表４　2000年以降の術前化学療法の治療成績

著者（発表年）	研究デザイン*	化学療法	用量（mg/m²）	放射線照射量（Gy）	検討症例数	平均生存期間（月）	切除率 R0（割合）	R0例の平均生存期間（月）	有害事象（GradeⅢ/Ⅳ：%）
Brunner (2000)	前向-単	5-FU/MMC	100/10	50.4	61	9	37%・R0 (100%)	2年生存率 50%	56
Pisters (2002)[36]	前向-複	paclitaxel	60	30±IORT (10～15)	37	12	57%・R0 (68%)	19	?
Moutardier (2002)	前向-単	5-FU/Cis	650/80	30 or 45	19	20	79%・R0 (93%)	2年生存率 52%	0
Magnin (2003)[37]	前向-単	5-FU (dl-5, d21-25) Cis (d2, 22)	650 80	30 or 45	32	16	59% R0 (59%)	30	?
Al-Sukhun (2003)	前向-単	Cis・cytarabin caffeine・5-FU	100/200/m² 400/250	39.6	20	13.4	15% R0 (0%)	n.a	n.a
Lin (2005)	前向-単	GEM	1,000	45	42	9.5	64%・R0 (67%)	18	65
Pipas (2005)	前向-単	GEM docetaxel	4,000 65	50.4	24	14	85%・R0 (76%)	18	83
Talamonti (2006)[38]	前向-単	GEM	1,000	36	20	n.r	85%・R0 (94%)	26	?
Mornex (2006)[39]	前向-単	5-FU (5d/wk) Cis (d1-5, d29-33)	300 20	50	41	9.4	63%・R0 (81%)	11.7	73
Palmar (2007)[40]	前向-複	GEM GEM/Cis	1,000 1,000/25	(−)	24 26	13.6	54%・R0 (66%)	28.4	38 38
Varadhachary (2008)[41]	前向-単	GEM/Cis	750/30	30	79	18.7	65%・R0 (96%)	31	85
Evans (2008)[42]	前向-単	GEM	400	30	86	22.7	74%・R0 (89%)	34	87
Heinrich (2008)[43]	前向-単	GEM/Cis	1,500/50	(−)	28	26.5	89%・R0 (80%)	19.1	7
Landy (2010)	前向-複	GEM GEM/Cis/5-FU	500 175/20/600	50.4	10 11	19.4 13.4	30% 18%　R040%	26.3	35

*単：１アーム，複：２アーム

Ohigashi ら[31]の報告は特記すべき成果を示している。また，③化学療法例の併用療法については，doxorubicin・mitomycin C・5-FU（AMF）療法，mitomycin C・5-FU（MF）療法，5-FU・cisplatin（FP）療法が検討され，いずれも有用性を示唆する結果は得られなかった，などとなる。

2. 進行中の臨床試験

化学療法として有用とされている 5-FU 剤あるいは erlotinib についての研究「ESPC-4」では，GEM をベースにして capecitabine の上乗せ効果について，「CONKO-005」では GEM をベースにして erlotinib の上乗せ効果を検討している。

本邦では，Japan Adjuvant Study Group of Pancreatic Cancer（JASPAC）-01 で GEM に対し S-1 の非劣性が確認されたことから，JSAP-04 にて GEM への S-1 上乗せ効果の優越性を検証する研究がなされている。なお，先に紹介した FOLFIRINOX については重篤な有害事象の発生率が高いため，術後補助療法として本邦で応用することについての適用が検討されている。

術前補助化学（放射線）療法

切除可能な膵癌であっても，その予後は一般に不良で，現状の化学療法では治療拮抗性を示す膵癌が圧倒的に多い。そこで，他の固型癌の治療動向と同様に局所切除可能例の予後改善を目的とした集学的治療を探る傾向にある。術後補助化学（放射線）療法については数多くの臨床研究があるのに対し，術前補助化学療法に関しては系統立てた大規模臨床研究はほとんど存在しないに等しい。しかし，小規模臨床研究成果などから推し測ると，ある限られた患者群については術前化学療法の意義が大きいことが考えられる。例えば，局所根治性の点で境界領域にある症例ではしばしば組織学的非根治術に終わることがあり，そのような症例での有用性が想定されている。しかし一方，術前補助化学療法により生じ得る外科的合併症のリスク因子に

表5　術前化学療法臨床研究のmeta分析の概要

分析項目	Group A（n=402）（化療前診断：切除可能）	Group B（n=134）（化療前診断：境界ないし切除不可能）
奏効率（%）		
CR	0.8	4.0
PR	9.5	31.8
SD	73.9	40.9
PD	17.0	21.8
手術内容		
切除率（%）	65.8	31.6
切除例中のR0の占める割合（%）	85.1	62.2
平均生存期間（月）	23.0	22.3
全症例	15.1	11.2
切除例	23.0	22.3

〔文献45)の成果を改変・要約〕

ついても考慮しなくてはならない。以下にこれまでの術前補助化学療法の概要を紹介する。

2000年以降の術前療法に限っての報告例に絞ったリストを表4に示した。その多くは放射線化学療法を施行した報告で，放射線照射を除いた化学療法については近年になってGEM単剤あるいはcisplatinと5-FUを併用した報告の2件のみ認められた。

術前診断で“resectable”，“borderline”あるいは“locally unresectable/borderline”と診断した症例を対象とするなど，対象については研究種間でまちまちであった。術前療法後の切除率については，15～89%，その中でのR0手術施行率0～100%とまちまちであった。このような状況から導き出される生命予後をend pointとした成果については，必ずしも正確なエビデンスにはつながらない。切除となった場合の平均生存期間は，18～34カ月と幅は大きく，対象症例間の背景因子に差があることが想定される。今後，対象症例条件を厳しく設定し，術前補助化学療法の有無と術後補助化学療法の統一によるRCTあるいはcomparative research methodにての分析に期待が寄せられる。また国内外で2アームによる臨床試験（GEM vs. S-1，GEM vs. GM+S-1，GEM vs. GEM+capecitabine[43]，GEM+placebo vs. GEM+erlotinib，GEM+placebo vs. GEM+sorafenib）が進んでおり，それらの成果から，さらなる適切な臨床研究が組まれていくことと思われる。なおAssifiら[45]はphaseⅡ試験を対象に術前補助化学療法の意義についてメタ分析を行っている（表5）。術前補助切除可能群では，奏効性の点でSDが多いのに対し，境界ないし切除不能群ではPRが多かったという理由については明確でないが，切除率，切除例中のRoの占める割合は前者で多かったのは当然の結果といえよう。平均生存期間については，両群間に顕著な差を認めなかったことは1つの特徴と課題といえよう。

おわりに

現時点で，切除不能高度進行膵癌では「GEM+erlotinib療法」あるいは「GEM単剤療法」，「S-1単剤療法」が，また切除例にあっては「切除+GEM術後化学療法」，「切除+S-1術後化学療法」が標準治療である。成績向上のための次のブレイクスルーを図るには術前治療に寄せられる期待は大きい。すでに，進行乳癌や胃癌では術前・術後の化学療法による延命効果を実証した報告も散見されることから，優れた薬剤を用いての基本アームに対する臨床試験による突出した成果を期待したい。

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（分担研究報告書）

がん登録からみたがん診療ガイドラインの普及効果に関する研究
－診療動向と治療成績の変化－
甲状腺癌の登録体制とガイドライン評価体制

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研究要旨
甲状腺腫瘍診療ガイドライン2010年版に関する評価を目的に関連学会員を対象にアンケート調査を行った。ガイドライン2010年版は概ね好評であり、ガイドラインによる診療の変化については「変わった」、「変わらない」、「何とも言えない」への回答はほぼ同率であった。ただし回収率は低く、過大に偏った評価の可能性もある。批判的フリーコメントも参考になると思われる。

A．研究目的

甲状腺腫瘍診療ガイドライン作成委員会は2014年に改訂版を刊行する予定である。そのためには2010年版を評価し、新たな目標設定を行い、目標達成のための方略を策定することが必須である。

B．研究方法

2012年4月、日本内分泌外科学会および日本甲状腺外科学会の学会員1660名にアンケートを送付した。アンケートではガイドラインの認知、アクセス、そしてアルゴリズム、クリニカル・クエスチョン、ガイドライン全体への評価、臨床実践の変化についてチェックリスト方式で回答を依頼した。また、ガイドラインに関してフリーコメントを寄せてもらう欄を設けた。回答者の年齢、診療科目、臨床経験年数、甲状腺腫瘍手術数（月）、甲状腺腫瘍患者診療数（月）も併せて尋ねた。

（倫理面への配慮）

アンケートは無記名方式で行った。

C．研究結果

339名から回答を得た（回収率20.4%）。回答者の年齢、臨床経験年数の中央値はそれぞれ49歳、24年であった。ガイドラインの存在を知っていた295名(87%)からの評価に関する回答を集計した。診療科目は内分泌外科114名(39%)、外科89名(30%)、耳鼻科49名(17%)、泌尿器科21名(7%)、その他・無回答22名(7%)であった。アルゴリズム、CQ、推奨文、解説について「分かりやすい」/「分かりにくい」と回答したのはそれぞれ68%/0.3%、73%/1%、66%/0.7%、72%/0.3%、「適切である」/「適切でない」と回答したのはそれぞれ68%/1%、68%/0.7%、63%/0%、68%/1%であった。52%が「使いやすい」、2%が「使いにくい」と答え、ガイドラインによる診療の変化については27%が「変わった」、28%が「変わらない」、28%が「何とも言えない」と回答した。

D．考察

回収率は低く、ガイドラインに関心をもつユーザーからの回答が多いと思われる。今後はガイドラインが推奨する管理方針の遵守度や治療成績など、より客観的な指標での評価を仕組みの構築が必要である。

E．結論

ガイドライン2010年版は概ね好評であったが、低い回収率を考慮すれば、過大に偏った評価の可能性もある。改訂に向けた新たな目標設定にはフリーコメントの批判的意見も参考になるであろう。

F．健康危険情報

G．研究発表

1.　論文発表

なし

2.　学会発表

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H．知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金
(分担研究報告書)

がん登録からみたがん診療ガイドラインの普及効果に関する研究
ー診療動向と治療成績の変化ー

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研究要旨
わが国における学会主導の肺がん登録事業の課題とその解決策および登録推進に向けた方策、また肺がん登録事業からみた肺がん診療ガイドラインの普及効果および診療動向の変化について検討する。

A．研究目的

今年度は、現在のわが国における肺癌患者の登録体制の一つである「肺癌登録合同委員会事業」のこれまでの事業内容と現状を検討し、本登録事業の課題を検討した。

B．研究方法

肺癌登録合同委員会事業の歴史と現状を調査し、登録体制、その方法論、これまでの成果、および今後の課題について検討した。

(倫理面への配慮)

現在の登録事業内容はすべて事務局がある大阪大学に倫理審査が行われた後に登録されている。

C．研究結果

肺癌登録合同委員会事業は、現在日本肺癌学会、日本呼吸器外科学会、日本呼吸器学会、日本呼吸器内視鏡学会の4学会により運営されている。第1次登録事業は1994年に、その後1999年、2002年、2005年、2010年と計5回の肺がん登録事業が遂行されている。そして現在（2012年）第6次事業として内科症例の前向き登録を行っている。

症例登録は「肺癌登録合同委員会」のホームページから行うように設定され、ユーザーID、パスワードなどにより情報の安全が担保されている。また、資金は各学会が分担金（年200万円）を負担して賄われている。

これまで5回の登録症例数は計50, 769例に上っている。またその成果は海外学術雑誌に報告され、これまで12編が公表されている。

さらに第2次から第5次事業までの47, 306例のデータが次期TNM分類改訂用の資料として提供され、国際的に当事業は高く評価されている。

一方、登録症例数は肺がん患者の増加に伴っては増えておらず、事業の一つの問題と思われた。

D．考察

肺癌登録合同委員会事業の課題として、①登録率の改善、②事業の継続性の維持、③NCDおよび地域がん登録事業との連携などがあげられる。①に関しては、登録作業の負担の軽減やインセンティブの付与をさらに考慮する必要があると思われた。②に関しては事務局の独立化、公的資金の援助・獲得も検討すべきと考えられた。③については、関連学会との協議が今後必要となると思われた。

E．結論

肺癌登録合同委員会事業は、ほぼ20年にわたる登録事業であり、その成果は国際的にも高い評価を受けている。一方、今後の事業の継続・発展については種々の危惧があり、関係学会や政府機関の関与も必要であると思われた。

F．健康危険情報

なし

G．研究発表

1．論文発表

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2．学会発表

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H．知的財産権の出願・登録状況

なし

Japanese Lung Cancer Registry Study of 11,663 Surgical Cases in 2004

Demographic and Prognosis Changes Over Decade

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Background: The Japan Lung Cancer Society, the Japanese Association for Chest Surgery, and the Japanese Respiratory Society jointly established the Japanese Joint Committee for Lung Cancer Registration, which has regularly conducted lung cancer registries for surgical cases in 5-year periods. We analyzed data obtained in these registries to reveal the most recent surgical outcomes and trends related to lung cancer surgery in Japan.

Methods: Using data from the registry in 2010 for cases of surgery performed in 2004, demographics, surgical results, and stage-specific prognoses were analyzed. In addition, trends for those parameters over 10 years were assessed.

Results: The 5-year survival rate for all cases (n = 11,663, 7369 males, mean age 66.7 years) was 69.6%. The 5-year survival rates by c-stage and p-stage were as follow: IA, 82.0% (n = 6295) and 86.8% (n = 4978); IB, 66.8% (n = 2339) and 73.9% (n = 2552); IIA, 54.5% (n = 819) and 61.6% (n = 941); IIB, 46.4% (n = 648) and 49.8% (n = 848); IIIA, 42.8% (n = 1216) and 40.9% (n = 1804); IIIB, 40.3% (n = 90) and 27.8% (n = 106); and IV, 31.4% (n = 256) and 27.9% (n = 434), respectively. The percentages of female patients, cases with adenocarcinoma, stage I or II disease, and tumors sized less than 2 cm were increased, while those of operative and hospital deaths were decreased. Furthermore, the prognoses of all cases and cases in each stage improved over the decade.

Conclusion: In Japanese cases of lung cancer surgery, demographics, surgical results, and stage-specific prognoses changed over the 10-year study period, while the 5-year survival rate for surgical cases improved to 69.6% in 2004.

Key Words: Japan, Lung cancer, Surgery, Registry.

(*J Thorac Oncol.* 2011;6: 1229–1235)

Lung cancer is one of the leading causes of death in most industrial countries.[1] As such, it is crucial to understand the demographics, tumor-specific backgrounds, and prognoses by related factors and stage. In addition, elucidation of trends for those parameters is helpful to compose strategies for lung cancer treatment.

The Japan Lung Cancer Society, the Japanese Association for Chest Surgery, and the Japanese Respiratory Society jointly established the Japanese Joint Committee of Lung Cancer Registry (JJCLCR), which has regularly conducted nationwide registrations every 5 years for cases treated surgically, with the results of cases treated in 1994 and 1999 published in English in 1999 and 2004, respectively.[2,3] Furthermore, additional studies related to specific issues encountered in registries for surgical cases in 1999, such as octogenarian cases,[4] pleural invasion,[5] gender,[6] and surgical results,[7] have been published. In addition to the regular registries, prospective enrollment and retrospective analyses of surgical and nonsurgical cases treated in 2002 were performed and the results published.[8] However, the investigated points regarding preoperative parameters are limited in that registry and fewer than those noted in the regular registry for surgical cases conducted every 5 years.

A new regular nationwide registry for lung cancer cases surgically treated in 2004 in Japan was conducted in 2010 by the JJCLCR. This registry investigated detailed tumor node metastasis (TNM) factors, thus it was possible to analyze the

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Disclosure: The authors declare no conflicts of interest.

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data using UICC-TNM ver. 7 (2009).[9] In this study, we analyzed data obtained by these registries to reveal the most recent surgical outcomes and trends related to lung cancer surgery in Japan.

PATIENTS AND METHODS

The JJCLCR conducted a retrospective observational study of patients who underwent surgery for lung cancer between January 1, 2004, and December 31, 2004. The committee asked the 605 teaching hospitals certified by the Japanese Board of General Thoracic Surgery to join the study, of which 253 (41.3%) participated. This registry was opened on January 1, 2010, and closed on June 31, 2010. In addition, 303 institutes (the number of invited institutes is unknown) participated in the registry for cases in 1994 that was performed in 2000, and 386 (75.2%) of 513 invited institutes participated in the registry for cases in 1999 that was performed in 2005.

The participating institutions took part in this registry by accessing a web site established by the JJCLCR, after receiving information that had been mailed to the 605 teaching hospitals. Each participating institute was sent a universal serial bus (USB) flash memory stick that contained software to be used for the registry. Each institute was authorized to use the registration form in the server located at the JJCLCR office after entering their ID and password, which was also mailed to the institution.

For these procedures, the JJCLCR used the secure sockets layer protocol for communication and digest (most reliable) certification, which was considered to be more secure than postal mail. The data sheet containing the patient's ID and registration no., used for anonymity in a linkable fashion, was kept in the USB flash memory stick and placed in a location that could be locked by each participating institution. In addition, each USB flash memory stick was coded with an individual serial key sent from the JJCLCR office and known only by the institution. The JJCLCR completed confirmation of participation in the registry by the end of 2009 and distributed the USB flash memory sticks to the institutions in 2009.

This registry followed the ethical guidelines for epidemiologic studies published jointly by the Japan Ministry of Science, Culture, and Education and the Japan Ministry of Health, Labor, and Welfare on June 17, 2002, which was revised on August 16, 2007. In addition, it was approved by the institutional review board of Osaka University Medical Hospital, where the registry office is located, after discussions published on August 13, 2009 (approval no. 09124).

Inclusion criteria were as follows: (1) pathological (including cytology findings) diagnosis of any type of lung cancer at a participating institution; (2) diagnosis obtained in 2004; and (3) treated by surgery. Patients with lung cancer recurrence or metastasis were excluded. The following points were investigated: (1) demographic background, (a) date of registry, (b) gender, (c) birth month and year, (d) date of diagnosis; (2) preoperative status, (a) Eastern Cooperative Oncology Group performance status (PS), (b) preoperative comorbidity, (c) smoking status, (d) status of serum tumor markers (CEA, SCC or CYFRA, SLX and NSE or Pro-GRP); (3) clinical T factors, (a) tumor size, (b) status of invasion at the main bronchus, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) status of atelectasis, (g) status of invaded organ; (4) clinical N factor (status of lymph nodes); (5) clinical M factor (metastasized organ); (6) surgery, (a) induction therapy, (b) operation, (c) place of tumor origin, (d) extent of lymph node removal, (e) gross curative status, (f) status of residual rumor, (g) lavage cytology findings, (h) combined resection; (7) postoperative morbidity; (8) tumor histology; (9) adjuvant therapy; (10) pathological T factors, (a) tumor size, (b) extent of bronchial involvement, (c) pleural invasion, (d) intrapulmonary metastasis, (e) status of pleural effusion, (f) pleural dissemination, (g) status of pleural effusion, (h) status of atelectasis, (i) status of invaded organ; (11) pathological N factor (status of removal of and metastasis to each lymph node); and (12) pathological M factor (metastasized organ). The extent of resection (exploration, R0, R1, or R2) was also registered.

Tumor size, detailed T factors, and lymph node status were classified using both UICC-TNM ver. 6 (1999)[10] and UICC-TNM ver. 7 (2009).[9] For this classification, the #10 lymph node of the Naruke map was converted to #7 of UICC-TNM ver. 7 (2009). To comprehend demographic and prognostic alterations over a decade, data from the Japanese nationwide registries in 1994 and 1999 are also presented. The data quoted were taken from official reports of the JJCLCR published in 2002[11] and 2005.[12] Data from the submitted cases were stored and converted to excel files, which were transferred to a JJCLCR member biological statistician (E.M.), who independently reviewed the files for cases from 1994, 1999, and 2004. The follow-up period was defined as the time from the date of surgery to the latest follow-up examination. Survival period was defined as the number of months from the day of surgery to the day of death or the latest day of confirmed survival. Cases of death immediately after the operation were included. Survival curves were estimated according to the Kaplan-Meier method for the subsets clinical stage, pathological stage, sex, and histological subtype of tumor. Differences in survival were tested using the log-rank method. A p value less than 0.05 was considered to be statistically significant.

RESULTS

The number of registered cases was 11,663, which were provided by 253 institutions. Demographic backgrounds are shown in Table 1. In 2004, there were 7369 males and 4294 females registered, with a mean age of 66.7 years (range, 14–91), a follow-up period that ranged from 2 to 78 months (median, 58 months), and a percentage of PS 0 or 1 of 96.7%. The rates of female patients, mean age, and percentage of PS 0 or 1 showed increasing trends. As shown in Table 2, the most frequent tumor histology in 2004 was adenocarcinoma, followed by squamous cell carcinoma, although the ratio of adenocarcinoma was increasing and that of squamous cell carcinoma was decreasing. Induction chemotherapy was performed in 518 (4.4%) and adjuvant therapy in 2903 (24.9%) cases. The rate of anti-epidermal growth factor receptor is

unknown, as it was not noted. The rate of R0 was 93.6% in 2004, 88.5% in 1999, and 80.4% in 1994. In addition, the 5-year survival rate (5-YSR) for each histology type improved. Moreover, the rate of small-sized tumor cases was also increasing, as the rates of tumors sized less than 1 and 2 cm were 9.1% and 36.9%, respectively (Table 3).

Clinical and pathological TNM factors based on UICC-TNM ver. 6 (1999) are shown in Table 4. In 2004, clinical T1 diseases comprised more than half of the cases, and the rate of clinical N0 disease was greater than 80%. Both showed increasing trends as compared with the 1999 results. Furthermore, a similar trend was shown in the pathological classification based on UICC-TNM ver. 6 (1999). Clinical and pathological stages based on UICC-TNM ver. 7 (2009) are shown in Table 5, while the distributions of clinical and pathological stages based on UICC-TNM ver. 6 (1999) and UICC-TNM ver. 7 (2009) are presented in Table 6. In 2004, the rate of clinical stage IA disease was greater than 50%, while that of pathological IA disease was less than 50%.

The trends for survival for all cases and each stage are also shown in Table 6. In 2004, the 5-YSR for all cases was 69.6%, which showed an improving trend for both total cases and each stage. The c-stage and p-stage (UICC-TNM ver. 7, 2009) specific 5-YSRs were as follows: IA, 82.0% (n = 6295) and 86.8% (n = 4978); IB, 66.8% (n = 2339) and 73.9% (n = 2552); IIA, 54.5% (n = 819) and 61.6% (n = 941); IIB, 46.4% (n = 648) and 49.8% (n = 848); IIIA, 42.8% (n = 1216) and 40.9% (n = 1804); IIIB, 40.3% (n = 90) and 27.8% (n = 106); and IV, 31.4% (n = 256) and 27.9% (n = 434), respectively (Table 7). The survival curves based on clinical and pathological stages determined with the modified UICC-TNM ver. 7 (2009) are shown in Figures 1 and 2, respectively. For clinical stage, there were no

TABLE 1. Demographics

	2004 n (%)	1999 n (%)	1994 n (%)
Total	11,663 (100.0)	13,344 (100.0)	7393 (100.0)
Gender			
Male	7369 (63.2)	8878 (66.5)	5154 (69.7)
Female	4294 (36.8)	4344 (32.6)	2197 (29.7)
Missing	0 (0.0)	122 (0.9)	42 (0.6)
Age (yr)			
10–19	4 (0.0)	9 (0.1)	2 (0.0)
20–29	12 (0.1)	15 (0.1)	17 (0.2)
30–39	85 (0.7)	122 (0.9)	84 (1.1)
40–49	495 (4.2)	731 (5.5)	512 (6.9)
50–59	2065 (17.7)	2312 (17.3)	1334 (18.0)
60–69	3713 (31.8)	4610 (34.5)	2984 (40.4)
70–79	4584 (39.3)	4823 (36.1)	2222 (30.1)
80–89	701 (6.0)	598 (4.5)	232 (3.1)
≥90	4 (0.0)	4 (0.0)	1 (0.0)
Missing	0 (0.0)	120 (0.9)	5 (0.1)
Mean ± SD	66.7 ± 9.9	65.8 ± 9.8	64.5 ± 9.7
Performance status			
0	9608 (82.4)	10158 (76.1)	NA
1	1688 (14.5)	2319 (17.4)	NA
2	154 (1.3)	230 (1.7)	NA
3	34 (0.3)	21 (0.2)	NA
4	1 (0.0)	0 (0.0)	NA
Unknown	178 (1.5)	0 (0.0)	NA
Missing	0 (0.0)	616 (4.6)	NA

NA, not assessed.

TABLE 3. Tumor Size in Detail

	2004			
Tumor Size (cm)	Clinical n (%)	Pathological n (%)	1999 n (%)	1994 n (%)
≤1.0	983 (8.4)	1057 (9.1)	746 (5.6)	249 (3.4)
1.1–1.5	1352 (11.6)	1459 (12.5)	1227 (9.2)	526 (7.1)
1.6–2.0	2038 (17.5)	1787 (15.3)	1972 (14.8)	942 (12.7)
2.1–2.5	1599 (13.7)	1730 (14.8)	1824 (13.7)	952 (12.9)
2.6–3.0	1409 (12.1)	1336 (11.5)	1527 (11.4)	926 (12.5)
3.1–4.0	2248 (19.3)	2091 (17.9)	2693 (20.2)	1621 (21.9)
4.1–5.0	970 (8.3)	1014 (8.7)	1426 (10.7)	887 (12)
5.1–6.0	468 (4.0)	497 (4.3)	740 (5.5)	510 (6.9)
6.1–7.0	358 (3.1)	375 (3.2)	949 (7.1)	727 (9.8)
≥7.1	238 (2.0)	317 (2.7)		
Missing	0 (0.0)	0 (0.0)	240 (1.8)	53 (0.7)
Total	11,663 (100.0)	11,663 (100.0)	13,344 (100.0)	7393 (100.0)

TABLE 2. Tumor Histology and Survival

	2004		1999		1994	
	n (%)	5-YSR (%)	n (%)	5-YSR (%)	n (%)	5-YSR (%)
Total	11,663 (100.0)		13,344 (100.0)		7393 (100.0)	
Tumor histology						
Adenocarcinoma	7921 (67.9)	74.9	8239 (61.7)	67.3	4116 (55.7)	56.0
Squamous cell carcinoma	2600 (22.3)	59.1	3700 (27.7)	52.3	2441 (33.0)	48.6
Large cell carcinoma	387 (3.3)	53.3	474 (3.6)	45.5	266 (3.6)	46.7
Adenosquamous cell carcinoma	225 (1.9)	50.8	207 (1.6)	42.1	185 (2.5)	35.7
Small cell carcinoma	243 (2.1)	52.6	390 (2.9)	48.1	248 (3.4)	36.7
Others	224 (2.0)	NA	265 (2.0)	NA	129 (1.8)	NA
Missing	0 (0.0)		69 (0.5)		8 (0.1)	

NA, not assessed; 5-YSR, 5-year survival rate.

TABLE 4. TNM Distribution by UICC-TNM ver. 6 (1999)

	2004 *n* (%)	1999 *n* (%)	1994 *n* (%)
Total	11,663 (100.0)	13,344 (100.0)	7393 (100.0)
c-T ver. 6			
T1	6780 (58.1)	6586 (49.4)	3162 (42.8)
T2	3840 (32.9)	5066 (38.0)	3092 (41.8)
T3	659 (5.7)	1111 (8.3)	786 (10.6)
T4	384 (3.3)	521 (3.9)	317 (4.3)
TX		60 (0.4)	14 (0.2)
Missing			22 (0.3)
c-N ver. 6			
N0	9733 (83.5)	10,164 (76.2)	4904 (66.3)
N1	936 (8.0)	1211 (9.1)	874 (11.8)
N2	939 (8.1)	1789 (13.4)	1458 (19.7)
N3	55 (0.5)	99 (0.7)	131 (1.8)
NX	0 (0.0)	81 (0.6)	26 (0.3)
c-M ver. 6			
M0	11,458 (98.2)	13,022 (97.6)	7208 (97.5)
M1	131 (1.1)	210 (1.6)	167 (2.3)
MX	74 (0.6)	112 (0.8)	14 (0.2)
p-T ver. 6			
T1	6459 (55.4)	6022 (45.1)	2925 (39.6)
T2	3685 (31.6)	4654 (34.9)	2854 (38.6)
T3	703 (6.0)	1120 (8.4)	781 (10.6)
T4	816 (7.0)	1217 (9.1)	771 (10.4)
TX		131 (1.0)	35 (0.5)
Missing	0 (0.0)	200 (1.5)	27 (0.4)
p-N ver. 6			
N0	8932 (76.6)	9163 (68.7)	4464 (60.4)
N1	1133 (9.7)	1587 (11.9)	980 (13.3)
N2	1550 (13.3)	2333 (17.5)	1616 (21.9)
N3	48 (0.4)	140 (1.0)	126 (1.7)
NX			201 (1.8)
Missing	0 (0.0)	121 (0.9)	6 (0.1)
p-M ver. 6			
M0	11,407 (97.8)	12,838 (96.2)	7092 (95.9)
M1	188 (1.6)	407 (3.1)	275 (3.7)
Mx	68 (0.6)		18 (0.2)
Missing	0 (0.0)	99 (0.7)	8 (0.1)

TNM, tumor, node, metastasis.

TABLE 5. TNM Distribution by Modified UICC-TNM ver. 7 (2009)

	2004 *n* (%)
c-T ver. 7	
T1a	4147 (35.6)
T1b	2649 (22.7)
T2a	3191 (27.4)
T2b	509 (4.4)
T3	1008 (8.6)
T4	159 (1.4)
c-N ver. 7	
N0	9733 (83.5)
N1	764 (6.6)
N2	1111 (9.6)
N3	55 (0.5)
c-M ver. 7	
M0	11,337 (97.2)
M1a	177 (1.5)
M1b	79 (0.7)
Mx	70 (0.6)
p-T ver. 7	
T1a	3598 (30.9)
T1b	2051 (17.6)
T2a	3887 (33.3)
T2b	533 (4.6)
T3	1376 (11.8)
T4	218 (1.9)
p-N ver. 7	
N0	8932 (76.6)
N1	908 (7.8)
N2	1775 (15.2)
N3	48 (0.4)
p-M ver. 7	
M0	11,166 (95.7)
M1a	345 (3.0)
M1b	89 (0.8)
Mx	63 (0.5)

For the N classification, all #10 lymph nodes in the Naruke map were converted to #7 in UICC-TNM ver. 7 (2009).
TNM, tumor, node, metastasis.

statistically significant differences between IIB and IIIA ($p = 0.5$), IIIA and IIIB ($p = 0.7$), IIB and IIIB ($p = 0.5$), and IIIB and IV ($p = 0.08$), whereas for pathological stage, there was no statistically significant difference between IIIB and IV ($p = 0.9$).

Postoperative morbidity and mortality are shown in Table 8. In 2004, the rate of severe postoperative complications (greater than National Cancer Institute Common Toxicity Criteria grade 3) had decreased from the former registry in 1999. Furthermore, the rate of operation-related deaths showed a decreasing trend, as the percentage of operative deaths (death within 30 days after the operation) was 0.4% and that of hospital deaths was 0.4% in the 2004 registry.

DISCUSSION

In cases of lung cancer that underwent surgery in Japan, demographics and stage-specific prognoses changed in the decade studied. In that time period, the percentages for female patients, adenocarcinoma, small-sized tumors (<2 cm), and aged patients increased, whereas the rate of surgery-related deaths decreased to only 0.8%. With those changes, the 5-YSR in 2004 of all lung cancer patients who underwent surgery was 69.6%.

A retrospective study of a large number of surgical cases carried out by JJCLRC in 2004 showed that gender is a prognostic indicator.[3] A more detailed analysis using the same registry data showed that women with non-small cell lung cancer, especially with adenocarcinoma histology, had better survival than men and were more likely to have stage

TABLE 6. Stage Distribution and Specific Survival by UICC-TNM ver. 6 (1999)

	Ver. 6					
	2004		1999		1994	
	n (%)	5-YSR (%)	*n* (%)	5-YSR (%)	*n* (%)	5-YSR (%)
Total	11,663	69.6	13,344	61.6	7238	51.9
C-stage						
IA	6295 (54)	82	5939 (45)	77	2618 (30.2)	71.5
IB	2788 (23.9)	63.4	3242 (24.5)	60.1	1646 (23)	50.1
IIA	203 (1.7)	55.4	226 (1.7)	53.8	169 (2.4)	47.8
IIB	899 (7.7)	48.6	1304 (9.9)	43.6	793 (11.1)	40.4
IIIA	940 (8.1)	43.3	1723 (13)	38	1385 (19.3)	34.6
IIIB	407 (3.5)	41.6	567 (4.3)	33.6	395 (5.5)	27.6
IV	131 (1.1)	29.1	211 (1.6)	27	162 (2.3)	19.9
Missing	0 (0)		132 (1)		70	
P-stage						
IA	5611 (48.1)	85.9	5007 (38.2)	83.3	2142 (30.4)	79.2
IB	2398 (20.4)	69.3	2803 (21.4)	66.4	1488 (21.1)	60.1
IIA	336 (2.9)	60.9	400 (3)	60.1	261 (3.7)	58.6
IIB	977 (8.4)	51.1	1388 (10.6)	47.2	785 (11.1)	42.2
IIIA	1354 (11.6)	41	1944 (14.8)	32.8	1337 (19)	28.4
IIIB	799 (6.9)	36.7	1179 (9)	30.4	759 (10.8)	20
IV	188 (1.6)	27.8	397 (3)	23.2	275 (3.9)	19.3
Missing	0 (0)		226 (1.7)		191 (2.6)	

TNM, tumor, node, metastasis; 5-YSR, 5-year survival rate.

TABLE 7. Stage Distribution and Specific Survival by Modified UICC-TNM ver. 7 (2009)

	Ver. 7 2004	
	n (%)	5-YSR (%)
Total	11,663	69.6
C-stage		
IA	6295 (54)	82
IB	2339 (20.1)	66.1
IIA	819 (7)	54.5
IIB	648 (5.6)	46.4
IIIA	1216 (10.4)	42.8
IIIB	90 (0.1)	40.3
IV	256 (2.2)	31.4
Missing	0 (0)	
P-stage		
IA	4978 (42.7)	86.8
IB	2552 (21.9)	73.9
IIA	941 (8.1)	61.6
IIB	848 (7.3)	49.8
IIIA	1804 (15.5)	40.9
IIIB	106 (0.9)	27.8
IV	434 (3.7)	27.9
Missing	0 (0)	

For the N classification, all #10 lymph nodes in the Naruke map were converted to #7 in UICC-TNM ver. 7 (2009).
TNM, tumor, node, metastasis; 5-YSR, 5-year survival rate.

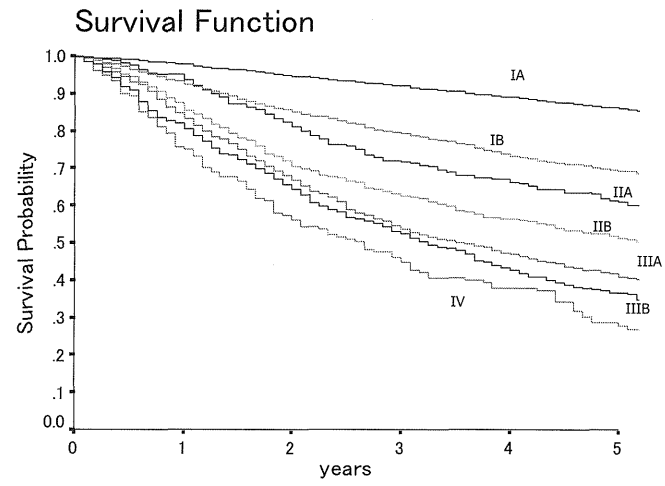

FIGURE 1. Clinical stage-specific survival curves by UICC-TNM ver. 7 (2009). The log-rank test results were not significantly different between IIB and IIIA ($p = 0.5$), IIIA and IIIB ($p = 0.7$), IIB and IIIB ($p = 0.5$), and IIIB and IV ($p = 0.08$). For the N classification, all #10 lymph nodes in the Naruke map were converted to #7 in UICC-TNM ver. 7 (2009).

IA disease, which might account for their better prognosis.[6] However, another study of propensity score-matched gender patients found no survival advantage.[13] Thus, the increase in number of females with adenocarcinoma may have contributed to the improvement of survival rate in the current JJCLCR registry.

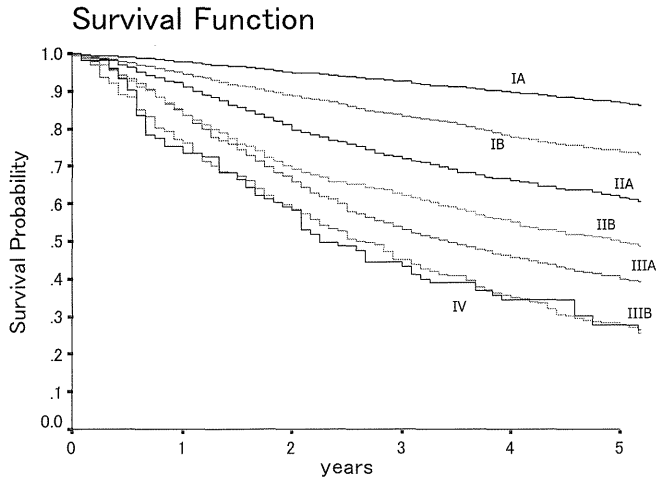

FIGURE 2. Pathological stage-specific survival curves by UICC-TNM ver. 7 (2009). The log-rank test results were not significantly different between IIIB and IV ($p = 0.9$). For the N classification, all #10 lymph nodes in the Naruke map were converted to #7 in UICC-TNM ver. 7 (2009).

TABLE 8. Postoperative Results

	2004 *n* (%)	1999 *n* (%)	1994 *n* (%)
Total	11,663 (100.0)	13,344 (100.0)	7393 (100.0)
Postoperative complications (grade > 3)			
+	523 (4.5)	1422 (10.7)	NA
−	11,140 (95.5)	11,913 (89.3)	NA
Unknown	0 (0.0)	9 (0.1)	NA
Causes of death			
Operative death (<30 d)	48 (0.4)	123 (0.9)	101 (1.4)
Hospital death (≥30 d)	46 (0.4)	146 (1.1)	122 (1.7)
Original cancer	2459 (21.1)	3397 (25.4)	2635 (35.6)
Other cancer	215 (1.8)	183 (1.4)	124 (1.7)
Other disease	570 (4.9)	680 (5.1)	461 (6.2)
Unknown	87 (0.7)	169 (2.3)	272 (1.9)

NA, not assessed.

Alteration of tumor size may also have contributed to survival in the JJCLCR registry. Tumor size itself is a prognostic factor, as that less than 2.0 cm was reported to be an indicator of good survival in N0M0 patients in the International Association for the Study of Lung Cancer staging project presented in 2007, in which the 5-YSR was 77%.[14] Thus, a tumor sized less than 2.0 cm is classified as T1a in UICC-TNM ver. 7 (2009).[6] In the current Japanese registry of surgical cases treated in 2004, pathological findings showed that the ratio of tumors sized less than 2.0 cm was 36.9% and that of those less than 1.0 cm in size was 9.1%, which indicated a gradual increase from 1994 and might be attributable to recent widespread use of computed tomography in Japan.[15]

In our study, the percentage of patients older than 70 years gradually increased from 1994. The 5-YSR of those aged patients was worse than that of younger patients.[3,7] However, the 5-YSR of aged patients is improving,[7] while their number has been estimated to increase in the future.[16] The contribution of those changes to the prognosis of patients with lung cancer who undergo surgery must be carefully watched.

Regardless of the increasing number of patients older than 70 years, the postoperative mortality and morbidity rates improved in the recent registry of surgical cases in Japan. This improvement may be related to the increase in cases of small-sized early-stage lung cancer, which can be treated by less invasive surgery. Furthermore, the decrease in percentage of postoperative deaths may also contribute to the recent trend of good survival.

The results of the current registry of surgical cases treated in 2004 in Japan include data from selected educational hospitals that participated in the registry. However, clinical diagnosis methods have recently changed, including widespread use of PET-CT, thus selection bias and "Will Rogers phenomenon" should be considered. Nevertheless, the data presented here provide an important reference source, as a large number of patients were registered and analyzed.

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Surgical Outcome of Stage IIIA- cN2/pN2 Non–Small-Cell Lung Cancer Patients in Japanese Lung Cancer Registry Study in 2004

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Background: The role of surgery in the treatment of non–small-cell lung cancer (NSCLC) with clinically manifested mediastinal node metastasis is controversial even in resectable cases because it is often accompanied by systemic micrometastasis. However, surgery is occasionally indicated for cases with single-station N2 disease or within multimodal treatment regimens, and in clinical trials. The aim of this study is to evaluate surgical outcomes in a modern cohort of patients with clinical (c-) stage IIIA-N2 NSCLC whose nodal metastasis was confirmed by pathology (cN2/pN2).

Methods: From the central database of lung cancer patients undergoing surgery in 2004, which was founded by the Japanese Joint Committee for Lung Cancer Registration, data of patients having all conditions of NSCLC, c-stage IIIA, cN2, and pN2 were extracted, and the clinicopathologic profile of patients and surgical outcomes were evaluated.

Results: Among 11,663 registered NSCLC cases, 436 patients (3.8%) (332 men and 104 women) had been extracted. Their mean age was 65 years, and histologic types included adenocarcinoma (n = 246), squamous cell carcinoma (n = 132), and others (n = 58). The proportion of R0 resection was 82.5% and the proportion of the hospital deaths among the cause of death was 2.3%. The 5-year survival rate was 30.1% for the selected group of patients. The postoperative prognosis was significantly better than those of corresponding populations extracted from the 1994 ($p = 0.0001$) and 1999 databases ($p = 0.0411$). Men and women experienced a significantly different survival outcome ($p = 0.025$) with 5-year survivals of 27.5% and 37.8%, respectively. Single-station N2 cases occupied 60.9 % of the cohort and showed a significantly better prognosis than multistation N2 ($p = 0.0053$, 35.8 % versus 22.0 % survival rate at 5 years).

Conclusions: The surgical outcomes of c-stage IIIA-cN2/pN2 NSCLC patients in 2004 were favorable in comparison with those ever reported.

Key Words: Non–small-cell lung cancer, Mediastinal node metastasis, Surgery.

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Surgery is not a generally accepted option for non–small-cell lung cancer (NSCLC) patients with clinically manifested mediastinal lymph node metastasis (cN2/pN2), because the presence of N2 metastasis is believed to be indicative of systemic disease. In reports published in the 1980s through the early 1990s,[1–4] surgery for c-stage IIIA-N2 often failed to result in local control and was often followed by early appearance of distant metastasis, even after complete resection. Since the 1990s, numerous researchers have reported clinical trials of induction chemotherapy or chemoradiotherapy followed by surgery[5–8]; however, the role of surgery in the treatment strategy for the disease is still controversial. A recent large-scale trial, the North American Intergroup Trial 0139,[9] demonstrated that surgery after induction chemoradiotherapy can be beneficial if lobectomy is adequate for complete resection, although overall survival (the primary end point) in the trimodal regimen group was equivalent to that in the chemoradiotherapy group. Adjuvant chemotherapy is another potential option; however, whether cN2/pN2 cases derive the same

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survival benefit from adjuvant chemotherapy as that reported for cN0-1pN2 cases has not yet been clarified.[10,11]

In Japan, a nationwide database has been managed by the Japanese Joint Committee of Lung Cancer Registration since 1989. Annual surgical series are collected at 5-year intervals, and surgical outcomes have been analyzed and reported.[12–14] Since then, there has been an increase in the proportions of patients who are women, have stage IA disease and adenocarcinoma, and 5-year survival rates have gradually improved from 52.6% in 1994,[12] to 61.8% in 1999,[13] and to 69.7% in 2004.[14] Such results clearly indicate that the clinical profile of lung cancers is dramatically changing in Japan. If so, and even if progress in radiological work-up biases candidates for surgery, the surgical outcomes of a modern series of c-stage IIIA-cN2/pN2 NSCLC patients should be reevaluated. In this study, stage III NSCLC patients with clinically manifested and pathologically proven N2 were collected from a nationwide registry data of resected lung cancer in Japan, and retrospectively investigated.

PATIENTS AND METHODS

Patients

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective survey for primary lung neoplasms resected in 2004. Data from 11,663 patients who were followed up for 5 years were registered from 253 teaching hospitals. Of these patients, data from those with all conditions of histologically confirmed NSCLC, c-stage IIIA, cN2, and pN2 were extracted from the master database, and the clinicopathologic profiles of patients and surgical outcomes were evaluated. In addition, the data were compared to those of similar populations from the 1994 and 1999 databases. The c-stage and p-stage were determined according to the 6th edition of the Union Internationale Contre le Cancer-TNM staging system,[15] and tumor histology was categorized according to the World Health Organization Classification.[16] A number of mediastinal node stations where metastases were recognized by surgical pathology were classified as single- or multistation. Each nodal station was determined according to Naruke's map.[17]

Statistical Analysis

Differences in clinicopathologic demographic variables were evaluated by the χ^2 test or Fisher's exact test as appropriate. The survival time was defined as time from the date of surgery to the date of the last follow-up. The survival curves were estimated by the Kaplan-Meier method. Differences in survival were assessed by the log-rank test. A multivariate analysis for prognostic factors was performed by the Cox proportional hazards regression model. Statistical significance was considered to be established when the associated p-value was less than 0.05.

TABLE 1. Demographic Data of c-stage IIIA-cN2/pN2 Patients

Category	Number of Patients (%)		
Year of Registry	**2004**	**1999**	**1994**
Total	436 (100)	823 (100)	580 (100)
Sex			
Male	332 (76.1)	633 (78.0)	438 (75.5)
Female	104 (23.9)	179 (21.7)	141 (24.3)
Unknown		11	1
Age (yrs)			
59	107 (24.7)	214 (26.0)[a]	167 (28.8)[b]
60–69	152 (34.9)	321 (39.0)	225 (38.8)
70–79	156 (35.8)	249 (30.3)	179 (30.9)
80	21 (4.8)	21 (2.6)	8 (1.4)
Unknown		18	1
Histologic type			
Adeno	246 (56.4)	458 (55.7)[a]	291 (50.2)[b]
Squ.	132 (30.2)	290 (35.2)	232 (40.0)
Other	58 (13.3)	75 (9.1)	57 (9.8)
cT-factor			
T1	137 (31.4)	183 (22.2)[b]	112 (19.3)[b]
T2	226 (51.8)	490 (59.5)	349 (60.2)
T3	73 (16.7)	150 (18.2)	119 (20.5)
pT-factor			
T0-1	116 (26.6)	161 (25.0)[a]	98 (17.0)[b]
T2	203 (46.6)	410 (49.8)	286 (49.6)
T3	68 (15.6)	118 (14.3)	92 (15.9)
T4	49 (11.2)	123 (14.9)	101 (17.5)
Unknown			3
Type of surgery			
Pn.	46 (10.6)	115 (14.0)[b]	114 (19.8)[b]
Lob./bilob.	332 (76.1)	656 (80.6)	442 (76.7)
Sublob.	30 (6.9)	41 (5.0)	20 (3.4)
Other	28 (6.4)[c]	2 (0.2)	0 (0.0)
Unknown		11	4
Residual disease			
R0	353 (82.5)	661 (80.3)	443 (77.4)
R1/2	75 (17.5)	130 (19.7)	120 (21.0)
Unknown	8	32	17
Perioperative treatment			
Induction	108 (24.8)[d]	141 (17.4)	53 (9.1)
Adjuvant[e]	151 (34.6)	—	—
None	137 (31.4)	—	—
Cause of death			
All	278 (63.8)	539 (65.5)	446 (76.9)
Hospital	10 (2.3)	30 (3.6)	32 (5.5)
Lung cancer	241 (55.3)	445 (54.1)	366 (63.1)
Other	27 (6.2)[f]	59 (7.2)	43 (7.3)

[a]Statistically significant difference ($p < 0.05$) compared to 2004.
[b]Statistically significant difference ($p < 0.01$) compared to 2004.
[c]Includes 20 exploratory thoracotomies.
[d]Eighty-four patients received chemotherapy, 23 received chemoradiotherapy, and 1 received other radiotherapy.
[e]Thirty-eight patients received oral chemotherapy.
[f]Includes deaths related to other cancers (n = 7), deaths related to noncancerous disease (n = 18), and deaths with unknown causes (n = 2).

RESULTS

Patient Profiles

Among 11,663 registered lung cancer patients, 800 cases of c-stage IIIA/ cN2/NSCLC were included. Of them, p-N0, 1, 2, and 3 were 271, 75, 436, and 18 patients, respectively, and the 436 cN2/pN2 patients were analyzed in this study. Patients with single- and multistation N2 were 235 and 151, respectively, and no information was available in the other 34. Demographic data for the patients are summarized in Table 1. These patients represented 3.8% of all 11,423 NSCLC patients in the 2004 registry, and comprised 332 men and 104 women. The mean age was 65.0 years, and 40.6% of patients were 70 years old or more. Histologic types include adenocarcinoma (n = 246), squamous cell carcinoma (n = 132), large cell carcinoma (n = 23), adenosquamous cell carcinoma (n = 17), and others (n = 18). Induction treatments such as chemotherapy and chemoradiotherapy were administered to 108 patients (24.8%), and adjuvant chemotherapy including oral tegafur/ uracil was given to 151 patients (34.6%). Surgical procedures included pneumonectomy (n = 46), lobectomy/bilobectomy (n = 332), sublobar resection (n = 30), and exploratory thoracotomy (n = 20); R0 surgery was achieved in 361 patients (82.5%). Overall, 278 patients died during the 5-year follow-up period. Of these, 10 deaths (2.3%) occurred in the hospital after surgery and 6 deaths (1.4%) occurred within 30 days after surgery. Patient profiles were compared to those of patients with the same disease stage from previous registry data (Table 1). A total of 540 and 823 patients were collected from the 1994 and 1999 databases, respectively, which represented 6.5% and 8.7% of the entire registry population, respectively. The 2004 cohort was characterized by a larger proportion of adenocarcinoma, more advanced age, less advanced clinical and pathologic T factors, and less pneumonectomy. In fact, the proportion of patients who underwent pneumonectomy in 2004 was almost half that of 1994. The R0 surgery rate tended to increase, but not to a statistically significant degree. Although statistical analysis could not be performed for "perioperative treatment" because adjuvant chemotherapy data were not collected until 1999, the proportion of patients who underwent induction treatment tended to increase.

Survival

The overall 5-year survival rate in the 2004 cohort was 30.1%, whereas that of 1994 and 1999 was 19.9% and 24.5%, respectively. When the survival curves were compared, the 2004 cohort was significantly better than the 1994 (p = 0.0001) and 1999 cohorts (p = 0.0411) (Fig. 1). The 5-year survival rates were 33.4% in 353 patients with R0 surgery, 21.7% in 24 patients with R1 surgery, and 0.0% in 51 patients with R2 surgery. The differences in survival between the R1 group and R2 groups and also between the R0 and R2 groups were statistically significant (p = 0.0098 and $p < 0.0001$, respectively), whereas no significant difference was found between the R0 and R1 groups (p = 0.6423) (Fig. 2*A*). The 5-year survival rate was for 27.5% for men was and 37.8% for women. The survival experience was significantly better for women than for men (p = 0.025) (Fig. 2*B*). As to the number of metastasized stations, there was a significant difference between single-station and multistation N2 patients (p = 0.0053) with the respective 5-year survival rates being 35.8% and 22.0% (Fig. 2*C*). Five-year survival rates were 28.1% in 105 patients who received induction treatment, 27.8% in 150 patients who received adjuvant chemotherapy, and 33.7% in 137 patients who underwent surgery alone.

DISCUSSION

Surgery is rarely indicated initially for c-stage IIIA-N2 NSCLC, because the disease is predisposed to possess serious local tumor burden and latent systemic disease. Surgery for cN2/pN2 resulted in a 5-year survival rate of approximately 10% 20 to 30 years ago[1,2] (Table 2). Reasons for this unfavorable prognosis included a high incidence of incomplete resection because of malignant pleurisy or extra nodal invasion, and of early recurrence in distant organs; 5-year survival was only 20% even in cases of complete resection.[3,4] Currently, many clinicians regard concurrent chemoradiotherapy as a standard care for resectable c-stage IIIA-N2 NSCLC, because a 20% 5-year survival rate has been achieved even for unresectable cases.[18,19] In our analysis of the 2004 nationwide registry, however, the outcome of 137 patients who underwent surgery alone showed 34% 5-year survival rate, which is more favorable in comparison with those of the early studies[1–4] or comparable to those of combined modalities[5–9] (Table 2). Although retrospectively analyzed, the present data are important as they reflect modern surgery results for cN2/pN2 NSCLC. One possible explanation for the above results is that selection of surgical candidate would have been sophisticated. The 2004 cohort was also characterized by less advanced T-parameter values and a smaller proportion of patients who underwent

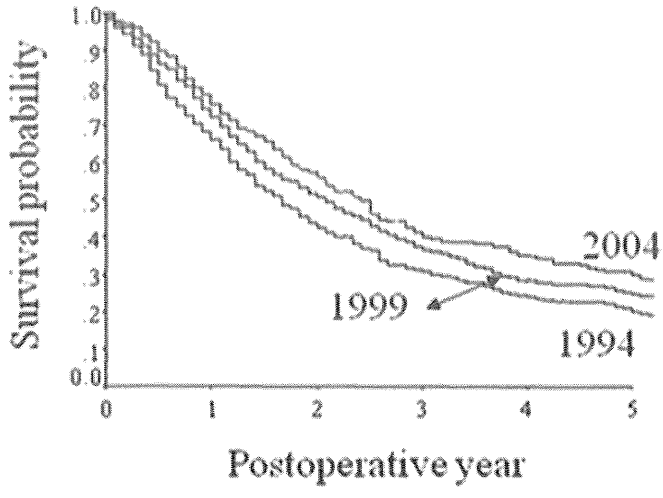

FIGURE 1. Survival curves for c-stage N2/pN2 non–small-cell lung cancer patients collected from the Japanese Lung Cancer Registry in 1994, 1999, and 2004. The postoperative 5-year survival rates of 554 patients in 1994, 823 patients in 1999, and 436 patients in 2004 were 19.9%, 24.5%, and 30.1%, respectively. Significant differences were observed between each series by log-rank test; p values were 0.0063 between 1994 and 1999, <0.0001 between 1994 and 2004, and 0.0411 between 1999 and 2004.

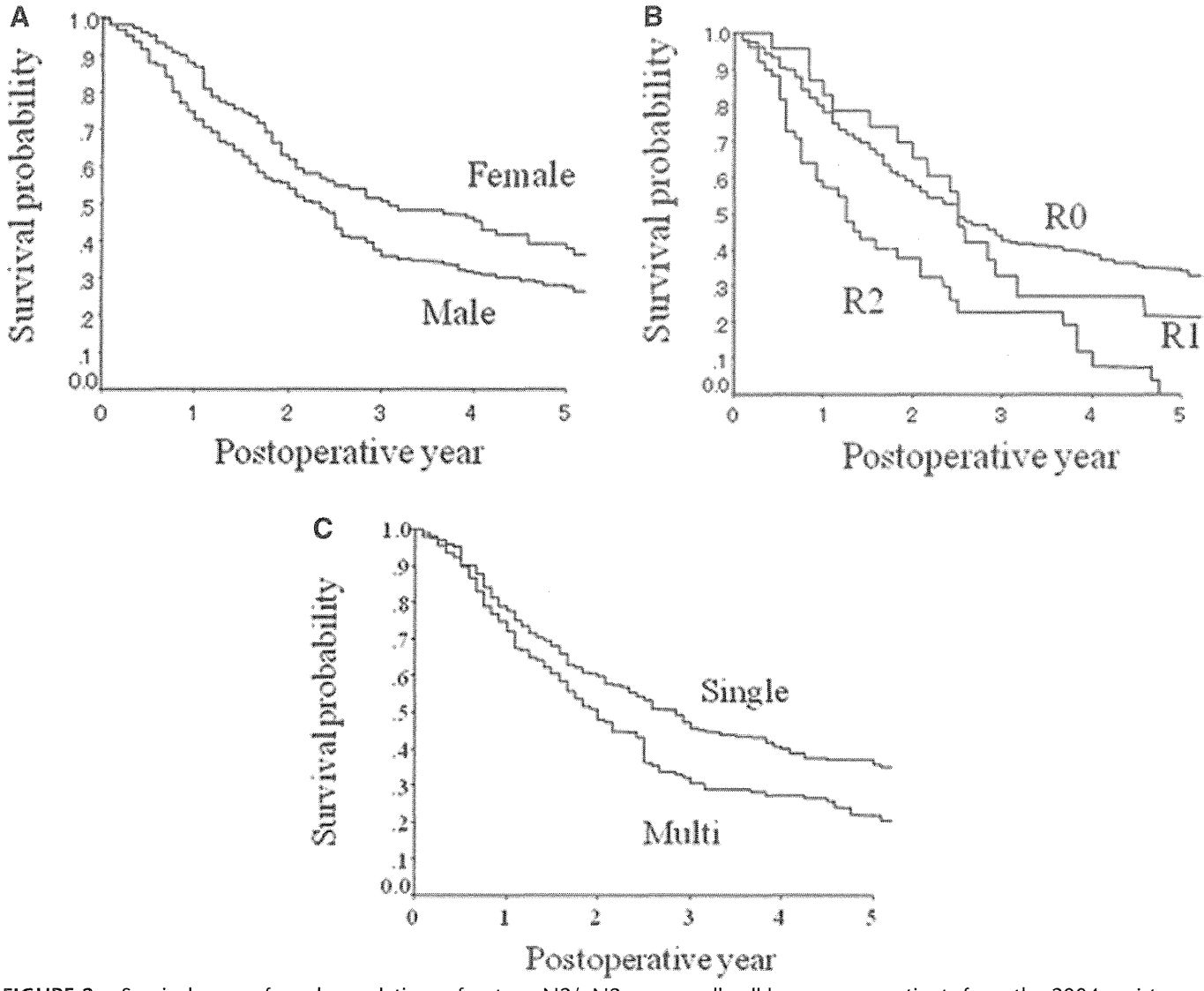

FIGURE 2. Survival curves for subpopulations of c-stage N2/pN2 non–small-cell lung cancer patients from the 2004 registry. *A*, Male and female survival curves. The 5-year survival rates were 27.5% in 324 males and 37.8% in 104 females; this difference was statistically significant ($p = 0.0245$). *B*, Subpopulations categorized by level of residual disease. The 5-year survival rates were 33.4% in 353 R0 patients, 21.7% in 24 R1 patients, and 0.0% in 51 R2 patients; the differences between R1 patients and R2 ($p = 0.0098$) and between R0 and R2 patients ($p < 0.0001$) were statistically significant, whereas no significant difference was observed between R0 and R1 patients ($p = 0.6423$). *C*, Single- and multistations N2. The 5-year survival rates were 35.8% in 235 patients with single-station N2 and 22.0% in 151 with multistation N2; this difference was statistically significant ($p = 0.0053$).

pneumonectomy. In 2004, 10.4% of the patients underwent pneumonectomy, compared to 14.0% in 1999 and 20.0% in 1994; thus, it seems that even among cN2/pN2 cases, less advanced cases were selected for surgery. The decreased rate of pneumonectomy may result in decreased hospital mortality. Actually, the series of the Japanese nationwide registry clearly revealed a time trend for improved survival of the stage IIIA-cN2/pN2 disease (Fig. 1). Several types of N2 cases, such as single-station or single-node N2 cases, have experienced a good prognosis after surgery.[20,21] The Japan Clinical Oncology Group conducted a questionnaire study regarding outcomes in stage IIIA-pN2 patients who underwent complete resection from 1992 to 1993.[21] Five-year survival rates were 31% for all pN2 cases, 27% for cN2 cases, and 43% for single-station N2 cases. In our series, the 5-year survival rate of single-station pN2 was also significantly higher than that of multistation pN2, and a proportion of single-station pN2 was 61 % in this study that was relatively higher than 52 % of the Japan Clinical Oncology Group study, which suggests that such a single-station N2 was likely to be selected for surgery in Japan of 2004.

Increase of adenocarcinoma may be another reason for the surgical results because the histology is associated with favorable prognosis.[13,14] Thus, recent cN2/pN2 NSCLC

TABLE 2. Historical Profile of Surgical Results for cN2/pN2 NSCLC

Report	Dates	Combined Modality	Number of Patients	Rate of R0 (%)	Rate of 5-year Survival (%)
Pearson et al.[1]	1964–1980	Induction R.	79	65	9
Martini and Flehinger[2]	1974–1981	Adjuvant R	179 (only CR)	—	18
Funatsu et al.[4]	1970–1989	S alone	91[a]	14	6
Watanabe et al.[3]	1980–1990	S alone	106[a]	50	16
Roth et al.[5]	1987–1993	Induction C	28	61	56 (at 3 years)
		S alone	30	66	19 (at 3 years)
Rosell et al.[6]	1989–1991	Induction C	30	85	25 (at 2 years)
		Adjuvant R	30	90	0 (at 2 years)
Choi et al.[8]	1988–1995	Induction CR (R: twice daily)	42	81	37
Ichinose[21]	1992–1993	S alone or S first	164 (only CR)	—	27
Albain et al.[9]	1994–2001	Induction CR	202	71	27
		Definite CR	194		20
Uy et al.[25]	1997–2004	Induction CR	40	93	52 (at 3 years)
Present	2004	Various (all)	436	83	30
			Single 235		36
			Multi151		22
		Adjuvant C	151		28
		Induction C/CR	108		28
		S alone	137		34

[a]Cases with exploratory thoracotomy were excluded from the study.
R, Radiation; C, chemotherapy; S, surgery; CR, chemoradiation; Single, single-station N2; Multi, multistation N2; NSCLC, non–small-cell lung cancer.

patients who undergo surgery are distinct from the cN2/pN2 NSCLC population of previous decades. Often, improvements in diagnostic facilities outpace changes in treatment outcomes, and such a transition of the medical environment may always influence the changes in patient selection and characteristics.

With respect to surgery alone, the present data are much valuable because cN2/pN2 is now usually contraindicated for surgery alone and the surgical outcome of modern series has been rarely presented. In our study, data of 137 patients with stage IIIA-cN2/pN2 patients treated by surgery alone in the particular period (2004) were retrospectively collected from the large-scale registry, and the relatively favorable outcome was revealed. Although the detailed reasons for surgical indication was unknown, they might be highly selected or might have unusual surgical indication because these cases only represented 1.2% of all resected NSCLC cases; therefore, surgery alone cannot yet be recommended as a treatment option in practice.

Although the prognosis of patients in the present study was superior to those previously reported, it remains unsatisfactory, especially considering that the majority of the patients underwent perioperative therapies. Whether or not induction therapy followed by surgery provides a survival benefit for resectable cN2/pN2 NSCLC patients has been the focus of much attention. Two meta-analyses of induction chemotherapy reported[22,23] demonstrated significance or tendency of favor of induction chemotherapy for stage III NSCLC; however, those analyses included two controversial studies. In the randomized trials conducted in the 1990s,[5,6] there was significant efficacy of neoadjuvant platinum-based chemotherapy in this patient population (Table 2); however, the results have not been widely accepted because of far lower survival of patients in the surgery-alone groups. Concurrent chemoradiotherapy as induction has been expected to be a more promising strategy for fit cases[7,8,24] (Table 2). Compared to chemotherapy, chemoradiotherapy results in better local control and a higher incidence of downstaging, which is a strong indicator of efficacy. In the present series, induction therapy was administered to 108 patients (24.8%), 84 of whom received chemotherapy and 23 received chemoradiotherapy; however, survival of these patients was equivalent to that of patients who underwent surgery alone. These results may be explained by the fact that the downstaged cases were automatically excluded from the present cohort through the retrospective selection of cN2/pN2 cases, and may also show that survival benefit of induction therapies was hardly recognized in non-downstaged cases. Taking into account that the indication of induction treatments could not be clarified in this retrospective study, no conclusion can be drawn for this issue.

The North America Intergroup Trial 0139, which compared concurrent chemoradiation followed by surgery (trimodal therapy) versus definitive chemoradiation (bimodal therapy) for resectable c-stage IIIA-N2 cases,[9] importantly revealed that no difference in overall survival occurred between the two treatment arms, although patients in the trimodal-therapy arm experienced superior recurrence-free survival. However, in a retrospective matched-cohort analysis, trimodal-therapy patients who underwent lobectomy experienced significantly better survival than bimodal-therapy patients who were selected by matching age, sex, performance status, and cT factor; thus, trimodal therapy was suggested to be effective for fit patients. Uy et al.[25] reported that in a study in which 40 out of 550 c-stage IIIA-N2 referrals received trimodal therapy in a community practice using the same regimen as that used in the North America Intergroup Trial 0139 (cisplatin/etoposide/45 Gy), the R0 resection rate was 92.5% and the 3-year overall

and disease-free survival rates both exceeded 50%. The above results indicate that induction treatments with chemoradiation could enhance the role of surgery for the disease if patients are properly selected.

Recent clinical trials have revealed that adjuvant cisplatin doublets increase postoperative 5-year survival rates by 15% in postoperative stage IIIA-N2 NSCLC cases[10,11]; however, no information regarding the c-stage of such cases was reported. In the present study, 151 patients who received adjuvant chemotherapy experienced a survival rate similar to the 137 patients who underwent surgery alone. In this retrospective study, however, indication of adjuvant therapy was not clarified for each case; hence, no conclusions about the efficacy of adjuvant therapy for c-stage IIIA-cN2/pN2 were determined.

Despite several limitations, this large nationwide database study has demonstrated the finding of a modern surgical outcome for selected patients with stage IIIA-cN2/pN2 NSCLC, and that the postoperative survival was favorable in comparison with those previously reported.

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