European Journal of Surgical Oncology 45 (2019) 838–844

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Lung squamous cell carcinoma: A postoperative recurrence analysis of keratinizing and nonkeratinizing subtypes

Rongrong Chen [a], Xiaohua Yang [b], Zhengping Ding [a], Lei Zhu [c], Shun Lu [a, **], Yongfeng Yu [a, *]

[a] Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West HuaihaiRoad, Xuhui District, Shanghai 200030, China
[b] Central Laboratory, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West HuaihaiRoad, Xuhui District, Shanghai 200030, China
[c] Department of Pathology, Shanghai Chest Hospital, Shanghai Jiao Tong University, 241 West Huaihai Road, Xuhui District, Shanghai 200030, China

ARTICLE INFO

Article history:
Received 11 July 2018
Received in revised form
21 September 2018
Accepted 24 October 2018
Available online 28 October 2018

Keywords:
Lung squamous cell carcinoma
Keratinizing
Nonkeratinizing
Recurrence

ABSTRACT

Background: There is currently no definite clinical implication for the subtypes of lung squamous cell carcinoma according to the 2015 WHO classification. This study aimed to investigate postoperative recurrence of the two major subtypes of lung squamous cell carcinoma: keratinizing squamous cell carcinoma (KSCC) and nonkeratinizing squamous cell carcinoma (NKSCC).

Methods: We identified the patients with KSCC and NKSCC who had undergone complete resection in Shanghai Chest Hospital between April 2015 and June 2016. Disease-free survival (DFS) was compared using Kaplan-Meier statistical analysis. Variables selected by univariate analysis were evaluated in multivariate analysis using the Cox proportional hazard model.

Results: A total of 334 patients included 231 (69.2%) cases with KSCC and 103 (30.8%) cases with NKSCC. There were more smokers in keratinizing than nonkeratinizing subtype (84.8% versus 72.8%, $p = 0.009$). The percentage of stage III was higher in NKSCC than that in KSCC (35% versus 22.9%, $p = 0.012$). The 2-year DFS rates of stage I, stage II and stage III were 90.1%, 66.4% and 37.7% in KSCC, 83.3%, 67.7% and 52.8% in NKSCC, respectively. There were no significant differences of 2-year DFS rates between KSCC and NKSCC. Furthermore, KSCC and NKSCC had no significant differences in recurrence patterns and metastatic sites.

Conclusion: There were no significant differences of postoperative recurrence between KSCC and NKSCC.

Introduction

Non–small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Lung adenocarcinoma and squamous cell carcinoma are the most frequent histologic subtypes, accounting for 50% and 30% of NSCLC cases, respectively [1]. Complete resection is a cornerstone of the management of localized NSCLC. However, 30–60% of the patients with stage IIor III disease who have undergone resection experience recurrence and may ultimately die from disease progression [2–4]. Even if the patients with stage I NSCLC after surgical resection have five-year survival rates of around 70% [5,6].

In recent years, NSCLC subtyping has been recognized as vital for patient management. Lung squamous cell cancer (LSCC), as a distinct clinical entity, is a particularly challenging disease to manage in clinical practices because of potential antiangiogenic-associated toxicity [7], and limited pemetrexed sensitivity [8], and decreased frequency of response to epidermal growth factor receptor (EGFR) inhibitors [9,10]. Discontinued the classification of papillary carcinoma, clear cell carcinoma and small cell variant of squamous cell carcinoma, the subtyping of lung squamous cell carcinoma was modified to incorporate keratinizing, nonkeratinizing, and basaloid subtypes in the 2015 classification scheme of World Health Organization (WHO) [11]. However, there is currently no definite clinical implication for the new subtyping of lung squamous cell carcinoma.

In this study, we investigated postoperative recurrence of the two major subtypes of lung squamous cell carcinoma: keratinizing squamous cell carcinoma (KSCC) and nonkeratinizing squamous cell carcinoma (NKSCC).

* Corresponding author.
** Corresponding author.
E-mail addresses: shunlu@sjtu.edu.cn (S. Lu), yuyongfeng212@126.com (Y. Yu).

https://doi.org/10.1016/j.ejso.2018.10.535
0748-7983/

Materials and methods

Patients and eligibility

Between April 2015 and June 2016, all consecutive cases of operable LSCC patients undergoing radical lobectomy or pneumonectomy in Shanghai Chest Hospital were subjected to retrospective review. Our inclusion criterion was a diagnosis of LSCC, with hematoxylin and & eosin–stained slides, and immunohistochemical slides available for pathologic review. Our exclusion criteria were positive resection margins (R1 or R2), less than 10 regional LNs resected [12] and pathological diagnosis of basaloid squamous cell carcinoma. Disease staging was based on the eighth edition TNM classification of NSCLC [3]. Histological typing was confirmed as LSCC according to the 2015 WHO classification [11]. After surgery, the patients with IIA-IIIA stage were recommended for adjuvant chemotherapy, and those with IIIA-N2 stage were recommended to receive postoperative chemoradiotherapy. This study was approved by the institutional review board of Shanghai Chest Hospital.

Histological evaluation

All these primary tumor samples were fixed in 10% neutral buffered formalin, embedded in paraffin and stained with hematoxylin and eosin in the routine manner. The average number of slides from each case reviewed in the present study was 10 (range 4–26). Tumors were classified according to 2015 classification scheme of World Health Organization (WHO) of lung squamous cell carcinoma as keratinizing, nonkeratinizing, and basaloid subtypes [11]. Tumors are classified as keratinizing subtype if any amount of keratinization is present, and basaloid squamous cell carcinoma if basaloid component is greater than 50% of the tumor, regardless of the presence of any keratinization. NKSCC, in the absence of unequivocal keratinization, was detected by immunohistochemistry with positive squamous markers. The following factors were also investigated: visceral pleural invasion, lymphatic and vascular invasion.

Follow-up

Follow-up information was collected from the case records, electronic medical records, and telephonic conversation with patients or their relatives. Each patient was followed up for 2 years and followed up every three months. The date of last follow-up was June 30, 2018. The end point of study was recurrence after initial resection with curative intent. Diagnosis of recurrence was confirmed via biopsy, and imaging (positron emission tomography or brain magnetic resonance imaging or chest computed tomography) was performed to support the clinical diagnosis. In our cohort, 153 (45.8%) patients received the positron emission tomography (PET)before surgery. 62 (61.4%) patients received the PET scan when they experienced relapse. Recurrences were defined as followed [13]: local recurrence was defined by evidence of a tumor at the surgical margins. Regional recurrence was defined by evidence of a tumor in a second ipsilateral lobe, in the ipsilateral hilar lymph nodes (N1), or in the ipsilateral mediastinal lymph nodes (N2). Distant recurrence was defined by evidence of a tumor in the contralateral lung, in the contralateral mediastinal or ipsilateral supraclavicular lymph nodes (N3), or elsewhere outside the hemithorax [13].

Statistical analysis

Data were analyzed using SPSS 22.0 (IBM). Categorical variables were demonstrated as frequencies with percentages and were compared between the two groups using chi-square test or Fisher's exact test. DFS curves were generated using the Kaplan–Meier method, and a log-rank test was used for comparison. Variables selected by univariate analysis (p value less than 0.1) were evaluated in multivariate analysis using the Cox proportional hazard model. P values were two-sided and considered significant if less than 0.05.

Results

We identified all consecutive patients with resected lung cancer in Shanghai Chest Hospital between April 2015 and June 2016. A total of 481 patients had lung squamous cell carcinoma. We excluded 16 patients undergoing sublobar resection, 17 patients with positive surgical margins, 57 patients who had less than 10 regional LNs resected, 18 patients with basaloid squamous cell carcinoma, 39 patients failed to follow up, leaving a final cohort of 334 patients with pathological diagnoses of keratinizing squamous cell carcinoma and nonkeratinizing squamous cell carcinoma. Eight patients died of other causes during follow-up.

A total of 334 patients included 231 (69.2%) cases with KSCC and 103 (30.8%) cases with NKSCC. Smokers accounted for 271/334 (81.1%) of all patients. There were more smokers in keratinizing subtype than nonkeratinizing subtype (84.8% versus 72.8%, $p = 0.009$). The percentage of stage III was higher in NKSCC than that in KSCC (35% versus 22.9%, $p = 0.012$). No significant relationship existed between pathological subtypes and other characteristics (Table 1). The representative pathological images of KSCC and NKSCC in this cohort were shown in Fig 1.

Of the 334 patients identified, 109 (32.6%) experienced recurrence in two years. On univariable analysis, smoking history ($p = 0.008$), pneumonectomy ($p = 0.022$), higher pathological stage

Table 1
Relationship between clinicopathologic characteristics and lung keratinizing/nonkeratinizing squamous cell carcinoma subtypes.

Characteristic	No. (%)	KSCC	NKSCC	P value
All patients	334	231 (69.2)	103 (30.8)	
Age				0.557
≤60	138 (41.3)	93 (40.3)	45 (43.7)	
>60	196 (58.7)	138 (59.7)	58 (56.3)	
Sex				0.108
Female	19 (5.7)	10 (4.3)	9 (8.7)	
Male	315 (94.3)	221 (95.7)	94 (91.3)	
Smoking history				0.009
Never	63 (18.9)	35 (15.2)	28 (27.2)	
Ever	271 (81.1)	196 (84.8)	75 (72.8)	
Surgical procedure				0.078
Lobectomy	304 (91.0)	206 (89.2)	98 (95.1)	
pneumonectomy	30 (9.0)	25 (10.8)	5 (4.9)	
Pathologic stage				0.012
I	107 (32.0)	71 (30.7)	36 (35.0)	
II	138 (41.3)	107 (46.3)	31 (30.1)	
III	89 (26.6)	53 (22.9)	36 (35.0)	
Location type				0.277
Central	231 (69.2)	164 (71.0)	67 (65.0)	
Peripheral	103 (30.8)	67 (29.0)	36 (35.0)	
Lymphovascular invasion				0.343
Yes	17 (5.1)	10 (4.3)	7 (6.8)	
No	317 (94.9)	221 (95.7)	96 (93.2)	
Visceral pleural invasion				0.116
Yes	73 (21.9)	45 (19.5)	28 (27.2)	
No	261 (78.1)	186 (80.5)	75 (72.8)	
Tumor location				0.860
Right lobe	184 (55.1)	128 (55.4)	56 (54.4)	
Left lobe	150 (44.9)	103 (44.6)	47 (45.6)	

KSCC, keratinizing squamous cell carcinoma, NKSCC, nonkeratinizing squamous cell carcinoma.

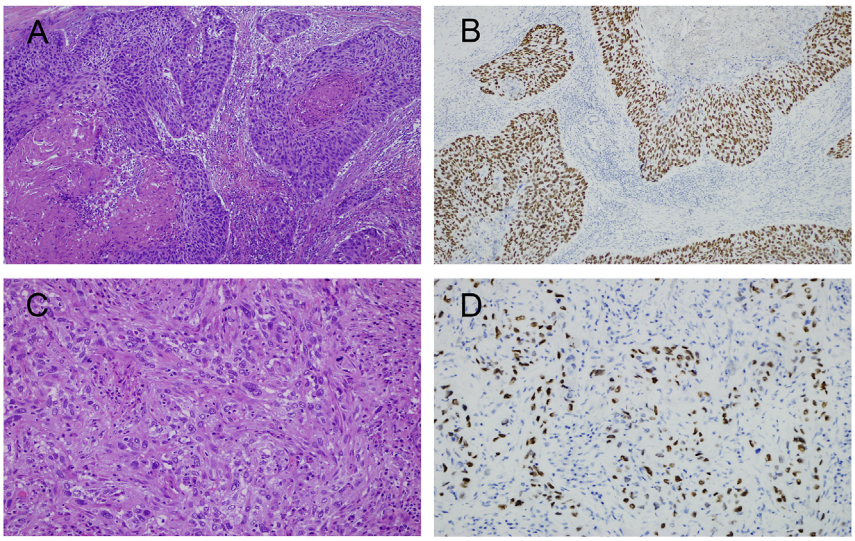

Fig. 1. Representative pathological images of KSCC and NKSCC. A, HE staining of KSCC. B, IHC result showed P40 positive in this patient with KSCC. C, HE staining of NKSCC. D, IHC result showed P40 positive in this patient with NKSCC.

(p = 0.000), lymphovascular invasion (p = 0.02) and visceral pleural invasion (p = 0.029) were correlated with a higher risk of recurrence for all patients; pneumonectomy (p = 0.018), higher pathological stage (p = 0.000), lymphovascular invasion (p = 0.049) and visceral pleural invasion (p = 0.012) were correlated with a higher risk of recurrence for the patients with KSCC; higher pathological stage (p = 0.000) was correlated with a higher risk of recurrence for the patients with NKSCC (Table 2). Multivariable analysis of primary tumor factors revealed that, smoking history (HR, 2.411; p = 0.006), pathological stageII (HR, 2.814; p = 0.001), and pathological stage III (HR, 5.596; p = 0.000) were significantly associated with higher risk of recurrence in all patients. Pathological stageII (HR, 3.722; p = 0.002), and pathological stage III(HR, 8.035; p = 0.000) were significantly associated with higher risk of recurrence for the patients with KSCC. Pathological stage III (HR, 3.825; p = 0.005) were significantly associated with higher risk of recurrence for the patients with NKSCC (Table 3).

The 2-year DFS rates of stage I, stage II and stage III were 87.9%, 66.7% and 43.8%, respectively (p = 0.000) (Fig 2A). The 2-year DFS rates of N0, N1 and N2 were 79.9%, 64.5% and 35.5%, respectively (p = 0.000) (Fig 2B). No differences in 2-year DFS rates of KSCC and NKSCC were observed in all patients (Fig 2C) and each pathologic stage (Fig. 2D–F). The further analyses based on treatment arm in

Table 2
Univariate analysis of DFS according to clinical factors.

Characteristic	Total		KSCC		NKSCC	
	2-Year DFS rate	P value	2-Year DFS rate	P value	2-Year DFS rate	P value
All patients	67.4	0.859	67.1		68.0	
Age		0.499		0.498		0.860
≤60	68.8		68.8		68.9	
>60	66.3		65.9		67.2	
Sex		0.645		0.117		NA
Female	73.7		50.0		100	
Male	67.0		67.9		64.9	
Smoking history		0.008		0.056		0.067
Never	82.5		82.9		82.1	
Ever	63.8		64.3		62.7	
Surgical procedure		0.022		0.018		0.753
Lobectomy	69.1		69.4		68.4	
pneumonectomy	50.0		48.0		60.0	
Pathologic stage		0.000		0.000		0.015
I	87.9		90.1		83.3	
II	66.7		66.4		67.7	
III	43.8		37.7		52.8	
Location type		0.063		0.129		0.295
Central	64.1		64.0		64.2	
Peripheral	74.8		74.6		75.0	
Lymphovascular invasion		0.02		0.049		0.195
Yes	41.2		40.0		42.9	
No	68.8		68.3		69.8	
Visceral pleural invasion		0.029		0.012		0.694
Yes	57.5		53.3		64.3	
No	70.1		70.4		69.3	

DFS, disease-free survival. KSCC, keratinizing squamous cell carcinoma, NKSCC, nonkeratinizing squamous cell carcinoma. NA: not applicable.

Table 3
Multivariate Cox proportional hazards model analyses of various factors affecting DFS.

Multivariate	Total		KSCC		NKSCC	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95%CI)	P value
Smoking history						
Never[a]						
Ever	2.411 (1.285–4.524)	0.006	2.088 (0.905–4.815)	0.084	2.615 (0.997–6.859)	0.051
Surgical procedure						
Lobectomy[a]						
pneumonectomy	1.194 (0.673–2.117)	0.544	1.181 (0.634–2.200)	0.601	NA	NA
Pathologic stage						
I[a]						
II	2.814 (1.502–5.271)	0.001	3.722 (1.647–8.413)	0.002	1.956 (0.708–5.403)	0.195
III	5.596 (2.890–10.837)	0.000	8.035 (3.404–18.964)	0.000	3.825 (1.503–9.738)	0.005
Location type						
Peripheral[a]						
Central	1.144 (0.701–1.866)	0.591	NA	NA	NA	NA
Lymphovascular invasion						
No[a]						
Yes	1.174 (0.595–2.316)	0.644	0.987 (0.414–2.357)	0.977	NA	NA
Visceral pleural invasion						
No[a]						
Yes	1.252 (0.784–1.999)	0.347	1.359 (0.803–2.301)	0.253	NA	NA

[a] Reference group, DFS, disease-free survival. NA: not applicable. KSCC, keratinizing squamous cell carcinoma, NKSCC, nonkeratinizing squamous cell carcinoma.

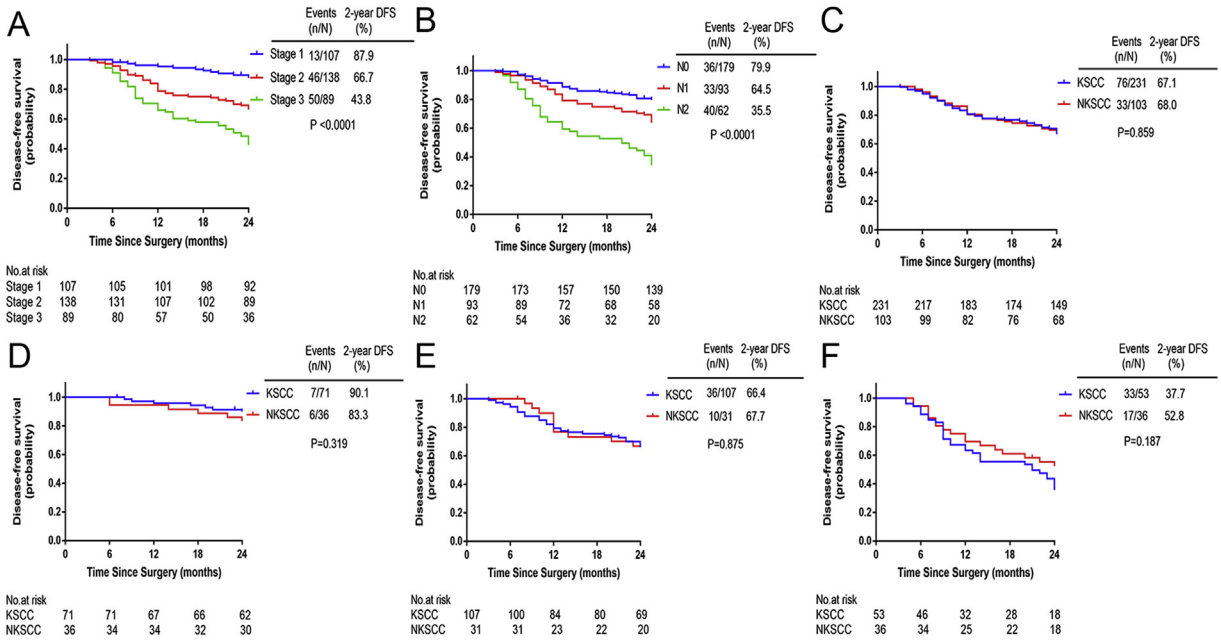

Fig. 2. 2-year disease-free survival (DFS) in this cohort. A, DFS based on pathologic stage. B, DFS based on lymph node involvement status. C, DFS based on histologic subtype. D, DFS of KSCC and NKSCC in stage I. E, DFS of KSCC and NKSCC in stage II. F, DFS of KSCC and NKSCC in stage III.

each pathologic stage showed that the 2-year DFS rate of NKSCC patients receiving adjuvant chemoradiotherapy in stage III was higher than that in KSCC patients (75% versus 30.8%, p = 0.049) (Fig 3G). All of 21 patients who received adjuvant chemoradiotherapy were treated with sequential chemoradiotherapy and the total dose of radiotherapy was 50.4 Gy, in 1.8 Gy per fraction. The chemotherapy regimens of them were vinorelbine plus cisplatin (seven cases), vinorelbine plus carboplatin (four cases), paclitaxel plus carboplatin (six cases), gemcitabine plus cisplatin (three cases) and gemcitabine plus carboplatin (one case), respectively. However, no differences in 2-year DFS rate were detected based on other treatment arms in each pathologic stage of KSCC and NKSCC (Fig. 3A–F).

Of the 109 patients who experienced relapse, 76 cases (69.7%) were KSCC and 33 cases (30.3%) were NKSCC. Among them, eight patients with recurrence did not have follow-up information, including five KSCC patients and three NKSCC patients. Analysis of recurrence patterns showed that 34.7% had locoregional recurrence, 34.6% had distant recurrence, and 30.6% had both. The proportions of intrathoracic metastasis and extrathoracic metastasis were 51.5% and 48.5%. The frequencies of single site recurrence and multiple sites recurrence were 48.5% and 51.5% respectively. The common metastatic sites were bone (24.8%), contralateral lung (20.8%), pleural effusion (19.8%), brain (11.9%), liver (9.9%), and adrenal (5.0%). KSCC and NKSCC had no significant differences in recurrence patterns and metastatic sites (Table 4).

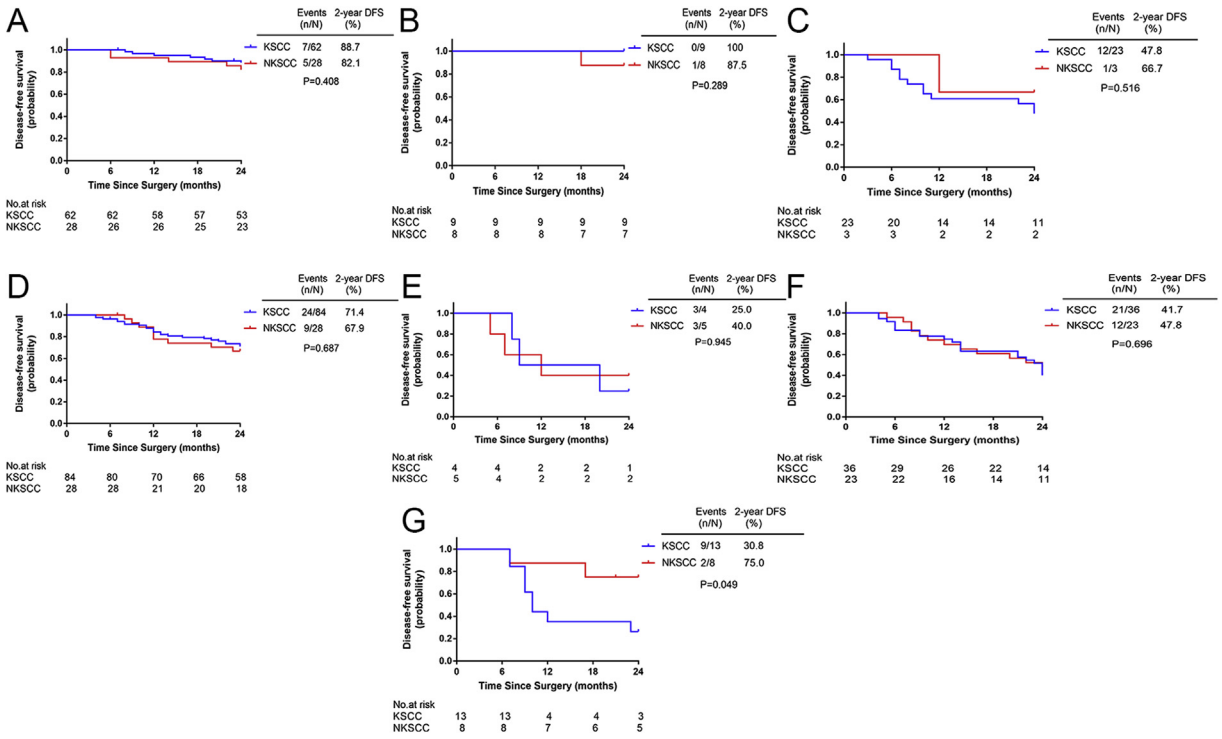

Fig. 3. 2-year disease-free survival (DFS) based on therapeutic regimen (adjuvant chemotherapy or adjuvant chemoradiotherapy vs observation) in each stage. A, DFS of KSCC and NKSCC receiving observation in stage I. B, DFS of KSCC and NKSCC receiving adjuvant chemotherapy in stage I. C, DFS of KSCC and NKSCC receiving observation in stage II. D, DFS of KSCC and NKSCC receiving adjuvant chemotherapy in stage II. E, DFS of KSCC and NKSCC receiving observation in stage III. F, DFS of KSCC and NKSCC receiving adjuvant chemotherapy in stage III. G, DFS of KSCC and NKSCC receiving adjuvant chemoradiotherapy in stage III.

Table 4
Recurrence patterns and metastatic sites of KSCC and NKSCC subtypes.

Variable	Total No. (%)	KSCC No. (%)	NKSCC No. (%)	P value
Total No. of patients	101 (100)	71 (70.3)	30 (29.7)	
Recurrence pattern				0.093
Locoregional	35 (34.7)	26 (36.6)	9 (30.0)	
Distant	35 (34.7)	20 (28.2)	15 (50.0)	
Both	31 (30.7)	25 (35.2)	6 (20.0)	
Recurrence pattern				0.529
Intrathoracic	52 (51.5)	38 (53.5)	14 (46.5)	
Extrathoracic	49 (48.5)	33 (46.7)	16 (53.3)	
Recurrence pattern				0.846
Single site	49 (48.5)	34 (47.9)	15 (50.0)	
Multiple site	52 (51.5)	37 (52.1)	15 (50.0)	
Bone metastasis				0.194
Absent	76 (75.2)	56 (78.9)	20 (66.7)	
Present	25 (24.8)	15 (21.1)	10 (33.3)	
Brain metastasis				1.000
Absent	89 (88.1)	63 (88.7)	26 (86.7)	
Present	12 (11.9)	8 (11.3)	4 (13.3)	
Contralateral lung metastasis				0.344
Absent	80 (79.2)	58 (81.7)	22 (73.3)	
Present	21 (20.8)	13 (18.3)	8 (26.7)	
Pleural effusion				0.289
Absent	81 (80.2)	55 (77.5)	26 (86.7)	
Present	20 (19.8)	16 (22.5)	4 (13.3)	
Adrenal metastasis				1.000
Absent	96 (95.0)	67 (94.4)	29 (96.7)	
Present	5 (5.0)	4 (5.6)	1 (3.3)	
Liver metastasis				1.000
Absent	91 (90.1)	64 (90.1)	27 (90.0)	
Present	10 (9.9)	7 (9.9)	3 (10.0)	

Note: Eight out of 109 relapsed patients did not have follow-up specific recurrence information, including 5 KSCC patients and 3 NKSCC patients.

Discussion

In the 2015 WHO classification, subtyping of lung squamous cell carcinoma was modified to incorporate keratinizing, non-keratinizing, and basaloid subtypes [11].To our knowledge, this was the first study to investigate postoperative recurrence of the two major subtypes of LSCC according to the new classification.

Tobacco smoking has been regarded as the most important risk factor for lung cancer. Toh et al.'s study showed that smoking was associated with a worse prognosis in NSCLC [14]. Sun et al.'s study also showed the similar results that never-smokers had a better prognosis than smokers in small cell lung cancer (SCLC) [15]. In this study, we found that smoking was an independent poor prognostic factor for DFS in LSCC patients. In addition, visceral pleural invasion and lymphovascular invasion were considered as poor factors of prognosis [16–20]. Our study showed that they were correlated with a higher risk of recurrence by univariable analysis. Takeda et al.'s study showed the 5-year-survival rate of the pneumonectomy group was lower than that of the sleeve lobectomy group [21].Our study also showed the pneumonectomy group correlated with a higher risk of recurrence by univariable analysis. The possible reason was that the patients who underwent pneumonectomies in clinical practice often had advanced stage, or heavy tumor burden.

To date, pathological stage of disease is considered as the most important prognostic factor [3,22]. The percentage of stage III was higher in NKSCC than that in KSCC. However, there were no differences of 2-year DFS rates between the two subtypes. Analyzing the two subtypes in each stage, we found that the trend of the DFS curves of KSCC and NKSCC from stage I to stage III was similar, and there were no significant differences between the two subtypes. Furthermore, we explored whether the differences existed based

on different treatments (adjuvant chemotherapy or adjuvant chemoradiotherapy versus observation) between the two subtypes in each stage. Up to date, postoperative radiotherapy (PORT) is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality [23]. In patients with pathologic stage N2 disease, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses. Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy [24–27]. The ongoing randomized European LungART trial (NCT00410683) will provide useful guidelines for PORT. However, in clinical practice, some patients give up postoperative radiotherapy. In this study, only 21 patients received postoperative radiotherapy in 62 patients with N2 disease. We found that the recurrence rate of NKSCC was significantly less than that of KSCC in the patients with stage III received adjuvant chemoradiotherapy. However, there was no significant difference in recurrence between KSCC and NKSCC patients who only received adjuvant chemotherapy. In 2015, the WHO classified lung squamous cell carcinoma as keratinizing, nonkeratinizing, and basaloid subtypes, similar to the Head and Neck WHO classification of nasopharyngeal carcinomas [28]. Radiotherapy is the standard of care for nasopharyngeal squamous cell carcinoma [29]. Reddy et al.'s study showed non-keratinizing carcinoma of the nasopharynx were more often controlled by ionizing radiation than keratinizing histology, and had better 5-year survival rate than keratinizing squamous cell carcinoma of the nasopharynx [30].The similar finding was also reported previously by Chan et al. [31] Vazquez et al.'s study showed when only patients who received radiation therapy were considered, overall survival was significantly higher for non-keratinizing carcinoma of the nasopharynx, and keratinizing carcinoma of the nasopharynx was associated with a nearly two-fold higher hazard of death [32]. Therefore, we suspect that postoperative radiotherapy may afford more benefits to the patients with pN2 NKSCC. This hypothesis needs large sample prospective studies to validate in future.

This study did not include statistical analysis of basaloid squamous cell carcinoma because of it was a rare histological subtype accounts for only 5% in our previous study [33]. Among 18 patients with pathological diagnosis of basaloid squamous cell carcinoma (BSCC), we followed up 17 cases. Among them, three patients (60%) in five cases with stage III had recurrence, two patients (33.3%) in six cases with stage II had recurrence, and one patient (16.7%) in six cases with stage I had recurrence.

However, there were still some inherent limitations in our study. The follow-up period was short because this study was based on the 2015 WHO classification scheme. On the other hand, the sample size of the current study was relatively small because this was a single-center study.

In conclusion, there were no significant differences of postoperative recurrence between KSCC and NKSCC. But in patients with pN2 diseases who received adjuvant chemoradiotherapy, the recurrence rate of NKSCC was lower than that of KSCC. Considering the sample size of patients who received adjuvant chemoradiotherapy was small, caution should be taken when drawing the conclusions.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgments

Author contributions: All the authors contributed to the design and coordination of the study and data collection, prepared the manuscript, and reviewed and approved the final version of the article.

Financial/nonfinancial disclosures: This work was supported by the National Key R&D Program of China (2016YFC1303300), the National Natural Science Foundation of China (81672272), the Key project of Shanghai Health & Family Planning (201540365), and Shanghai Municipal Science & Technology Commission Research Project (17431906103 to S. Lu and 16431903200 to Y. Yu).

References

[1] Perez-Moreno P, Brambilla E, Thomas R, Soria JC. Squamous cell carcinoma of the lung: molecular subtypes and therapeutic opportunities. Clin Canc Res 2012;18(9):2443–51.
[2] Andre F, Grunenwald D, Pignon J-P, et al. Survival of patients with resected N2 non–small-cell lung cancer: evidence for a subclassification and implications. J Clin Oncol 2000;18(16):2981–9.
[3] Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016;11(1):39–51.
[4] Wisnivesky JP, Smith CB, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study. BMJ 2011;343:d4013.
[5] Wisnivesky JP, Yankelevitz D, Henschke CI. The effect of tumor size on curability of stage I non-small cell lung cancers. Chest 2004;126(3):761–5.
[6] Ujiie H, Kadota K, Chaft JE, et al. Solid predominant histologic subtype in resected stage I lung adenocarcinoma is an independent predictor of early, extrathoracic, multisite recurrence and of poor postrecurrence survival. J Clin Oncol 2015;33(26):2877–84.
[7] Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. J Clin Oncol 2008;26(4):650–6.
[8] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3543–51.
[9] Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 2004;101(36):13306–11.
[10] Lee SY, Kim MJ, Jin G, et al. Somatic mutations in epidermal growth factor receptor signaling pathway genes in non-small cell lung cancers. J Thorac Oncol 2010;5(11):1734–40.
[11] Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10(9):1243–60.
[12] Ludwig MS, Goodman M, Miller DL, Johnstone PAS. Postoperative survival and the number of lymph nodes sampled during resection of node-negative non-small cell lung cancer. Chest 2005;128(3):1545–50.
[13] Nitadori J, Bograd AJ, Kadota K, et al. Impact of micropapillary histologic subtype in selecting limited resection vs lobectomy for lung adenocarcinoma of 2cm or smaller. J Natl Cancer Inst (Bethesda) 2013;105(16):1212–20.
[14] Toh CK, Gao F, Lim WT, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. J Clin Oncol 2006;24(15):2245–51.
[15] Sun JM, Choi YL, Ji JH, et al. Small-cell lung cancer detection in never-smokers: clinical characteristics and multigene mutation profiling using targeted next-generation sequencing. Ann Oncol 2015;26(1):161–6.
[16] Shimizu K, Yoshida J, Nagai K, et al. Visceral pleural invasion classification in non-small cell lung cancer: a proposal on the basis of outcome assessment. J Thorac Cardiovasc Surg 2004;127(6):1574–8.
[17] Manac'h D, Riquet M, Medioni J, Le Pimpec-Barthes F, Dujon A, Danel C. Visceral pleura invasion by non-small cell lung cancer: an underrated bad prognostic factor. Ann Thorac Surg 2001;71(4):1088–93.
[18] Yoshida J, Nagai K, Asamura H, et al. Visceral pleura invasion impact on non-small cell lung cancer patient survival: its implications for the forthcoming TNM staging based on a large-scale nation-wide database. J Thorac Oncol 2009;4(8):959–63.
[19] Mollberg NM, Bennette C, Howell E, Backhus L, Devine B, Ferguson MK. Lymphovascular invasion as a prognostic indicator in stage I non-small cell lung cancer: a systematic review and meta-analysis. Ann Thorac Surg 2014;97(3):965–71.
[20] Kuo SW, Chen JS, Huang PM, Hsu HH, Lai HS, Lee JM. Prognostic significance of histologic differentiation, carcinoembryonic antigen value, and lymphovascular invasion in stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2014;148(4):1200–7. e1203.
[21] Takeda S, Maeda H, Koma M, et al. Comparison of surgical results after pneumonectomy and sleeve lobectomy for non-small cell lung cancer: trends over time and 20-year institutional experience. Eur J Cardio Thorac Surg 2006;29(3):276–80.
[22] Ichinose Y, Yano T, Asoh H, Yokoyama H, Yoshino I, Katsuda Y. Prognostic

factors obtained by a pathologic examination in completely resected non-small-cell lung cancer: an analysis in each pathologic stage. J Thorac Cardiovasc Surg 1995;110(3):601–5.
[23] Wang EH, Corso CD, Park HS, et al. Association between radiation dose and outcomes with postoperative radiotherapy for N0-N1 non-small cell lung cancer. Am J Clin Oncol 2018;41(2):152–8.
[24] Zou B, Xu Y, Li T, et al. A multicenter retrospective analysis of survival outcome following postoperative chemoradiotherapy in non–small-cell lung cancer patients with N2 nodal disease. Int J Radiat Oncol Biol Phys 2010;77(2):321–8.
[25] Corso CD, Rutter CE, Wilson LD, Kim AW, Decker RH, Husain ZA. Re-evaluation of the role of postoperative radiotherapy and the impact of radiation dose for non-small-cell lung cancer using the National Cancer Database. J Thorac Oncol 2015;10(1):148–55.
[26] Shen WY, Ji J, Zuo YS, et al. Comparison of efficacy for postoperative chemotherapy and concurrent radiochemotherapy in patients with IIIA-pN2 non-small cell lung cancer: an early closed randomized controlled trial. Radiother Oncol 2014;110(1):120–5.
[27] Mikell JL, Gillespie TW, Hall WA, et al. Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol 2015;10(3):462–71.
[28] Barnes L, Everson JW, Reichart P, Sidransky D. Pathology and genetics: Head and neck tumors. Lyon: International Agency for Research on Cancer; 2005.
[29] Lee N, Xia P, Quivey JM, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 2002;53(1):12–22.
[30] Reddy SP, Raslan WF, Gooneratne S, Kathuria S, Marks JE. Prognostic significance of keratinization in nasopharyngeal carcinoma. Am J Otolaryngol 1995;16(2):103–8.
[31] Ou SH, Zell JA, Ziogas A, Anton-Culver H. Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. Ann Oncol 2007;18(1):29–35.
[32] Vazquez A, Khan MN, Govindaraj S, Baredes S, Eloy JA. Nasopharyngeal squamous cell carcinoma: a comparative analysis of keratinizing and non-keratinizing subtypes. International Forum of Allergy & Rhinology. 2014;4(8):675–83.
[33] Chen R, Ding Z, Zhu L, Lu S, Yu Y. Correlation of clinicopathologic features and lung squamous cell carcinoma subtypes according to the 2015 WHO classification. Eur J Surg Oncol 2017;43(12):2308–14.