48.2)	4 (14.8)	10 (37.0)		7（25.9）	6（22.2）	14（51.9）	
Marital status					>0.05				<0.05
never married	94	33 (35.1)	38 (40.4)	23 (24.5)		19（20.2）	24（25.5）	51（54.3）	
Married	185	82 (44.3)	57 (30.8)	46 (24.9)		50（27.0）	48（25.9）	87（47.1）	
Divorced or Separated orWidowed	172	58 (33.7)	70 (40.7)	44 (25.6)		52（30.2）	43（25.0）	77（44.8）	
Radiation records					<0.001				<0.05
no	151	78 (51.7)	37 (24.5)	36 (23.8)		82（27.3）	70（23.3）	148（49.4）	
yes	300	95 (31.7)	128 (42.7)	77 (25.6)		39（25.8）	45（29.8）	67（44.4）	
Chemotherapy records					<0.001				<0.05
no	247	117 (47.4)	74 (30.0)	56 (22.6)		55（27.0）	46（22.5）	103（50.5）	
yes	204	56 (27.5)	91 (44.6)	57 (27.9)		66（26.7）	69（27.9）	112（45.3）	
surgery records									<0.05
no	194	56 (28.9)	87 (44.8)	51 (26.3)		69（26.8）	63（24.5）	125（48.7）	
yes	257	117 (45.5)	78 (30.4)	62 (24.1)		52（26.8）	52（26.8）	90（46.4）	
GRADE					<0.05				<0.05
I-II	180	77 (42.8)	69 (38.3)	34 (18.9)		55（30.6）	48（26.7）	77（42.8）	
III-IV	162	51 (31.5)	64 (39.5)	47 (29.0)		33（20.4）	37（22.8）	92（56.8）	
unknown	109	45 (41.3)	32 (29.4)	32 (29.4)		33（30.3）	30（27.5）	46（42.2）	

Table 2. The impact of demographic characteristics and clinical features of cervical cancer on pathological types and clinical stages of lung cancer in CC-NSCLC patients

Cervical cancers	cause of death					P value
	Total	Lung and Bronchus(%)	Cervix Uteri(%)	Alive(%)	Other(%)	
Total	451	202（44.8）	53（11.8）	115（25.5）	81（18.0）	
Latency						<0.001
≤1year	100	42（42.0）	18（18.0）	12（12.0）	28（28.0）	
（1year，≤5years	187	86（46.0）	24（12.8）	42（22.5）	35（18.7）	
（5years，≤10years	117	54（46.2）	9（7.7）	40（34.2）	14（12.0）	
（10years	47	20（42.6）	2（4.3）	21（44.7）	4（8.5）	
Race						（0.05
White	338	153（45.3）	43（12.7）	85（25.1）	57（16.9）	
Black	80	35（43.8）	8（10.0）	18（22.5）	19（23.8）	
Other	33	14（42.4）	2（6.1）	12（36.4）	5（15.2）	
Age at cervical cancer diagnosis						<0.001
25-39	35	7（20.0）	10（28.6）	15（42.9）	3（8.5）	
40-49	77	35（45.5）	11（14.3）	19（24.7）	12（15.5）	
50-59	133	61（45.9）	16（12.0）	38（28.6）	18（13.5）	
60-69	124	55（44.4）	11（8.9）	33（26.6）	25（20.1）	
70-79	68	37（54.4）	3（4.4）	8（11.8）	20（29.4）	
≥80	14	7（50.0）	2（14.3）	2（14.3）	3（21.4）	
Year of cervical cancer Diagnosis						（0.05
1998-2000	112	51（45.5）	14（12.5）	26（23.2）	21（18.8）	
2001-2005	216	104（48.1）	27（12.5）	55（25.5）	30（13.9）	
2006-2010	123	47（38.2）	12（9.8）	34（27.6）	30（24.4）	
Stage at breast cancer diagnosis						<0.05
localized	213	96（45.1）	12（5.6）	67（31.5）	38（17.8）	
regional	238	106（44.5）	41（17.2）	48（20.2）	43（18.1）	
Histology						p<0.05
AC	89	32（36.0）	7（7.9）	33（37.1）	17（19.0）	
SCC	335	155（46.3）	41（12.2）	80（23.9）	59（17.6）	
other	27	15（55.6）	5（18.5）	2（7.4）	5（18.5）	
Marital status						<0.05
never married	94	44（46.8）	7（7.4）	26（27.7）	17（18.1）	
Married	185	75（40.5）	29（15.7）	56（30.3）	25（13.5）	
Divorced or Separated or Widowed	172	83（48.3）	17（9.9）	33（19.2）	39（22.7）	
Radiation records						<0.05
yes	300	134（44.7）	46（15.3）	64（21.3）	56（18.7）	
no	151	68（45.0）	7（4.6）	51（33.8）	25（16.6）	
Chemotherapy records						<0.05
yes	204	85（41.7）	37（18.1）	47（23.0）	35（17.2）	
no	247	117（47.4）	16（6.5）	68（27.5）	46（18.6）	
surgery records						<0.05
yes	257	110（42.8）	24（9.3）	83（32.3）	40（15.6）	
no	194	92（47.4）	29（14.9）	32（16.5）	41（21.1）	
GRADE						<0.05
I-II	180	73（40.6）	18（10.0）	60（33.3）	29（16.1）	
III-IV	162	82（50.6）	24（14.8）	32（19.8）	24（14.8）	
unknown	109	47（43.1）	11（10.1）	23（21.1）	28（25.7）	

Table 3. The impact of demographic characteristics and clinical features of cervical cancer on the cause of death in CC-NSCLC patients

DIAGNOSIS	cervical cancer	CC-NSCLC	P-value
Histology			<0.05
AC	3705 (24.12%)	89 (19.73%)	
SCC	10506 (68.41%)	335 (74.28%)	
other	1147 (7.47%)	27 (5.99%)	
Age			<0.05
25-39	5101 (33.21%)	35 (7.76%)	
40-49	4413 (28.73%)	77 (17.07%)	
50-59	2680 (17.45%)	133 (29.49%)	
60-69	1588 (10.34%)	124 (27.49%)	
70-79	993 (6.47%)	68 (15.08%)	
≥80	583 (3.80%)	14 (3.10%)	
Race			<0.05
White	11492 (74.83%)	338 (74.94%)	
Black	1716 (11.17%)	80 (17.74%)	
Other	2150 (14.00%)	33 (7.32%)	
Year			<0.05
1998-2000	4008 (26.10%)	112 (24.83%)	
2001-2005	6224 (40.53%)	216 (47.89%)	
2006-2010	5126 (33.38%)	123 (27.27%)	
Stage			<0.05
localized	9123 (59.40%)	213 (47.23%)	
regional	6235 (40.60%)	238 (52.77%)	
Marital status			<0.05
unmarried	4480 (29.17%)	94 (20.84%)	
Married	7371 (47.99%)	185 (41.02%)	
Divorced or Separated or Widowed	3507 (22.84%)	172 (38.14%)	
Surgery records			<0.05
no	4687 (30.52%)	194 (43.02%)	
yes	10671 (69.48%)	257 (56.98%)	
Radiation records			<0.05
no	7820 (50.92%)	151 (33.48%)	
yes	7538 (49.08%)	300 (66.52%)	
Chemotherapy records			<0.05
no	9904 (64.49%)	247 (54.77%)	
yes	5454 (35.51%)	204 (45.23%)	
Grade			<0.05
I-II	6100 (39.72%)	180 (39.91%)	
III-IV	4485 (29.20%)	162 (35.92%)	
unknown	4773 (31.08%)	109 (24.17%)	

Table 4. Risk factors of secondary primary lung cancer in cervical cancer patients

Figures

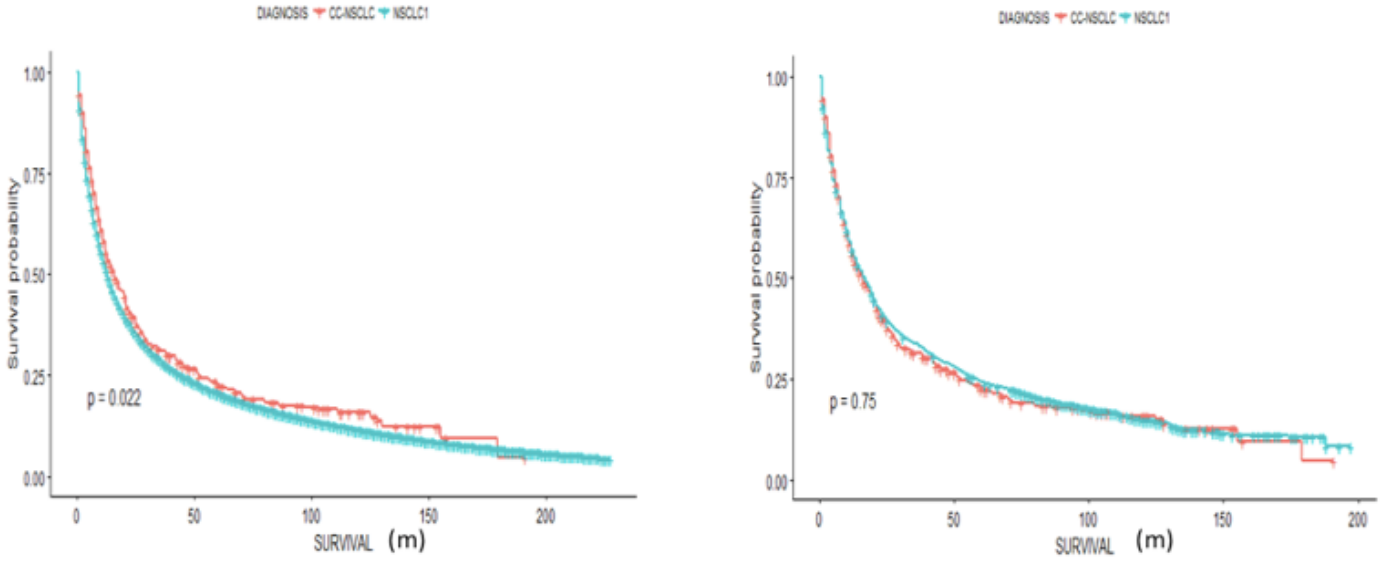

Figure 1

mOS for CC-NSCLC and NSCLC1 before and after PSM

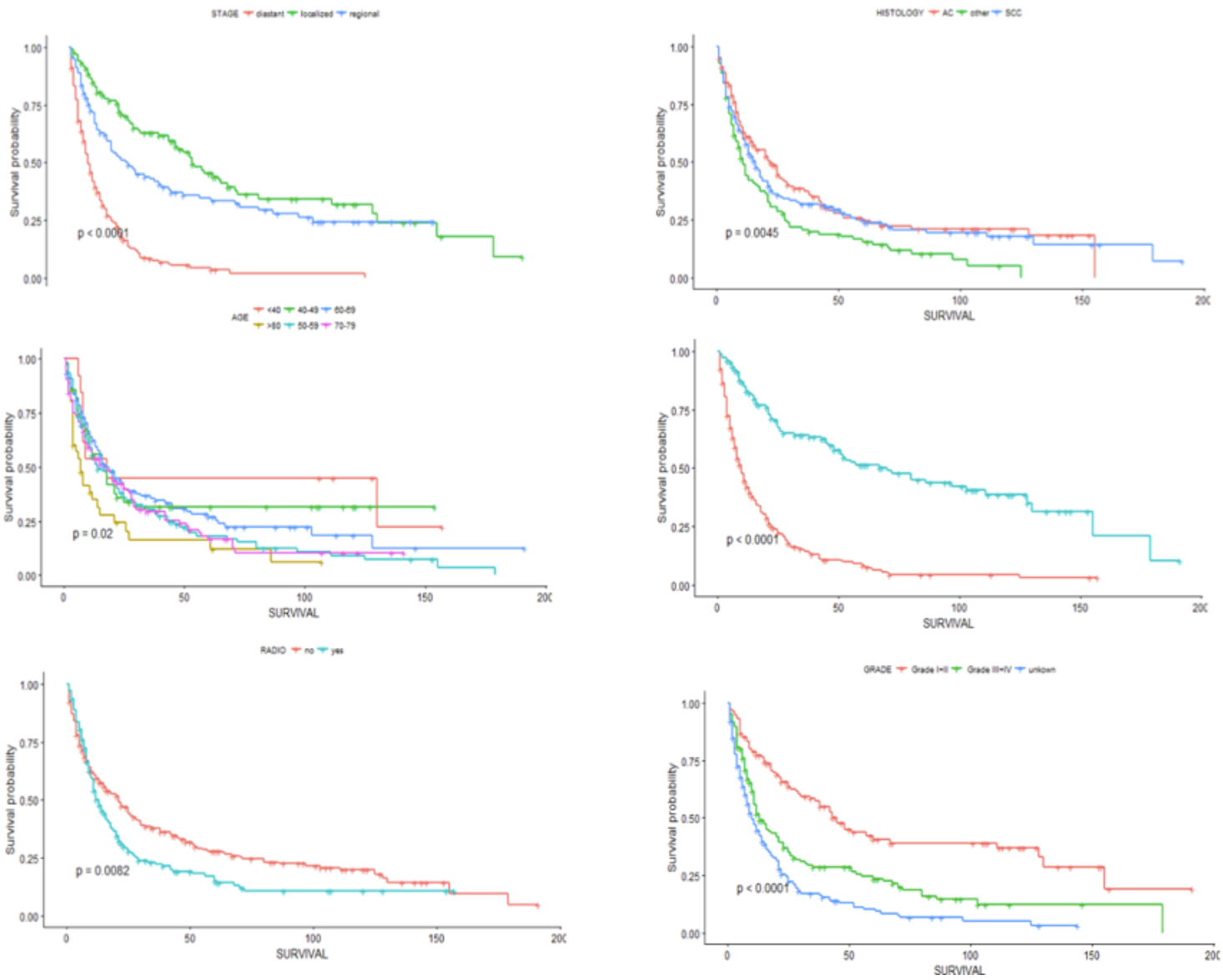

Figure 2

Influence of stage, pathological type, age, surgical record, radiotherapy record and differentiation grade on OS in CC-NSCLC.