撮影されている[9]．実際に病気がある場合には画質が優先されるために高線量での撮影が一般的であるが，検診の場合は大半が健常者なので，低線量でも通常の胸部X線写真1枚に比べると10倍程度の被曝量があるとされているので，検診や人間ドックでのCT撮影は低線量で行うことを原則とすべきである．

低線量CT検診の有効性

CTを肺がん検診に導入した場合に，肺がんは年齢や性別により発生頻度が異なるので一概に発見率だけで優劣を決めることはできないが，X線での検診に比べ3～10倍の頻度で肺がんが発見でき，発見される肺がんの80%程度はリンパ節や遠隔臓器への転移のないⅠ期であることが明らかになっている．

X線での検診の有効性は本邦では認められているのであるから，それよりも精度の高い検査法を取り入れて精度が落ちるはずはないという考えから，低線量CT検診は導入されてきている．しかし欧米ではX線での検診の有効性もまだ証明されていないという考えから，改めてCT検診の有効性を証明しようという研究が進められている．多くはRCTでの研究が行われており，まもなくその成果が発表される予定になっている．本邦では研究費の関係もあり完全なRCTを行うことができないので，通常の検診受診群と低線量CT検診受診群の予後を比較する研究が行われ，これもまもなく最終結果が報告される予定になっている．

CT検診の肺がん以外への効果

一方，低線量CT検診には肺がん発見以外にも二つのメリットがあることが明らかになってきている．

第一は肺がん以外の疾患も発見できる点で，呼吸器では肺気腫や肺線維症などのびまん性疾患や初期の肺結核も指摘可能になり，循環器では心筋梗塞などと関連のある冠動脈の石灰化の指摘や大動脈瘤も容易に指摘が可能になった．肺がん以外の腫瘍性病変としては悪性胸膜中皮腫，各種の縦隔腫瘍や甲状腺，乳腺の腫瘍あるいは撮影範囲の腎腫瘍，副腎腫瘍などが発見できることもある．また撮影部位を腹部まで広げることで，内臓脂肪の蓄積の診断も容易になることや，表示条件の変更で骨粗鬆症の診断も可能になると考えられている．

第二はCTでは各種の疾患の発症前の状態を指摘することが可能になることにより，この画像を示しながら禁煙指導や栄養指導を行うとその達成度が高い点である．喫煙者の大半には気腫状変化や線維化を認めるので，これらを示しての禁煙指導の効果は高いとされている．また内臓脂肪については定量的な評価も可能なので，食事療法や運動療法の効果も視覚的な評価と同時に数量的にも評価が可能になり，生活指導の効果も上昇するとされている．

特に喫煙は肺がんをはじめ多くのがんや循環器疾患の最大の要因であり，喫煙率の低下は本人のみならず，受動喫煙の防止も含めて多くの疾患の予防が可能になり，今後はこれらの効果も含めた総合的な評価も必要と考える．

低線量CT検診普及への課題

CTによる肺がん検診を全国的に普及するにあたり，解決しなくてはならない大きな問題が三つ存在している．

第一は発見された陰影に対する確定診断の問題であり，第二は低侵襲治療の開発であり，第三は検診の精度管理と標準化の問題である．

確定診断に関しては，肺野の病変に対しては一般にはX線透視下での経気管支鏡生検，CTガイドでの経皮針生検，開胸あるいは胸腔鏡による手術的な生検の三種類が行われている．しかしCT発見のような微小陰影を的確に気管支鏡で生検するのは困難な場合が多く，針生検では気胸や胸膜播種，空気塞栓などの合併症も存在し，開胸あるいは胸腔鏡による手術的な生検は100%診断がつくが侵襲も大きい．

CT検診で発見される1 cm前後の微小結節は，図1に示すような3タイプに分けられることが多く，日本CT検診学会ではそれぞれに対して図2のようなガイドラインを出しているが，経過観察例の増加という問題が生じている．的確な確定診断方法が確立しないと不用な経過観察のためのCT撮影が繰り返し行われたり，良性疾患に対する無用な開胸生検が行われたりすることにもなりかねない．

発見肺がんの治療の面からは，微小ながんに対してはできる限り低侵襲の治療が望ましい．消化管の場合には早期がんに対してはほとんど侵襲のない内視鏡的な粘膜切除あるは粘膜下剥離術が行われている．しかし肺がんに関しては肺門部がんにはレーザー治療などもあるが，CTでのみ発見されるような微小肺野末梢部肺がんに関しては，部分切除も行われているが，いずれにしても開胸あるいは胸腔鏡の挿入が必要で，その侵襲はかなり大きいのが現状である．消化管の粘膜切除に匹敵するような低侵襲治療法の開発が必要である．

精度管理と標準化に関しては，現行の肺がん検診の問題点として，全国的な精度管理のシステムがない点と，胸部X線写真の読影に関しての資格制度のない点が挙げられている．低線量CT検診を普及させるにあたっては，X線と喀痰細胞診での検診の轍を踏まないように全国的な精度管理，認定制度を確立することが必要と考えている．日本CT検診学会が中心になり，日本医学放射線学会をはじめとする6学会と連携して「NPO法人CT検診認定制度機構」を立ち上げ，低線量CT肺がん検診の認定医師，認定技師の認定のための講習や試験を行い，認定施設の基準を作成し，今後は認定施設の更新などと関連して全国的な精度管理も行うことを検討している．

現在オプションも含めると，大半の人間ドックでCTが組み込まれているが，撮影条件の統一や，

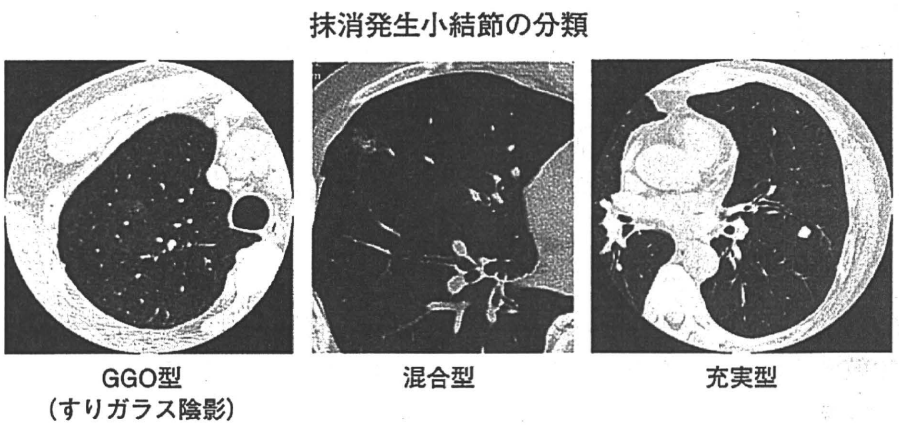

図1　CT検診で発見される小型陰影の分類

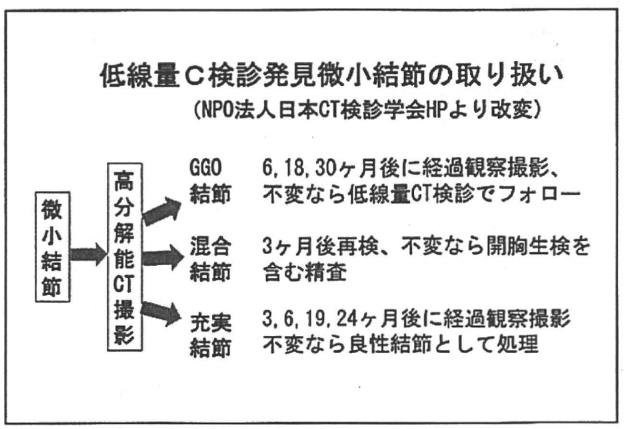

図2　小型陰影の所見による取り扱い基準

全国的なデータの集積には人間ドック学会との連携が不可欠であり，それなしに精度の高い肺がん検診の普及は不可能と考えられる．日本人間ドック学会にも是非CT検診認定機構には加盟していただき，互いに連携して精度の向上と正しい方法の普及をはかる必要があると考えている．

おわりに

胸部X線とハイリスク例に対する喀痰細胞診による肺がん検診は，定められた方式を遵守して行えば一定の効果はあるが，他の臓器のがん検診に比べその成績は不良である．

検診精度を高めるために低線量CTの導入が人間ドックを中心に行われている．死亡率減少効果についてはまだ充分には証明されていないが，発見精度の高さは明らかであり，さらに肺がん以外の各種の疾患の発見も可能で，CT画像を示しての禁煙指導の効果の高いことも示されている．

今後のCT検診の問題としては，発見された微小陰影の取り扱い方法の確立，低侵襲治療方法の開発，検診の精度管理と標準化の問題がある．NPO法人日本CT検診学会が中心になり，NPO法人「肺がんCT検診認定機構」が発足しているので，人間ドック学会とも密接な連携を保ちながら正しい方法の普及をはかる必要があると考えられている．

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Multiple Primary Cancers or Multiple Metastases, That Is the Question

Hisao Asamura, MD

The current therapeutic strategy for patients with lung cancer is based on a combination of the histologic type, tumor, node, metastasis (TNM) stage, and physical status of the patients, and therefore, these are categories for which accurate information must be obtained before the initiation of treatment. In the course of assessment of patients with non-small cell lung cancer, the additional tumor nodules (ATNs) are often found in addition to the main tumor nodule, either in the same lobe or in the contralateral lobe/side. The existence of ATNs crucially influence on the determination of the TNM stage and the treatment (Figure 1). In the revised new TNM classification for lung cancer (UICC-7), which has already been in effect since January 2010, the inclusion of ATN is one of the important revisions.[1] In the event that ATNs are found in the same lobe as the main tumor nodule, the tumor is categorized as T3 (formerly T4). If the ATN is in a different lobe but the same side, it is categorized as T4 (formerly M1). If present on the contralateral side, it is categorized as M1a (formerly M1). The prognostic appropriateness of such categorization needs to be evaluated further; however, these categories are based on the assumption that these ATNs are metastases from the original main lung cancer. There are other possibilities that arise in the course of daily practice.

In fact, when multiple synchronous lung tumors are present, it is quite difficult to differentiate multicentric lung cancers from a single lung cancer with either intrapulmonary metastases or pulmonary metastases from a primary cancer in a different organ. The possibility that the additional nodules are inflammatory granulomas, despite the malignant status of the primary nodule, must be also addressed. There are no specific clinical or radiologic features that can reliably differentiate the multiple primary lung cancers (MPLCs) and intrapulmonary metastases. There have been many attempts to define MPLCs in terms of clinical presentation, histopathology, and more recently, the molecular/genetic profile. In 1975, Martini and Melamed[2] proposed the criteria for the diagnosis of MPLC. It has been defined as occurring when (1) the histologies are different, and (2) the histologies are the same but the following criteria are met: the origin is from a carcinoma in situ, with no lymph node involvement in the common lymphatic pathways, and no extrathoracic metastasis. Because of the easy applicability of these criteria, they have entered standard use by clinicians and pathologists ever since the original publication in mid-1970s.

Subsequently, modified criteria have been proposed with the addition of new factors such as the histologic subtype and molecular/genetic profiles. Antakli et al.[3] modified the original Martini and Melamed criteria by adding premalignant lesions and DNA ploidy. With regard to DNA ploidy, a different ploidy pattern was suggested as an indicator of different tumor cell origin. However, it must be addressed that a different DNA ploidy pattern does not exclude the possibility of the same tumor cell origin, because of the heterogeneity of the DNA ploidy within the same tumor and also the change in the ploidy pattern that comes with tumor progression. In 2007, the American College of Chest Physicians (ACCP guidelines prepared by Shen et al.[4]) presented a new classification in which even for the same histologies, MPLC could be identified if these tumors possessed

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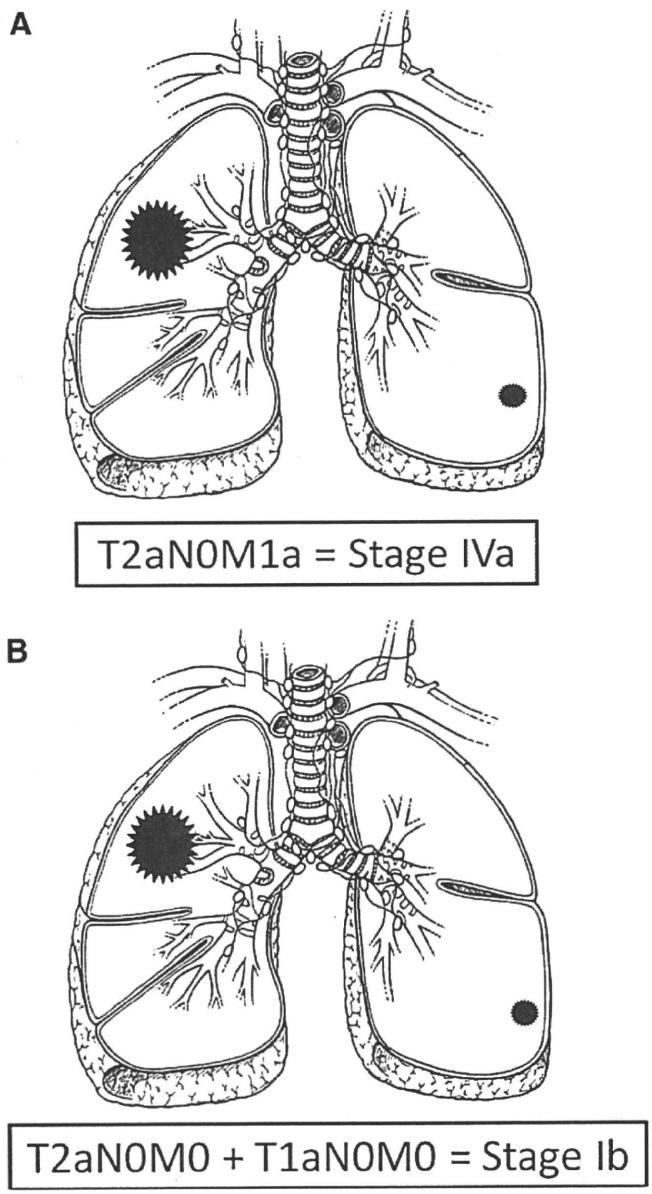

FIGURE 1. Tumor, node, metastasis (TNM) stage based on the UICC-7 of a tumor with additional tumor nodules (ATNs) in the contralateral side (*A*) and multiple primary lung cancers (MPLCs) in both sides of the lung (*B*). In the case of a tumor with ATN in the contralateral side of the lung, the TNM stage is IVa. In case of MPLC, the TNM stage is determined by the highest stage of all lesions (stage Ib).

different molecular/genetic characteristics. In the reported literature, the mutation of p53[5] and epidermal growth factor receptor/KRAS[6] has been used as a marker to demonstrate the clonal relationships among separate tumors. Certain discrepancies between the results obtained by clinicopathological criteria and by genetic/molecular criteria have also been reported.

In a report by Tanvetyanon et al.[7] entitled "Relationship between tumor size and survival among patients with resection of multiple synchronous lung cancers," the authors studied the prognostic impact of the size of the main tumor in patients who had undergone surgical resection for at least two simultaneous MPLCs in two or more lobes. They used both the size of the largest tumor and the sum of the tumor sizes and found tumor size to be an independent predictor of survival by multivariate analysis. They also showed that the size of the largest tumor performs slightly better that the sum of the tumor sizes in survival prediction. The results of this article suggest a means of dealing with patients afflicted with MPLCs based on tumor size. When tumor size determination is made before treatment, it allows for a rough prognosis after the resection, and thus it may impact the treatment of choice.

However, there is still no definitive method of identifying MPLCs before treatment. It is only very recently that the genetic/molecular profiles have begun to be incorporated into the diagnosis of MPLCs. Moreover, even if a method of gene/molecular profiling with a small specimen is established, the issue of tissue sampling from the smaller ATNs remains. Most ATNs are generally less than 1 cm in diameter in the lung parenchyma, and sampling from such multiple tiny locations in the lung is intrinsically difficult, even with sophisticated computed tomography-guided techniques.

In terms of the current outstanding issues facing MPLCs, we need to make progress both in establishing the definitive diagnostic method and a safe, reliable tissue sampling technique from small lung nodules.

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Japanese Lung Cancer Registry Study

First Prospective Enrollment of a Large Number of Surgical and Nonsurgical Cases in 2002

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Purpose: To investigate prognoses of lung cancer patients prospectively enrolled in the Japan Lung Cancer Registry Study.

Methods: Patients newly diagnosed as having lung cancer exclusively in 2002 were enrolled. Follow-up surveys were performed twice, in 2004 and 2009, and the final follow-up data with prognoses were analyzed for 14,695 patients (79%). Clinical stages were defined according to the sixth edition of the International Union Against Cancer-tumor, node, metastasis classification (2002).

Results: The mean age was 67.1 years (range, 18–89 years), and there were 10,194 men (69.3%) and 4315 women (29.7%). The most frequent histology was adenocarcinoma (n = 8325, 56.7%), followed by squamous cell carcinoma (n = 3778, 26%) and small cell carcinoma (n = 1345, 9.2%). The distribution of clinical stages was as follows: IA, 4245 cases (29.3%); IB, 2248 (14.5%); IIA, 208 (1.4%); IIB, 918 (6.3%); IIIA, 1700 (11.8%); IIIB, 2110 (16.3%); and IV, 3037 (21.0%). The 5-year survival rates were 44.3% for all patients, 46.8% for those with non-small cell lung cancer, and 14.7% for those with small cell lung cancer. According to the clinical stage of non-small cell lung cancer and small cell lung cancer, the 5-year survival rates were 79.4 and 52.7% for stage IA, 56.9 and 39.3% for IB, 49.0 and 31.7% for IIA, 42.3 and 29.9% for IIB, 30.9 and 17.2% for IIIA, 16.7 and 12.4% for IIIB, and 5.8 and 3.8% for IV, respectively.

Conclusion: Analysis of a large cohort in the Japanese registry study found that stage-specific prognosis was within a range similar to other reports. The data presented should provide an important reference for future clinical trials in Japan.

Key Words: Lung cancer, Japan, Registry.

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In Japan, nationwide registration of surgically treated lung cancer patients has been conducted three times, in 1994, 1999, and 2004, for cases surgically treated in 1989, 1994, and 1999, respectively. The latter two registrations were conducted by the Japanese Joint Committee for Lung Cancer Registry, which was established in 1998, and their results have been published.[1–2] In 1999, the number of cases registered increased to 7393 from the 3643 registered in 1994,[3,4] whereas those registered in 2004 further increased to 13,340. Currentaly, the Japanese Joint Committee for Lung Cancer Registry is jointly coordinated by three associations, the Japanese Respiratory Society, the Japanese Lung Cancer Society, and the Japanese Association for Chest Surgery.

The three registry studies noted earlier were retrospective surveys of patients who were resected 5 years earlier. Data from the latest study performed in 2004[2] were used by the staging project of the International Association for Study of Lung Cancer (IASLC) and contained 7393 Japanese cases, which represented 9.1% of all cases subjected to analysis. Cases from North America, Europe, and Australia consisted of a greater percentage of nonsurgical cases with more advanced stages compared with the cases from the Japanese Joint Committee for Lung Cancer Registry, which were mainly surgical cases and earlier stages. The efforts of the IASLC staging committee have resulted in a number of published studies, including one in 2007,[5] all of which led to the proposal of tumor, node, metastasis (TNM) staging in the seventh edition of the International Union Against Cancer (UICC).[6,7] Results of more detailed analyses of the data obtained in the 2004 survey conducted by the Japanese Joint Committee for Lung Cancer Registry have also been published.[8,9] However, because those studies were retrospective and consisted of only surgically treated patients, they were biased toward earlier stage and non-small cell lung cancer (NSCLC) cases. As a result, prospective enrollment including

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nonsurgical cases representing a large, nonbiased number of lung cancer patients was considered necessary.

Herein, the Japanese Joint Committee for Lung Cancer Registry reports the demographics and survival of 14,695 Japanese patients with lung cancer who were diagnosed and prospectively enrolled in 2002.

PATIENTS AND METHODS

The Japanese Joint Committee for Lung Cancer Registry conducted a prospective observational study of patients who were first diagnosed as having primary lung cancer exclusively in 2002. The committee asked 570 teaching hospitals in Japan to participate in the study; 358 (63%) participated in the program. Inclusion criteria were as follows: (1) pathologically (including cytology) diagnosed as any lung cancer at an institute; (2) exclusively in 2002; and (3) regardless of treatment modality (including supportive care alone). Patients with lung cancer recurrence, metastasis, or double cancer were excluded. Nine variables were recorded at the time of registration in 2002: (1) sex, (2) age, (3) date of diagnosis, (4) performance status (PS), (5) clinical stage, (6) clinical T factor, (7) clinical N factor, (8) clinical M factor, and (9) histologic subtype of lung cancer. Two years later in 2004, treatment modalities and prognoses were reported for these cases. In 2009, the following 20 points were investigated for all surgical cases: (1) type of operation, (2) extent of lymph node resection, (3) radicality of resection, (4) residual tumor, (5) location of tumor, (6) tumor size, (7) tumor histology, (8) invaded organ, (9) pleural invasion, (10) pleural dissemination, (11) pulmonary metastasis, (12) cytology of pleural effusion, (13) pathologic stage, (14) pathologic T factor, (15) pathologic N factor, (16) pathologic M factor, (17) lymph node metastasis, (18) survival period, (19) presence or absence of recurrence, and (20) cause of death. For cases that did not undergo surgery, survival period, recurrence, and cause of death were reported. All patients were staged clinically according to the sixth version of the UICC-TNM classification.[10] Because the

TABLE 1. Patients' Background Characteristics

	Total	Surgery	No Surgery	Missing Data
n	14,695	8454 (57.5%)	5735 (39.0%)	506 (3.5%)
Gender				
Male	10,194	5457	4349	388
Female	4315	2878	1322	115
Missing value	186 (1.3%)	119	64	3
Age (yr), mean±SD	67.1 ± 10.1	66.4 ± 9.9	68.2 ± 10.4	
PS				
0	8714	6827	1717	170
1	4076	1364	2460	252
2	1077	192	837	48
3	516	40	453	23
4	240	3	226	11
Missing value	72 (0.5%)	28	42	2
Treatment				
Pre-OP CTx[a]		395		
Pre-OP RTx[a]		180		
Post-OP CTx[a]		1749		
Post-OP RTx[a]		624		
CTx			2575	
RTx			684	
CTx + RTx			1300	
SC			1162	
Missing value			14 (0.2%)	

[a] Redundancy permitted.

SD, standard deviation; PS, performance status; OP, operation; CTx, chemotherapy; RTx, radiotherapy; SC, supportive care.

TABLE 2. Tumor Characteristics

	Total	Surgery	No Surgery	Missing Data
n	14,695	8454 (57.5%)	5735 (39.0%)	506 (3.5%)
c-Stage				
0	38	28	9	1
IA	4245	4029	174	42
IB	2248	2009	206	33
IIA	208	152	51	5
IIB	918	709	184	25
IIIA	1700	919	707	74
IIIB	2110	357	1621	132
IV	3037	169	2687	181
Occult	5	0	4	1
Missing value	186 (1.3%)	82	92	12
cT				
0	47	25	18	4
1	5135	4422	629	84
2	4985	3045	1783	157
3	1286	578	668	40
4	3154	360	2578	216
Tis	12	6	6	0
Tx	43	7	32	4
Missing value	33 (0.2%)	11	21	1
cN				
0	7925	6647	1134	144
1	1332	751	536	45
2	3491	959	2333	199
3	1908	87	1704	117
Missing value	39 (0.3%)	10	28	1
cM				
0	11,536	8247	2971	318
1	3099	188	2725	186
Missing value	60 (0.4%)	19	39	2
Histology				
SM	1345	165	1104	76
AD	8325	5463	2643	219
SQ	3778	2151	1506	121
ADSQ	116	76	38	2
LA	439	211	186	42
Other	485	222	256	7
Missing value	207 (1.4%)	166	2	39

c-Stage, clinical stage; cT, clinical T factor; Tis, carcinoma in situ; Tx, primary carcinoma cannot be assessed; cN, clinical N factor; cM, clinical M factor; SM, small cell carcinoma; AD, adenocarcinoma; SQ, squamous cell carcinoma; ADSQ, adenosquamous cell carcinoma; LA, large cell carcinoma.

TABLE 3. Patients' Characteristics by Histology

	Non-small Cell Carcinoma					Small Cell Carcinoma
	AD	SQ	ADSQ	LA	Total	
n	8325	3778	116	439	12,658	1345
Gender						
Male	4742	3334	82	372	8530	1122
Female	3469	400	32	61	3962	209
Missing value	114	44	2	6	166	14
Age (yr), mean ± SD	65.7 ± 10.6	69.6 ± 8.6	67.8 ± 10.2	65.3 ± 10.7	67.0 ± 10.1	68.7 ± 9.2
PS						
0	5556	2024	68	223	7871	471
1	1925	1222	37	149	3333	549
2	447	332	8	33	820	170
3	215	132	3	24	374	109
4	114	60	0	9	183	36
Missing value	68	8	0	1	77	10
c-Stage						
IA	3239	686	29	57	4011	96
IB	1301	712	30	52	2095	57
IIA	85	88	1	3	177	20
IIB	355	434	9	40	838	40
IIIA	684	670	11	72	1437	221
IIIB	901	656	18	92	1667	356
IV	1685	523	18	118	2344	533
Missing value	75	9	0	5	89	22
Treatment						
Surgery	5463	2151	76	211	7901	165
No surgery	2643	1506	38	186	4373	1088
CTx	1275	514	18	72	1879	607
RTx	262	309	2	24	597	37
CTx + RTx	472	372	11	42	897	359
SC	634	311	7	48	1000	85
Missing value	219	121	2	42	384	92

c-Stage, clinical stage; AD, adenocarcinoma; SQ, squamous cell carcinoma; ADSQ, adenosquamous cell carcinoma; LA, large cell carcinoma; SD, standard deviation; PS, performance status; CTx, chemotherapy; RTx, radiotherapy; SC, supportive care.

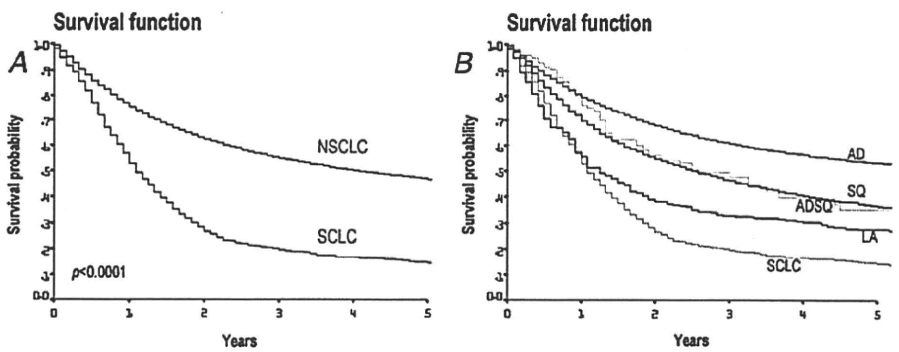

FIGURE 1. *A* and *B*, Survival curves by histology. The 5-year survival rates for NSCLC and SCLC are 46.8% and 14.7%, respectively. The 5-year survival rates and *p* values are shown in Table 4. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; AD, adenocarcinoma; SQ, squamous cell carcinoma; ADSQ, adenosquamous cell carcinoma; LA, large cell carcinoma.

registry included nonsurgical patients, analyses in this report were carried out using clinical stage.

This registry was approved by the Institutional Review Boards of Kyorin Medical University Hospital (former registration office) and Osaka University Graduate School of Medicine (current registration office).

In 2002, 18,552 cases of primary lung cancer were registered from 358 institutions, with treatment modalities and survival recorded in the survey conducted in 2004. Additional survival data were available for 10,183 of these cases (55%) from the survey conducted in 2009. As a result, survival was analyzed for a total of 14,695 cases (79%), for which survival data were available.

TABLE 4. Survival by Histology

	Histology				
	AD	SQ	ADSQ	LA	SM
n (%)	8325 (64.1)	3778 (29.1)	116 (0.9)	439 (3.4)	1345 (10.4)
5-Year survival rate (%)	53.2	36.5	35.5	27.7	14.7
p					
AD		<0.0001	<0.0001	0.001	<0.0001
SQ			<0.0001	0.8	<0.0001
ADSQ				0.003	0.0001
LA					<0.0001

AD, adenocarcinoma; SQ, squamous cell carcinoma; ADSQ, adenosquamous cell carcinoma; LA, large cell carcinoma; SM, small cell carcinoma.

The survival period was defined as the time between the dates of diagnosis and latest follow-up. Survival curves were estimated according to the Kaplan-Meier method for subsets such as clinical stage, sex, histologic subtype of tumor, treatment modality, and PS. Differences between survival rates were evaluated using the log-rank method. Multivariate analyses were performed with a Cox proportional hazards model to identify patient characteristics. Clinical stage, sex, histologic subtype, treatment modality, and PS were entered as variables. The pathologic stages of surgical patients were revealed at the survey in 2009, and survival analyses by pathologic stage were carried out exclusively in surgical patients. Because the rate of missing data was less than 3.5%, statistical analyses were performed after excluding cases with missing values for relevant variables. A p value of less than 0.05 was considered statistically significant.

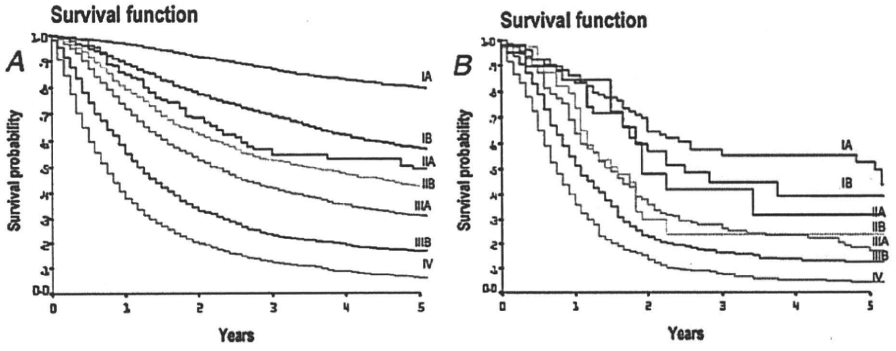

FIGURE 2. Clinical stage-specific survival curves for patients with (*A*) non-small cell carcinoma and (*B*) small cell carcinoma, by clinical stage. The 5-year survival rates and *p* values are shown in Table 5.

TABLE 5. Clinical Stage-Specific Survival

		c-Stage						
Histology	Total	IA	IB	IIA	IIB	IIIA	IIIB	IV
Non-small cell carcinoma								
n (%)	12,993 (100)[a]	4020 (31)	2133 (16.4)	184 (1.4)	860 (6.6)	1441 (11.1)	1714 (13.2)	2447 (18.8)
5-Year survival rate (%)	46.8	79.4	56.9	49	42.3	30.9	16.7	5.8
p								
IA			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
IB				0.003	<0.0001	<0.0001	<0.0001	<0.0001
IIA					0.2	<0.0001	<0.0001	<0.0001
IIB						<0.0001	<0.0001	<0.0001
IIIA							<0.0001	<0.0001
IIIB								<0.0001
Small cell carcinoma								
n (%)	1323 (100)[b]	96 (7.3)	57 (4.3)	20 (1.5)	40 (3)	221 (16.7)	356 (26.9)	533 (40.3)
5-Year survival rate (%)	14.7	52.7	39.3	31.7	29.9	17.2	12.4	3.8
p								
IA			0.4	0.3	0.004	<0.0001	<0.0001	<0.0001
IB				0.8	0.2	0.004	<0.0001	<0.0001
IIA					0.1	0.1	0.006	<0.0001
IIB						<0.0001	<0.0001	<0.0001
IIIA							0.0006	<0.0001
IIIB								<0.0001

[a] Includes histology type other than adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma, and large cell carcinoma.
[b] Excludes missing data.

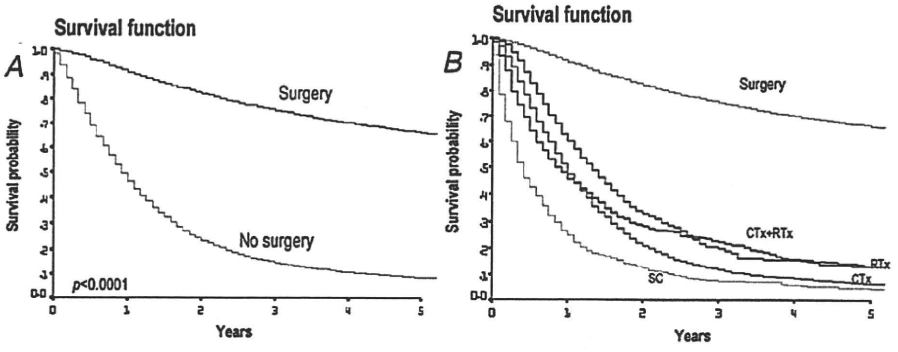

FIGURE 3. *A* and *B*, Survival curves by treatment. The 5-year survival rates for surgical and nonsurgical cases are 66.0% and 8.5%, respectively. The 5-year survival rates and *p* values are shown in Table 6. CTx, chemotherapy; RTx, radiotherapy; SC, supportive care including chest drainage and pleurodesis.

TABLE 6. Survival by Treatment

	Treatment				
		No Surgery			
	Surgery	CTx	RTx	CTx + RTx	SC
n (%)	8454 (57.4)	2575 (17.6)	684 (4.7)	1300 (8.9)	1162 (7.9)
5-Year survival rate (%)	66	6.5	13.3	13.3	4.3
p					
Surgery		<0.0001	<0.0001	<0.0001	<0.0001
CTx			0.1	<0.0001	<0.0001
RTx				<0.0001	<0.0001
CTx + RTx					<0.0001

CTx, chemotherapy; RTx, radiotherapy; SC, supportive care.

RESULTS

The characteristics of the 14,695 patients are shown in Table 1. Because the form used in 2004 (2 years after the first registration) required the dichotomous choice of surgery or no surgery, the backgrounds of patients both with and without surgery are also shown. The mean age was 67.1 years (range, 18–98 years), and there were 10,194 men (70.3%) and 4315 women (29.7%). The majority (87%) of patients had a good PS score (0 or 1).

Tumor characteristics are shown in Table 2. The most frequent clinical stage was IA (29.3%) followed by IV (21.0%), IB (14.5%), IIIB (16.3%), IIIA (11.8%), IIB (6.3%), and IIA (1.4%). Of the patients undergoing surgery, 85% were staged as clinical I or II. In addition, 34% of the surgical cases received adjuvant therapy. In contrast, of the nonsurgical patients, 40% were staged as clinical III, and 47% were staged as clinical IV.

As for histologic type, adenocarcinoma was the most common (56.7%), followed by squamous cell carcinoma (25.7%) and small cell carcinoma (9.2%). Characteristics by histologic type are shown in Table 3. Sex distribution was significantly different for adenocarcinoma and squamous cell carcinoma. Overall, 83% of women and 47.6% of men had adenocarcinomas, which was in contrast to squamous cell carcinomas, which were noted in 33.5% of men and only 10.0% of women.

The 5-year survival rate (5YSR) for the entire group of patients was 44.3%. For women, the survival rates at 1, 2, 3, 4, and 5 years are 82.8, 77.3, 66.2, 62.0, and 59.0%, respectively, whereas survival rates for men are 69.2, 53.6, 45.5, 40.9, and 37.7%, respectively, which shows that women had superior survival. Survival curves by major histologic type are shown in Figure 1, and 5YSRs are shown in Table 4. The 5YSR was 14.7% for small cell carcinoma and 46.8% for non-small cell carcinoma. Patients with adenocarcinoma had a 5YSR of 53.2%, which was markedly better than that for those with squamous cell carcinoma (36.5%) or adenosquamous carcinoma (35.5%). Small cell carcinoma cases had very poor survival (14.7%).

According to the clinical stages of NSCLC and small cell lung cancer (SCLC; Figure 2 and Table 5), the 5YSRs were 79.4 and 52.7% for stage IA, 56.9 and 39.3% for IB, 49.0 and 31.7% for IIA, 42.3 and 29.9% for IIB, 30.9 and 17.2% for IIIA, 16.7and 12.4% for IIIB, and 5.8 and 3.8% for IV, respectively. Survival by treatment modality is shown in Figure 3 and Table 6. The 5YSRs were 66.0and 8.5% for surgical and nonsurgical cases, respectively. In the nonsurgical cases, chemotherapy plus radiation therapy provided the best survival, whereas those who received only supportive care (including chest drainage and pleurodesis) had the worst survival. Survival by PS is shown in Table 7; those with poor PS had a poor prognosis.

Results of multivariate analyses are shown for NSCLC in Table 8 and for SCLC in Table 9. Clinical stage, sex, histologic subtype, treatment modality, and PS were entered as variables. Analysis of NSCLC showed that clinical stage, sex, histology, treatment, and PS were all independent significant prognostic factors. In contrast, in the analysis of SCLC, advanced clinical stage (III or IV), sex, chemotherapy alone or radiotherapy alone, and PS were independent prognostic factors.

Survivals for surgical cases by pathologic stage are shown in Table 10 and Figure 4. The 5YSR for pathologic stage IA was 89.3%. In advanced pathologic stages, the 5YSRs were 46.8% for pathologic stage IIIA, 53.0% for IIIB, and 41.0% for IV.

TABLE 7. Survival by Performance Status

	Performance Status				
	0	1	2	3	4
n (%)	8714 (59.6)	4076 (27.9)	1077 (7.4)	516 (3.5)	240 (1.6)
5-Year survival rate (%)	59.3	24	13.7	5.6	3.1
p					
0		<0.0000	<0.0000	<0.0000	<0.0000
1			<0.0000	<0.0000	<0.0000
2				<0.0000	<0.0000
3					<0.0000

TABLE 8. Multivariate Analysis of Non-small Cell Lung Cancer

Variable	Relative Risk	95% CI	*p*
c-Stage			
IA	Reference		
IB	2.196	1.978–2.437	<0.0001
IIA	2.412	1.899–3.063	<0.0001
IIB	2.966	2.612–3.369	<0.0001
IIIA	3.475	3.112–3.880	<0.0001
IIIB	3.736	3.326–4.195	<0.0001
IV	5.179	4.615–5.813	<0.0001
Gender			
Female	Reference		
Male	1.504	1.408–1.607	<0.0001
Histology			
AD	Reference		
SQ	1.168	1.097–1.242	<0.0001
LA	1.478	1.295–1.686	<0.0001
ADSQ	1.407	1.087–1.821	0.01
Treatment			
Surgery	Reference		
No surgery			
CTx	2.566	2.331–2.825	<0.0001
RTx	2.516	2.224–2.847	<0.0001
CTx + RTx	1.964	1.763–2.187	<0.0001
SC	4.69	4.193–5.246	<0.0001
PS			
0	Reference		
1	1.362	1.275–1.455	<0.0001
2	1.953	1.768–2.158	<0.0001
3	2.795	2.441–3.201	<0.0001
4	3.765	3.126–4.534	<0.0001

AD, adenocarcinoma; SQ, squamous cell carcinoma; ADSQ, adenosquamous cell carcinoma; LA, large cell carcinoma; c-Stage, clinical stage; CTx, chemotherapy; RTx, radiotherapy; SC, supportive care; PS, performance status.

TABLE 9. Multivariate Analysis of Small Cell Lung Cancer

Variable	Relative Risk	95% CI	*p*
c-Stage			
IA	Reference		
IB	1.082	0.644–1.817	0.8
IIA	1.324	0.641–2.737	0.5
IIB	1.649	0.977–2.785	0.06
IIIA	1.807	1.204–2.713	0.004
IIIB	2.285	1.514–3.448	<0.0001
IV	2.791	1.859–4.190	<0.0001
Gender			
Female	Reference		
Male	1.321	1.094–1.595	0.004
Treatment			
Surgery	Reference		
No surgery			
CTx	2.481	2.267–2.714	0.005
RTx	2.530	2.248–2.847	<0.0001
CTx + RTx	1.824	1.654–2.013	0.6
SC	4.828	4.345–5.365	<0.0001
PS			
0	Reference		
1	1.217	1.034–1.432	0.020
2	1.551	1.236–1.947	<0.0001
3	3.270	2.530–4.226	<0.0001
4	2.143	1.423–3.228	<0.0001

c-Stage, clinical stage; CTx, chemotherapy; RTx, radiotherapy; SC, supportive care; PS, performance status.

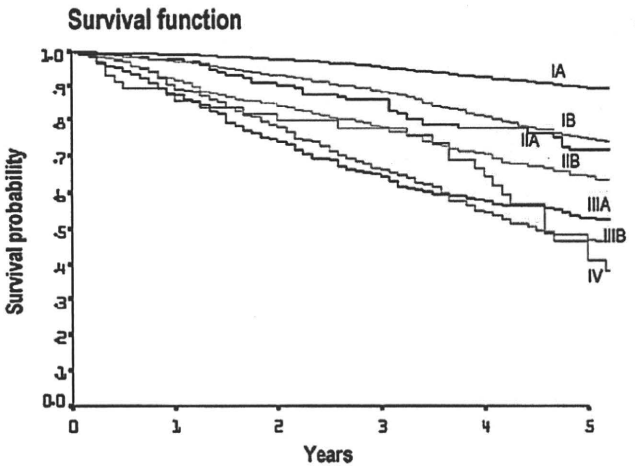

FIGURE 4. Stage-specific survival curves for surgical cases by pathologic stage. The 5-year survival rates and *p* values are shown in Table 10.

DISCUSSION

A large cohort of Japanese patients with lung cancer who were registered in 2002 and followed up was analyzed. This population differs from the cohorts of former Japanese registries; former Japanese registries included cohorts of only surgical cases. This registry included nonbiased patients who underwent surgery, chemotherapy, radiotherapy, a combina-

TABLE 10. Survival by Pathologic Stage

		p-Stage						
Stage Version	Total	IA	IB	IIA	IIB	IIIA	IIIB	IV
UICC-TNM (1997)								
n (%)	4170 (100)	1926 (46.2)	962 (23.1)	132 (3.2)	370 (8.9)	444 (10.6)	277 (6.6)	59 (1.4)
5-Year survival rate (%)		89.3	74.5	71.4	64.3	46.8	53.0	41.0
p								
IA			<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
IB				0.7	<0.0001	<0.0001	<0.0001	<0.0001
IIA					0.03	<0.0001	0.0002	0.0002
IIB						<0.0001	0.01	0.02
IIIA							0.1	0.9
IIIB								0.5

p-Stage, pathologic stage; UICC, International Union Against Cancer; TNM, tumor, node, metastasis.

tion of these modalities, or supportive care. This is the first prospective registry in Japan, and the results present a selection of the patterns of practice and outcomes at a fraction of the teaching hospitals in the country.

For survival analysis, 14,695 cases, including 8454 surgical and 5735 nonsurgical cases, were analyzed using survival data obtained in 2004 and updated in the 2009 survey. The rate of missing data was at most 3.5%, lower than the rate of missing data in the staging project of the IASLC 2009; the rate of incomplete stage information was 8.0%[11] in the IASLC project.

Patients who underwent surgery had quite a different background from those who were treated without surgery, because (1) the mean age of surgical cases was 2 years younger than that of nonsurgical cases, (2) the dominant majority of PS scores was 0 or 1 in surgical cases, whereas 30% of the nonsurgical cases were at PS 2 or more, (3) clinical stage was I or II in 80% of the surgical cases and in only about 10% of the nonsurgical cases, and (4) small cell carcinoma represented 2% of the surgical and 19% of the nonsurgical cases.

Based on the UICC-TNM sixth edition classification (2002),[10] each clinical stage of NSCLC had a significantly different rate of survival from its neighboring stage, except for clinical stages IIA and IIB. The same finding was reported in a previous Japanese registry of surgical patients.[1]

In pathologic stages using variable data based on the 2009 survey, the 5YSRs for pathologic stages IIIA, IIIB, and IV were 46.8, 53.0, and 41.0%, respectively. These rates were much higher than expected, which might be attributed to the high rate (60%) of clinical nonadvanced stages (clinical stage I, 46%; and clinical stage II, 24%) among patients whose pathologic stages were defined. It has been reported that among cases with pathologic advanced stages, those who were diagnosed as a nonadvanced clinical stage showed a better prognosis than those who were diagnosed as an advanced clinical stage.[12]

Although this registration program was conducted in a prospective setting in an accrual manner, the follow-up findings were retrospective; thus, 21% of the patients were lost to follow-up in 2004 and 45% in 2009. Therefore, the accuracy of the prognoses may be limited in ths current analyses. Because a large number of patients treated with both surgical and nonsurgical modalities was prospectively accrued, the data presented here should provide an important reference for future clinical trials in Japan.

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Survival Differences by Gender for Resected Non-small Cell Lung Cancer

A Retrospective Analysis of 12,509 Cases in a Japanese Lung Cancer Registry Study

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Introduction: Women with non-small cell lung cancer (NSCLC) are more likely to have better survival than men. This study intended to assess gender differences in the survival of these patients in a large registry population.

Methods: In 2005, the Japanese Joint Committee for Lung Cancer Registration performed a nationwide retrospective registry study regarding the prognosis and clinicopathologic profiles of patients who underwent resection for primary lung neoplasms in 1999. The registry data of 12,509 patients with NSCLC were analyzed in terms of gender differences in prognosis and clinicopathologic features.

Results: There were 8353 (66.8%) men and 4156 (33.2%) women with a mean age at operation of 66.4 and 65.0 years, respectively ($p < 0.001$). Women had a higher incidence of adenocarcinoma ($p < 0.001$) and stage IA disease ($p < 0.001$) than men. The overall survival was significantly better in women than men. The 5-year survival rates (5-YSRs) for women and men were 75.6 and 57.9%, respectively ($p = 0.0000$). According to histology, the overall survival of women was significantly better than that of men for both adenocarcinoma (5-YSR, 77.7 versus 61.9%, $p = 0.0000$) and nonadenocarcinoma (5-YSR, 59.3 versus 53.1%, $p = 0.035$). In adenocarcinoma, women had a significantly better prognosis than men for pathologic stage I/II disease. However, in nonadenocarcinoma, there was no significant prognostic difference between the two genders in pathologic stage I/II disease.

Conclusions: Women with NSCLC, especially with an adenocarcinoma histology, had better survival than men. Women were more likely to have adenocarcinoma and stage IA disease, which might account for the better prognosis in women.

Key Words: Gender, Non-small cell lung cancer, Prognosis, Cancer registry.

(*J Thorac Oncol.* 2010;5: 1594–1601)

Previous studies have reported that lung cancer may represent a somewhat different disease in men and women, and some gender-specific differences have been suggested.[1–6] Gender differences in the distribution of histologic types, stage at presentation, and survival rates have been discussed. Women with lung cancer are more likely to have adenocarcinoma histologically and a better prognosis than men.[2–4,7–13]

Several important prognostic factors have been identified, such as tumor, node, metastasis stage; performance status; gender; age; and histology.[14–16] Among these, the female gender has been repeatedly mentioned as one of the most important factors in both early and advanced lung cancers. Although it has been speculated that women show better survival, the relationship between gender and prognosis has not been clearly demonstrated in a large cohort.

In Japan, the task force committee of the Japanese Joint Committee for Lung Cancer Registration has periodically performed nationwide registry studies on the prognosis and clinicopathologic profiles of lung neoplasms.[14,17] The studies are planned at 5-year intervals to observe changes and trends in clinicopathologic features, such as the prognosis, staging, and histologic distribution, of resected lung cancer patients in Japan. Recently, the committee reported a retrospective registry study that focused on 13,010 cases of lung cancer resected in 1999 after a 5-year follow-up period.[14] This study deals with the retrospective registry for patients with lung cancer resected in 1999.

The aim of this study was to evaluate the characteristics of non-small cell lung cancer (NSCLC) by gender with regard

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Disclosure: The authors declare no conflicts of interest.

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to clinicopathologic features and the relationship between gender and prognosis.

PATIENTS AND METHODS

Registry

In 2005, the Japanese Joint Committee for Lung Cancer Registration performed a nationwide retrospective registry study on the prognosis and clinicopathologic profiles of resected lung neoplasms in Japan. Only primary lung neoplasms that had been resected in 1999 at certified teaching hospitals in Japan were considered for the registry, which gave a follow-up period of at least 5 years. The committee received the registries of 13,344 patients from 387 teaching hospitals. The following 32 items were included in the questionnaire: gender, age, smoking status, clinical (c-) T, c-N, c-M, c-stage, preoperative treatment, surgical procedure, extent of lymph node dissection, curability, residual tumor, primary site by lobe, tumor diameter, histology, organ invasion, pathologic (p-) T, p-N, p-M, p-stage, pleural dissemination, intrapulmonary metastasis, pleural cytology, location of nodal metastasis, survival time, recurrence, and cause of death. Recurrent or multiple lung cancers were not included in this registry. Smoking status was recorded as to whether a patient was a smoker within 1 month before the operation. Operative mortality was defined as fatality from any cause within 30 days of the operation or during the same hospitalization. All patients were staged on the basis of the sixth edition of the International Union Against Cancer tumor, node, metastasis classification of the malignant tumor staging system published in 2002,[18] and tumor histology was described according to the World Health Organization classification.[19]

Patients

Sixty-nine patients (0.5%) with incomplete descriptions of their tumor histology and 655 patients (5.0%) with low-grade malignant tumor, nonepithelial tumor histology, or histology of small cell carcinoma were excluded from the study. In addition, 111 patients (0.8%) for whom gender was not given were also excluded from this study. Therefore, this study focused on the remaining 12,509 patients with non-small cell histology (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and adenosquamous carcinoma).

Statistical Analysis

The χ^2 and Student's t tests were used to evaluate the differences in categorical variables and continuous variables, respectively. The survival time was defined as the time between the date of surgery and the last follow-up date. The survival curves were estimated by the Kaplan-Meier method, and differences in survival were assessed by the log-rank test. Overall survival (OS) was defined as the time between operation and death from any cause, except for cases of a death within 30 days of the operation and during the same hospitalization. Disease-specific survival (DSS) was defined as the time between operation and cancer-related death, where deaths from causes other than lung cancer were considered censored. Multivariate analysis by Cox's proportional hazards ratio model was used to test the significance of prognostic factors including gender, age, smoking status (current smoker versus non-/ex-smoker), surgical procedure, histology, curability, tumor size, p-T status, and p-N status. Significance was defined as a p value less than 0.05.

RESULTS

Clinicopathologic Features

There were 8353 (66.8%) men and 4156 (33.2%) women. The clinicopathologic characteristics of the genders are summarized in Table 1. There were 107 (0.9%), 29 (0.2%), 134 (1.1%), and 181 (1.4%) patients who were missing data regarding operative mode, lymph node dissection, surgical curability, and pathologic stage, respectively. These percentages were within an acceptable range as a registry database.

The mean age at surgical resection for women (65.0 years) was significantly younger than that for men (66.4 years). With regard to smoking status according to histology, the proportion of current smoker was 17.3% for men and 2.4% for women in adenocarcinoma histology ($p < 0.001$). In

TABLE 1. Characteristics of Patients with Resected Non-small Cell Lung Cancer

Characteristics	Men (n = 8353)	Women (n = 4156)	p
Age (yr)			
Mean	66.4 ± 9.4	65.0 ± 10.1	<0.001
Smoking status			
Current smoker	1598 (19.2%)	145 (3.5%)	<0.001
Nonsmoker/ex-smoker	6746 (80.8%)	3985 (96.5%)	
Operative mode			
Pneumonectomy	560 (6.7%)	98 (2.4%)	<0.001
Lobectomy	6750 (81.5%)	3500 (84.6%)	0.226
Segmentectomy/wedge	975 (11.8%)	537 (13.0%)	0.097
Lymph node dissection			
Mediastinohilar	6375 (76.5%)	3101 (74.7%)	0.410
Hilar only/none	1907 (22.9%)	1023 (24.7%)	0.086
Unknown	48 (0.6)	26 (0.6)	0.732
Surgical curability			
Complete	7423 (89.9%)	3734 (90.7%)	0.736
Incomplete	735 (8.9%)	320 (7.8%)	0.052
Unknown	101 (1.2%)	62 (1.5%)	0.199
Operative mortality	222 (2.7%)	31 (0.7%)	<0.001
Histology			
Adenocarcinoma	4498 (53.9%)	3670 (88.3%)	<0.001
Squamous cell carcinoma	3305 (39.6%)	359 (8.6%)	<0.001
Large cell carcinoma	403 (4.8%)	69 (1.7%)	<0.001
Adenosquamous cell carcinoma	145 (1.7%)	58 (1.4%)	0.162
Pathologic stage			
IA	2627 (31.9%)	2105 (51.4%)	<0.001
IB	1912 (23.2%)	694 (16.9%)	<0.001
IIA	255 (3.1%)	105 (2.6%)	0.106
IIB	1074 (13.1%)	242 (5.9%)	<0.001
IIIA	1349 (16.4%)	498 (12.1%)	<0.001
IIIB/IV	1014 (12.3%)	453 (11.1%)	0.070

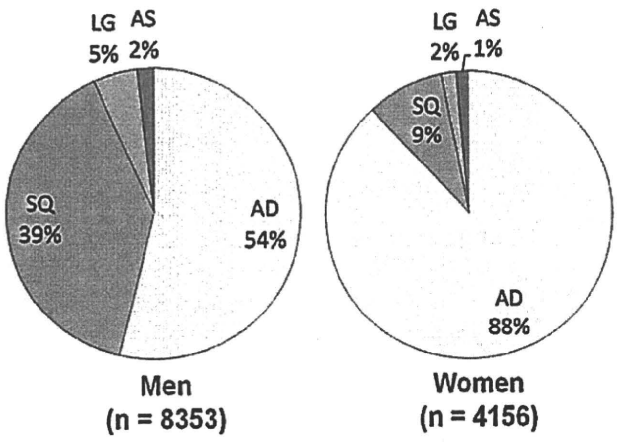
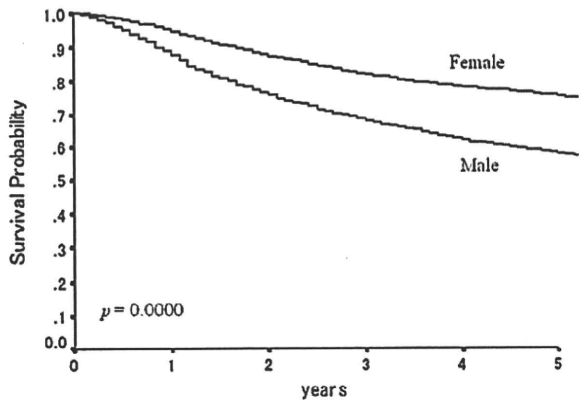
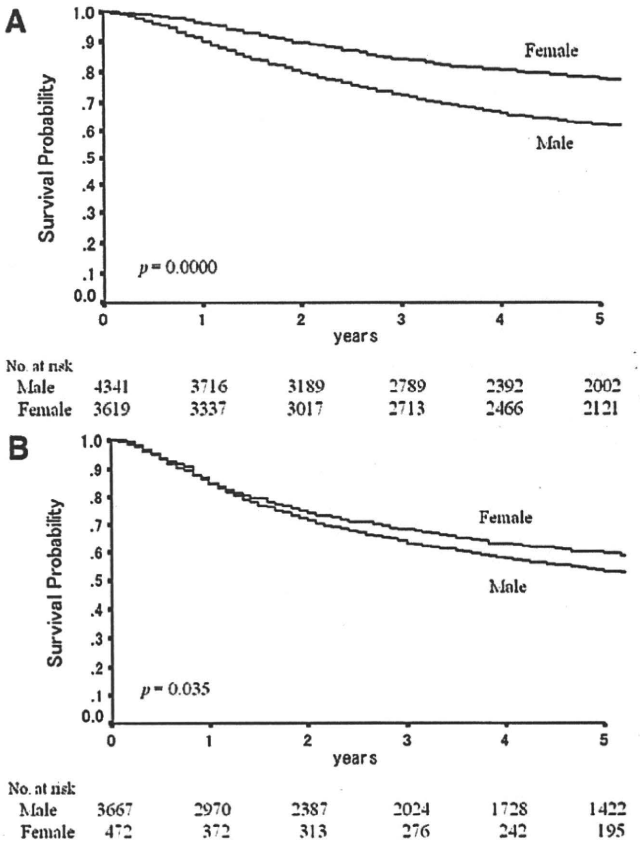


FIGURE 1. Distribution of histologic types between men and women. AD, adenocarcinoma; SQ, squamous cell carcinoma; LG, large cell carcinoma; AS, adenosquamous cell carcinoma.



No. at risk						
Male	8008	6686	5576	4813	4120	3424
Female	4091	3709	3330	2988	2708	2316

FIGURE 2. Overall survival curves based on gender. The 5-year survival rates of female (n = 4091) and male (n = 8008) patients are 75.6 and 57.9%, respectively. The difference in survival between the genders is significant (p = 0.0000).



No. at risk						
Male	4341	3716	3189	2789	2392	2002
Female	3619	3337	3017	2713	2466	2121

No. at risk						
Male	3667	2970	2387	2024	1728	1422
Female	472	372	313	276	242	195

FIGURE 3. Overall survival curves according to gender in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for adenocarcinoma is 61.9% for male patients and 77.7% for female patients. The difference in survival is significant (p = 0.0000). The 5-year survival rate for nonadenocarcinoma is 53.1% for male patients and 59.3% for female patients. The difference in survival is significant (p = 0.035).

nonadenocarcinoma histology, the proportion of current smoker was 21.3% for men and 12.1% for women ($p < 0.001$). In addition, the proportion of current smoker in women also showed significant difference between histologic types (adenocarcinoma versus nonadenocarcinoma) ($p < 0.001$), and the difference between histologic types was also significant in men ($p < 0.001$). Deaths within 30 days of the operation, which were included in operative mortality, were 97 patients (1.2%) for men and 22 (0.5%) for women ($P < 0.001$). Although adenocarcinoma was the most common histologic type in both genders, the distribution of histologic types was significantly different between the genders. The distribution according to histologic type in men and women is shown in Figure 1. Women had significantly more adenocarcinoma ($p < 0.001$) and less squamous cell carcinoma ($p < 0.001$) than men. As for the pathologic stage, women had a significantly higher incidence of stage IA disease than men ($p < 0.001$).

Survival by Gender

The overall 5-year survival rates (5-YSRs) for men and women were 57.9 and 75.6%, respectively. The survival curves are shown in Figure 2. Women had significantly better survival than men (p = 0.0000). According to the histologic type, women had significantly better overall survival (OS) than men with adenocarcinoma (5-YSR, 77.7 versus 61.9%, p = 0.0000). In nonadenocarcinoma, women again had significantly better OS than men (5-YSR, 59.3 versus 53.1%, p = 0.035) (Figure 3). The prognosis between women and men was further studied with regard to histologic type and pathologic stage. In patients with adenocarcinoma histology and pathologic stage I/II disease, women had significantly better OS than men (Figures 4*A* and 5*A*). In contrast, there was no significant OS difference between the genders among

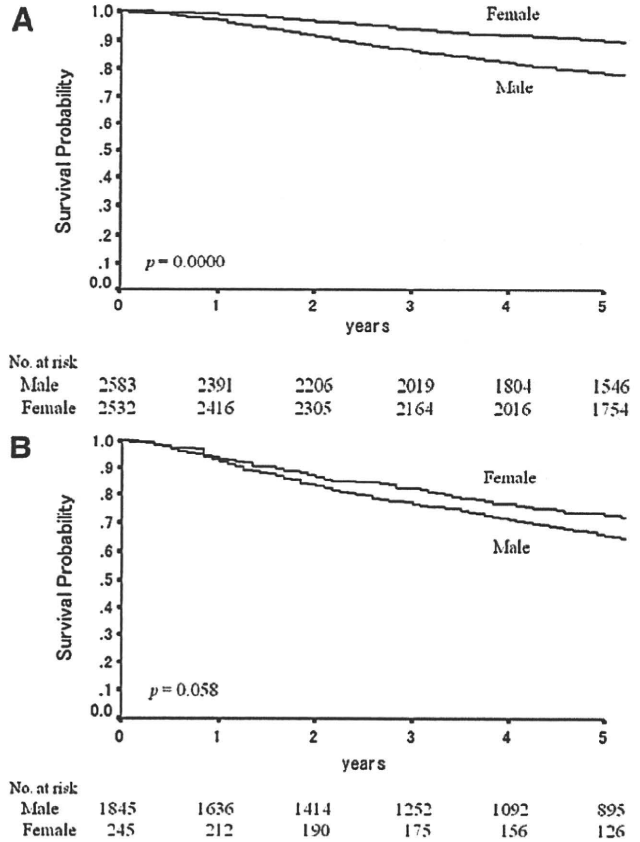


FIGURE 4. Overall survival curves according to gender of pathologic stage I in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage I in adenocarcinoma is 78.6% for male patients and 90.0% for female patients ($p = 0.0000$). The 5-year survival rate for pathologic stage I in nonadenocarcinoma is 65.4% for male patients and 72.8% for female patients ($p = 0.058$).

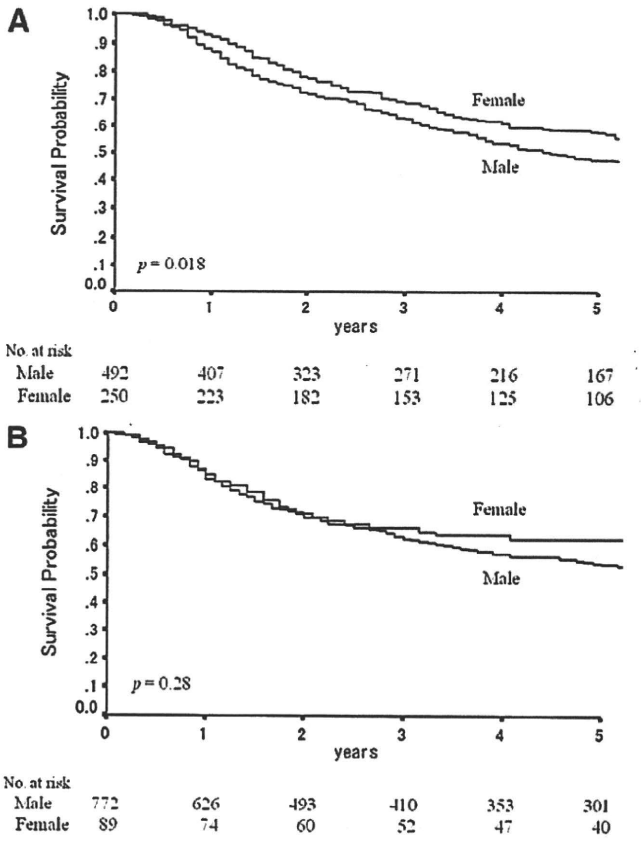


FIGURE 5. Overall survival curves according to gender of pathologic stage II in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage II in adenocarcinoma is 47.5% for male patients and 57.5% for female patients ($p = 0.018$). The 5-year survival rate for pathologic stage II in nonadenocarcinoma is 53.5% for male patients and 61.9% for female patients ($p = 0.28$).

patients with nonadenocarcinoma histology and pathologic stage I/II disease (Figures 4*B* and 5*B*).

Disease-specific 5-YSRs for men and women were 64.9 and 79.2%, respectively (Figure 6). Women had significantly better DSS than men ($p = 0.0000$). According to histologic type, women had significantly better 5-year DSS than men with adenocarcinoma (Figure 7*A*). However, in nonadenocarcinoma, there was no statistical difference in DSS between genders (Figure 7*B*). Regarding histologic type and pathologic type, the difference between genders in DSS was significant only in patients with adenocarcinoma histology and pathologic stage I disease (Figures 8 and 9).

In a Cox proportional hazards model to predict OS, the following factors persisted as important prognostic factors: gender, age, surgical procedure, histology, curability, tumor size, p-T status, and p-N status (Table 2). Gender had impact on survival with relative risk for women of 0.63 ($p = 0.000$; 95% confidence interval 0.58–0.68). Smoking status was not statistically significant or important determinant of survival, with relative risk for current smoker of 1.00 ($p = 0.94$; 95% confidence interval 0.93–1.09).

DISCUSSION

In this Japanese Lung Cancer Registry Study of 12,509 patients with resected NSCLC, women showed significantly better survival than men after resection. Female gender was one of the statistically positive independent predictors of survival in this registry. This better survival for women was observed regardless of the histologic type (adenocarcinoma or nonadenocarcinoma). Many other studies that have evaluated the effect of gender on the lung cancer prognosis have also suggested that women have a survival advantage, but the reasons for this survival advantage have remained unknown.[3,4,8,11,20] Genetic, metabolic, and hormonal factors have been proposed as potential explanations for the survival benefit experienced by women.[21–23]

The histology of NSCLCs among women was distinctly different from that among men, although adenocarcinoma was the most common histologic type in both genders in this study. Women had so much higher incidence of adenocarcinoma than men. Adenocarcinoma accounted for approximately 90% of resected NSCLC in women, in contrast to only 54% in men. In addition, a large proportion of

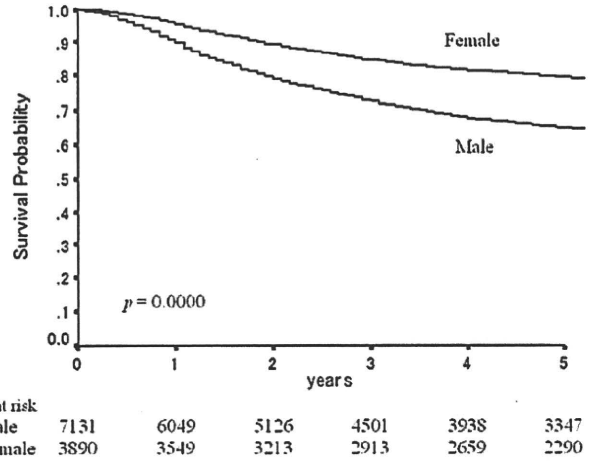


FIGURE 6. Disease-specific survival curves based on gender. The 5-year survival rates of female (n = 3890) and male (n = 7131) patients are 79.2 and 64.9%, respectively. The difference in survival between the genders is significant (p = 0.0000).

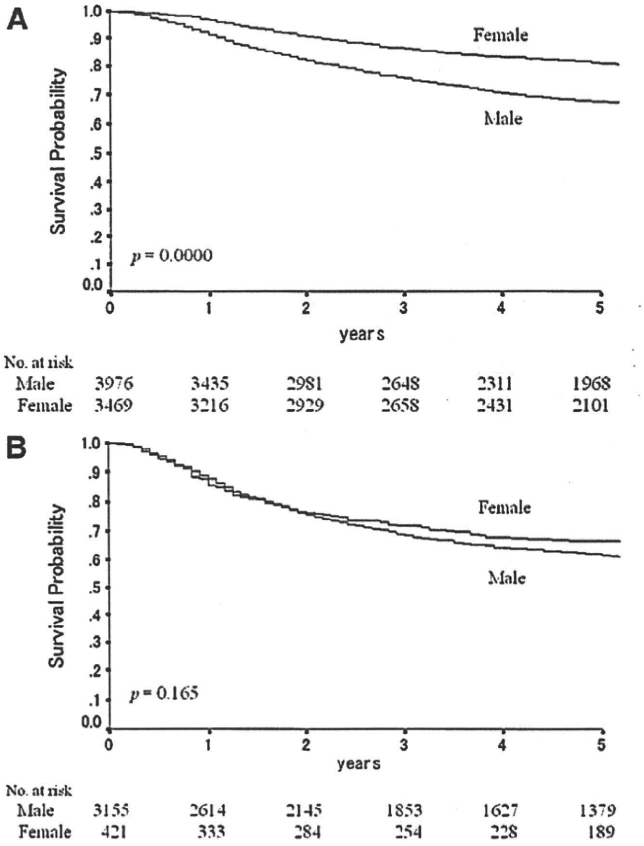


FIGURE 7. Disease-specific survival curves according to gender in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for adenocarcinoma is 67.5% for male patients and 80.8% for female patients. The difference in survival is significant (p = 0.0000). The 5-year survival rate for nonadenocarcinoma is 61.6% for male patients and 66.3% for female patients. The difference in survival is not significant (p = 0.17).

resected NSCLC in females was stage IA disease. In Japan, there have been opportunities of resecting small-sized lung cancers since a computed tomography (CT) screening for lung cancer was introduced in early 1990s. Most of the lung cancers detected by CT screening were likely to be small-sized and slow-growing adenocarcinomas.[24,25] In addition, people with lung cancer detected by CT screening accounted for a large proportion of women.[26] This would be one of the reasons for the increased incidence of early-stage lung cancers among women. In fact, it has been reported that early-stage lung cancers such as bronchioloalveolar carcinoma or adenocarcinoma mixed bronchioloalveolar subtype tend to occur frequently in nonsmoking women.[27,28] These data indicated that the difference in the pathobiologic characteristics of adenocarcinoma between genders should be addressed.

The increased incidence of adenocarcinoma among women may be attributed to several causes, including genetic, biologic, and environmental factors. Genetic polymorphisms and the mutation of specific genes have been examined as possible causes of the predominance of the adenocarcinoma histology in women.[29–31] Epidermal growth factor receptor and *K-ras* gene mutations have been detected more commonly in women than men and have been found mainly in adenocarcinomas of the lung.[29–32] Several reports[33,34] have investigated the relationship between the hormonal effects of estrogen and the development of lung cancer, especially adenocarcinoma, because the obvious biologic differences between men and women are hormonal. These findings in this study and the literature also suggest that the pathway of carcinogenesis might be different between women and men.

On the other hand, we observed that women with adenocarcinoma had a significantly better prognosis in both stage I disease and stage II disease, whereas there was no significant gender difference in nonadenocarcinoma patients with either stage I or stage II. Based on the fact that adenocarcinoma was more common in women and they have better prognosis, adenocarcinoma in women may be supposed to have different pathobiologic behaviors than that in men. The differences in lung cancer and its occurrence between women and men have been found or hypothesized to be related to several factors, such as differences in smoking habits and genetic, biologic, hormonal, and other differences between the genders.[22,33,35,36] Adenocarcinoma has always represented the majority of lung cancer cases among nonsmoking patients.[7,22,23] The association between smoking and lung cancer is much stronger for small cell carcinoma, squamous cell carcinoma, and large cell carcinoma than for adenocarcinoma.[10,37] The proportion of smokers among men is known to be significantly higher than that among women according to several previous reports,[1,38] although we were not able to directly evaluate the effect of potential gender differences in smoking habits because detailed data on tobacco exposure were not recorded in this registry. According to a report by the Health and Welfare Statistics Association in Japan, the proportion of Japanese smokers was 70 to 60% for men,

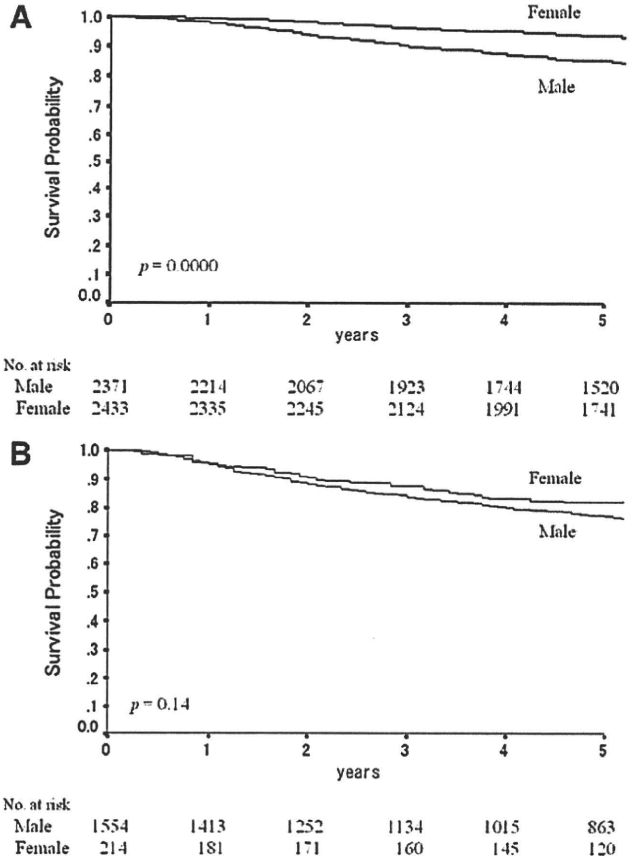


FIGURE 8. Disease-specific survival curves according to gender for pathologic stage I in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage I in adenocarcinoma is 85.3% for male patients and 93.5% for female patients ($p = 0.0000$). The 5-year survival rate for pathologic stage I in nonadenocarcinoma is 77.1% for male patients and 81.9% for female patients ($p = 0.14$).

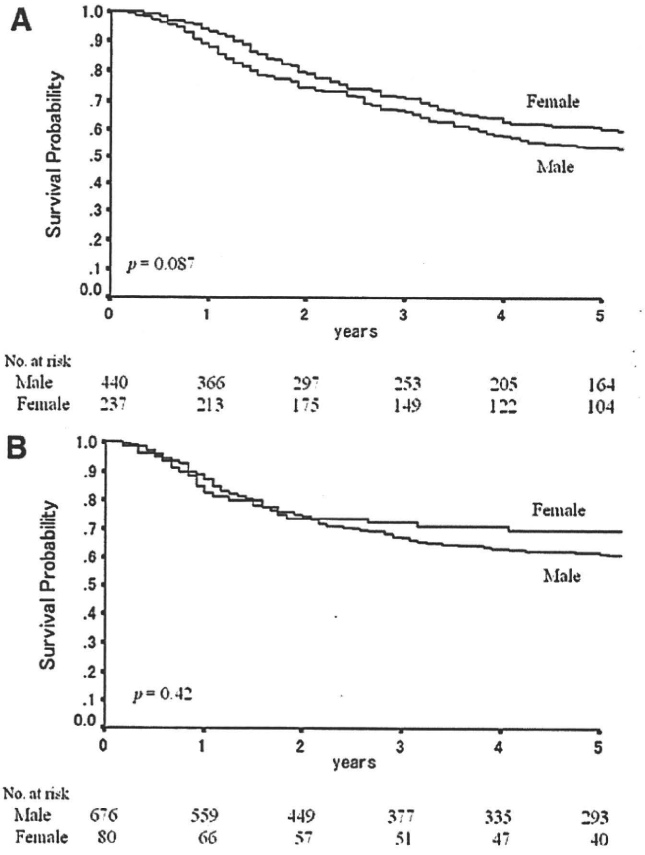


FIGURE 9. Disease-specific survival curves according to gender for pathologic stage II in adenocarcinoma (*A*) and nonadenocarcinoma (*B*). The 5-year survival rate for pathologic stage II in adenocarcinoma is 53.4% for male patients and 60.0% for female patients ($p = 0.087$). The 5-year survival rate for pathologic stage II in nonadenocarcinoma is 61.1% for male patients and 69.3% for female patients ($p = 0.42$).

invariable 14% for women, from 1980s to 1990s.[38] The proportion of smokers for men is still higher than that for women, although it has been reducing little by little.[38] Smoking is also closely related to cardiovascular and pulmonary diseases, e.g., ischemic heart disease, cerebrovascular disorder, and pulmonary emphysema.[39] These diseases might lead to noncancerous death before cancer-specific death. Thus, the better prognosis in women among patients with adenocarcinoma might be partially attributed to the differences in the incidence of noncancerous death between genders because women would include fewer smokers than men. In fact, Chang et al.[8] reported that the female-gender advantage in survival for resected NSCLC changed to no survival advantage for females after propensity score matching (variables: age, smoking status, histologic types, and pathologic stages) between males and females. Hanagiri et al.[40] showed that there was no gender difference in cancer-related survival regardless of a significant female-gender advantage in OS for patients with resected lung adenocarcinoma.

In this registry study, according to relationship between prognosis and the combination of histologic type and pathologic stage, women had significantly better DSS than men only in patients with adenocarcinoma histology and pathologic stage I disease. Therefore, at the least, deaths of causes other than lung cancer are likely to affect survival difference between genders except for patients with stage I adenocarcinoma. A significant female-gender advantage in stage I adenocarcinoma persisted in DSS and OS. Stage I adenocarcinoma in women would presumably include many bronchioloalveolar carcinomas, which tend to occur often in nonsmoking women, although histologic subtypes in adenocarcinoma was recorded in this registry.

Although the identification of factors that predispose to operative mortality is beyond the scope of this study, an older age at surgical resection and a higher number of pneumonectomies for men could be related to the higher 30-day mortality among men in this series. The higher operative mortality rate in male patients with lung cancer has been previously reported.[41,42]

TABLE 2. Multivariate Analysis of Overall Survival for Resected Cases of Non-small Cell Lung Cancer: Cox Proportional Hazard Model (n = 12,509)

Variable	RR	95% CI	p
Gender			
Men	1.00		
Women	0.626	0.580–0.675	0.000
Age (yr)			
<50	1.00		
50–70	1.287	1.118–1.482	0.000
>70	1.880	1.630–2.167	0.000
Smoking status			
Non-/ex-smoker	1.00		
Current smoker	1.003	0.926–1.087	0.938
Operative mode			
Pneumonectomy	1.00		
Lobectomy	0.926	0.826–1.038	0.189
Segmentectomy	1.155	0.959–1.391	0.128
Wedge resection	1.469	1.250–1.726	0.000
Surgical curability			
Complete	1.00		
Incomplete	1.630	1.480–1.796	0.000
Histology			
Squamous cell carcinoma	1.00		
Adenocarcinoma	0.938	0.874–1.007	0.076
Large cell carcinoma	1.418	1.237–1.627	0.000
Adenosquamous cell carcinoma	1.647	1.348–2.014	0.000
Tumor size (cm)			
≤1.0	1.00		
1.1–1.5	1.276	1.006–1.620	0.045
1.6–2.0	1.646	1.323–2.049	0.000
2.1–2.5	1.712	1.378–2.128	0.000
2.6–3.0	1.748	1.402–2.178	0.000
3.1–4.0	1.576	1.257–1.975	0.000
4.1–5.0	1.914	1.519–2.412	0.000
5.1–6.0	1.977	1.552–2.520	0.000
≥6.1	2.365	1.869–2.994	0.000
p-T status			
T0	1.00		
T1	0.897	0.602–1.335	0.591
T2	1.475	0.985–2.209	0.059
T3	1.923	1.277–2.895	0.002
T4	2.070	1.378–3.107	0.000
p-N status			
N0	1.00		
N1	1.874	1.716–2.047	0.000
N2	3.039	2.825–3.269	0.000
N3	4.872	3.965–5.986	0.000

RR, relative risk; CI, confidence interval.

In conclusion, we found that women showed significantly better 5-year survival than men after surgical resection of NSCLC. Especially in adenocarcinoma, the survival advantage for women was significant in pathologic stages I and II, whereas in nonadenocarcinoma, this gender difference was not significant in pathologic stage I or II. Although adenocarcinoma is the most common histologic type in both genders, the proportion of adenocarcinoma and stage IA disease in women was much greater than that in men. The incidence of early-stage adenocarcinoma might reasonably account for a better prognosis in women as a whole. Further studies should focus on the identification of differences in the pathobiological nature of early lung adenocarcinoma between women and men.

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