Title	Differences in postoperative prognosis between early-stage lung adenocarcinoma and squamous cell carcinoma
Author(s)	Yu Izaki, ; Mimae, Takahiro; Kagimoto, Atsushi; Handa, Yoshinori; Tsutani, Yasuhiro; Miyata, Yoshihiro; Okada, Morihito; Takeshima, Yukio
Citation	Japanese Journal of Clinical Oncology , 54 (7) : 813 - 821
Issue Date	2024-04-27
DOI	
Self DOI	
URL	https://ir.lib.hiroshima-u.ac.jp/00055859
Right	This is a pre-copyedited, author-produced version of an article accepted for publication in Japanese Journal of Clinical Oncology following peer review. The version of record Volume 54, Issue 7, July 2024, Pages 813-821 is available online at: https://doi.org/10.1093/jjco/hyae049. This is not the published version. Please cite only the published version. この論文は出版社版ではありません。引用の際には出版社版をご確認、ご利用ください。
Relation	

Title

Differences in postoperative prognosis between early stage lung adenocarcinoma and squamous cell carcinoma

Authors

Yu Izaki MD[1], Takahiro Mimae MD PhD[1], Atsushi Kagimoto MD[1], Yoshinori Handa MD[1], Yasuhiro Tsutani MD PhD[1], Yoshihiro Miyata MD PhD[1], Morihito Okada MD PhD[1], Yukio Takeshima MD PhD[2]

Institution

[1]Hiroshima University Hospital, Department of Surgical oncology, 1-2-3, Kasumi, Hiroshima city, Hiroshima, 734-8551, Japan

[2]Hiroshima University Hospital, Department of Pathology, Graduate School of Biomedical and Health Sciences, 1-2-3, Kasumi, Hiroshima city, Hiroshima, 734-8551, Japan

Corresponding author;

Prof. Morihito Okada

Department of Surgical Oncology, Hiroshima University 1-2-3, Kasumi, Minami-ku, Hiroshima, Japan, 734-8551

Tel: +81-82-257-5869, Fax: +81-082-256-7109, E-mail address: morihito1217@gmail.com

Running head

Postoperative prognosis of early-stage NSCLC

Word count: 2594 words (not including the title page, abstract, and references)

2

26

Abstract (245 words)

Background: Although prognosis and treatments differ between small-cell- and non-small-cell carcinoma (NSCLC), comparisons of the histological types of NSCLC are uncommon. Thus, we investigated the oncological factors associated with the prognosis of early-stage adenocarcinoma (Ad) and squamous cell carcinoma (Sq).

Methods: We retrospectively compared the clinicopathological backgrounds and postoperative outcomes of patients diagnosed with pathological stage I–IIA Ad and Sq primary lung cancer completely resected at our department from January 2007 to December 2017. Multivariable Cox regression analysis for overall survival (OS) and recurrence-free survival (RFS) was performed.

Results: The median follow-up duration was 55.2 months. The cohort consisted of 532 Ad and 96 Sq patients. A significant difference in survival was observed between the two groups, with a 5-year OS rate of 90% (95% confidence interval [CI] 86%–92%) for Ad and 77% (95% CI 66%–85%) for Sq ($p < 0.01$) patients. Sq patients had worse outcomes compared to Ad patients in stage IA disease, but there were no significant differences between the two groups in stage IB or IIA disease. In multivariate analysis, invasion diameter was associated with OS in Ad (hazard ratio [HR] 1.76, 95% CI 1.36–2.28), but there was no such association in Sq (HR 0.73, 95% CI 0.45–1.14).

Conclusions: The importance of tumor invasion diameter in postoperative outcomes was different between Ad and Sq. Thus, it is important to consider that NSCLC may have different prognoses depending on the histological type, even for the same stage.

Mini-abstract

Although it is known that lung adenocarcinoma and squamous cell carcinoma have different clinical backgrounds, this study found that the oncological properties of each histologic type may also differ.

Keywords

surgery; prognosis; lung cancer; adenocarcinoma; squamous cell carcinoma

Abbreviations

TNM = tumor, node, and metastasis

NSCLC = non-small cell lung cancer

Ad = adenocarcinoma

Sq = squamous cell carcinoma

EGFR = epidermal growth factor receptor

ALK = anaplastic lymphoma kinase

BRAF = V-raf murine sarcoma viral oncogene homolog B

ROS1 = c-ros oncogene 1

CT = computed tomography

OS = overall survival

RFS = recurrence-free survival

IQR = interquartile range

CI = confidence interval

Lp+ Ad = adenocarcinoma which have lepidic growth pattern

Lp- Ad= adenocarcinoma which don’t have lepidic growth pattern

pl = pleura invasive

HR = hazard ratio

Ly = lymphatic invasion

V = vascular invasion

Introduction

The 8th edition of the Tumor, Node, and Metastasis (TNM) classification for non-small cell lung cancer (NSCLC) was published in 2017 based on clinical data, and it provides a more accurate prognosis of NSCLC regardless of histological type [1]. Adenocarcinoma (Ad) and squamous cell carcinoma (Sq) are the two major histologic types of NSCLC, and some reports have demonstrated that both have different prognosis not only because of their oncological features, but also because of variety of therapeutic drugs, for instance, frequency of driver gene mutations, e.g., EGFR, ALK, BRAF, and ROS1 [2-4]. Furthermore, recent developments in computed tomography (CT) have enabled the detection of many small Ads that have lepidic components and less malignant potential than pure invasive tumors without lepidic components. In addition, basic studies have reported a different environment inside and outside the cell between Ad and Sq, suggesting that this may have a different impact on the oncological behavior, such as metastatic potential and invasiveness, of the two histologic types that have been prognostically classified in the same category as NSCLC to date [5,6]. On the other hand, in the staging of esophageal cancer, which, like lung cancer, has Ad and Sq histologic types, Ad and Sq are classified differently in the 8th edition of the Cancer Staging Manual of the AJCC/UICC [7]. There are many differences in the clinical or molecular background of Ad and Sq, for instance, with regard to smoking status, sex, and lung disease status of Ad and Sq, and we hypothesized that there may also be different oncological factors.

In the present study, we retrospectively analyzed the influence of oncological factors, such as invasive diameter and vascular invasion, on Ad and Sq by comparing the prognostic data of relatively early Ad and Sq without lymph node and distant metastasis and to reinterpret the existing staging system, based on a database of postoperative lung cancer patients at our institution. Although it is very difficult to match Ad and Sq background factors, it is desirable to examine and analyze data from certain clinical backgrounds to determine if it is appropriate

to treat the two histologic types similarly in the current classification. We decided to use our own data for a more detailed history and to evaluate cases that had been classified according to the TNM classification prior to the 7th edition by changing the method of measuring invasive and noninvasive diameters and the T classification to the 8th edition.

Patients and Methods

Ethical statement

The Institutional Review Boards at the participating institutions approved this retrospective review of a prospective database and waived the requirement for informed consent from individual patients (06/13/2018, E1216).

Patients

From January 2007 through December 2017, 628 consecutive patients with pathological Stage IA1–IIA pulmonary Ad or Sq underwent complete resection at Hiroshima University Hospital. Complete resection was defined as segmentectomy or greater, with or without systematic ipsilateral hilar and mediastinal lymph node dissection but with no evidence of residual cancer either macroscopically or histologically. Patients with evidence of residual tumor at the surgical margin, malignant effusion, or distant metastasis, verified intraoperatively or via postoperative pathologic examination, were excluded from this study.

Cases were pathologically staged based on the 8th Edition of the TNM Classification for Lung and Pleural Tumors. Histopathologic examinations were performed according to the World Health Organization criteria fourth edition. We reviewed the medical records of all patients for the following clinicopathologic factors: age, sex, smoking history (never- or ever-smoker), past medical history pathological differentiation, pathological stage, and operation method. Both

Elastica–Van Gieson staining (EVG) and D2-40 were used to evaluate invasion into the lympho-vascular spaces. At our institution, the staff regularly updates the database manually, and all cases prior to the 7th edition of the WHO TNM classification were evaluated by modifying the 8th edition classification based on data such as invasion diameter.

Follow-up evaluation

All patients who underwent lung resection were followed up from the day of the surgery. For the first two years, postoperative follow-up comprised a physical examination and chest radiography every three months and chest and abdominal CT examinations every six months. In subsequent years, physical examination and chest radiography were performed every six months, and chest CT was performed every year. Positron emission tomography and CT were also performed when appropriate. Recurrence was diagnosed based on the findings of the physical examination or diagnostic imaging, and the diagnosis was histologically confirmed when clinically feasible. The date of recurrence was defined as the date of cytohistological proof. However, in cases diagnosed based on clinicoradiological findings, the date of recurrence was defined as the date of identification by a physician. The last follow-up observation was censored when the patient was alive or lost to follow-up.

Statistics analyses

We compared overall survival (OS) and recurrence-free survival (RFS) between Ad and Sq in all patients according to pathological stage IA1–IIA. Zero time was the date of pulmonary resection. The endpoint of OS was defined as the date of death from any cause, and the last follow-up observation was censored when the patient was alive or lost to follow-up. The endpoint of RFS was defined as the date of death from any cause or when recurrence was confirmed.

OS and RFS durations were calculated using the Kaplan–Meier method, and differences were assessed using the log-rank test. Independent predictors of OS and RFS were determined using univariable and multivariable analysis with Cox proportional-hazards models. A p-value less than.05 was considered statistically significant. Categorical variables were compared using the $\chi 2$ test, and small samples were analyzed using the Fisher exact test. All data were analyzed using JMP software, version 14 (SAS Institute, Cary, NC).

Results

Differences in characteristics between Ad and Sq patients

Table 1 shows the characteristics of the patients in this study. The patient cohort included 361 male and 267 female patients (median age 69 years, range 32–89). The median follow-up period for the surviving patients was 55.2 months (IQR: 34.3–84.5). The cohort consisted of 532 Ad patients and 96 Sq patients. Table 1 summarizes the clinicopathological characteristics of the Ad and Sq patients.

Female sex and no history of smoking were distinct characteristics of Ad patients ($p < 0.01$, for each parameter). There was no significant difference in age between the two groups. Pathological stage IA1 disease was found in 177 (33%) patients with Ad but in only 9 (9%) patients with Sq.

Survival analysis

A significant difference in survival was observed between the Ad and Sq patients, with a 5-year OS rate of 90% (95% confidence interval [CI] 86%–92%) for Ad patients and 77% (95% CI 66%–85%) for Sq patients (Fig. 1, $p < 0.01$). The comparisons of OS and RFS according to pathological stage are shown in Figure 2. Sq patients had worse outcomes when limited to

patients with stage IA, whereas no significant differences in survival were observed between Sq and Ad patients with stage IB or IIA disease. Therefore, the differences in OS and RFS between Ad and Sq patients were considered to be due to the differences in the outcomes of patients with stage IA disease.

To elucidate this result and provide a fair comparison of prognosis, Ad patients with a lepidic growth pattern (Lp+) were distinguished from others, and the OS and RFS of those with pure invasive Ad (Lp-) and Sq were analyzed. There was a significant difference in prognosis for both OS and RFS between Lp+ and Sq up to Stage IA3. Lp- also showed a better prognostic curve than Sq for OS up to Stage IA2, but was not significantly different in stage IA3. Furthermore, for RFS, the curve overlapped with Sq at Stage IA3 (Fig. 3A, 3B, 3D, and 3E). In stage IB and IIA, there was no significant difference in OS and RFS between each histological type (Fig. 3C and 3F).

In the Ad group, multivariate analysis showed that age, V factor, lung disease (e.g., chronic obstructive pulmonary disease, and interstitial pneumonia), and maximum tumor invasive diameter (invasive size) were all independent prognostic factors for OS. In addition to these, pleura invasion (pl), was also an independent prognostic factor in RFS. On the other hand, acinar subtype was an independent favorable prognostic factor in OS and lepidic subtype in RFS. In Sq, however, there was no independent OS or RFS prognostic factor. Regarding invasive size in particular, the hazard ratio was less than 1.00 (OS 0.70, 95%CI 0.40–1.16, p = 0.18; RFS 0.74, 95%CI 0.46–1.15, p = 0.19) (Table 2).

Discussion

Our study was a retrospective study investigating the clinicopathological features of patients with early-stage NSCLC who underwent radical surgery. Cases that had progressed beyond

stage IIB were excluded from this study because they had already passed to the point of lymph node metastasis and were considered unlikely to reflect the original oncological characteristics. We found that in early-stage lung cancer, the prognosis of Ad progressively worsened with stage progression, i.e., increase in invasive diameter, whereas in Sq, the correlation between invasive diameter and prognosis was not significant.

Ad is the most common subtype of lung cancer worldwide and is also the most frequently occurring histology in non-smokers. Sq is the second most common histological type of NSCLC but is known to differ significantly from Ad in terms of sex and patient background such as smoking history. Although reports have mentioned the difference in prognosis between Ad and Sq, it has been speculated that the inclusion of non-invasive cancers in Ad and non-cancer deaths due to smoking related comorbidities may have contributed to the poor prognosis of Sq [8,9]. A large-scale, nationwide registry study conducted by the Japanese Joint Committee of Lung Cancer Registry reported the surgical outcomes of 11,663 lung cancer patients treated in 2004 [10]. In that report, the 5-year survival rates of 7921 patients with Ad and 2600 patients with Sq were 74.9% and 59.1%, respectively. The outcome of Ad cases seemed to be more favorable than that of Sq cases, although it was not described whether the survival difference between the two histological groups in the same stage was statistically significant. Chansky et al. analyzed 9137 patients with stage I to IIIA NSCLC who were surgically managed, and they found that Ad histology was mostly found in stage I, whereas Sq mostly occurred in stage II and IIIA [11]. Considering these reports, Sq is more aggressive than Ad possibly because of a more advanced tumor at the time of diagnosis. However, we found the survival rates of Sq were worse than those of Ad even at the same stage, especially, stage IA. This indicates that Sq shows more aggressive phenotypes compared with Ad, especially for tumors $\leq$ 3 cm.

Although few previous reports have comprehensively analyzed and described the

clinicopathological and survival differences between Ad and Sq lung cancers [12], Kawase et al. reported that significantly more Sq patients have died of causes other than lung cancer [13]. To exclude confounding factors due to preoperative systemic conditions, we excluded patients who underwent limited resection due to low performance status, low pulmonary function, or severe comorbidities. In addition, because OS is influenced by non-cancer mortality, we also examined RFS. Consequently, there was a significant difference in prognosis between Ad and Sq in RFS and OS.

It has been reported that the prognosis of non-invasive cancers is very good, and pure GGO lepidic pattern Ad is now treated as stage 0 in the latest staging system [1]. In our study, the prognosis of Lp+ and Lp- Ad worsened in a stepwise manner, and the prognosis of the Lp- group tended to be generally worse than that of the Lp+ group as noted in a previous report [14,15]. Thus, we compared the RFS and OS of Sq and Ad (Lp+ and Lp-) and found that up to stage IA2, the prognosis of Lp- Ad was better than that of Sq, and in stage IB+IIA, the prognosis of Lp+ Ad was comparable to that of Sq. In other words, Lp+ Ad has a good prognosis at smaller sizes, but when the invasion diameter exceeds 3 cm, the prognosis is similar to that of Lp-, Ad, and Sq. Thus, Lp+ might not be a favorable prognostic factor in all stages.

However, as mentioned earlier, the clinical backgrounds of Ad and Sq are notably different, making it difficult to directly compare their prognoses. Therefore, we focused on the differences in the prognosis of Ad and Sq separately. Based on the prognostic curve of Ad, the prognosis generally worsens as the stage progresses. However, for Sq, there is little difference from stage IA to IIA, except for stage IA1 with a small number of cases. Thus, we predicted that the prognostic impact of stage progression, mainly the size of the tumor that defines it, may differ between Sq without lymph node metastasis and Ad. Thereafter, we performed a multivariable analysis of OS and RFS, including background factors, such as smoking, sex, and age, Ly factor, V factor, adjuvant chemotherapy, and comorbidity, in addition to tumor size

and pl factors that define stage. Histological subtypes of Ad were also included in the analysis. To determine their independent prognostic factors, Ad and Sq were analyzed separately. The analysis revealed that tumor size was an independent prognostic factor for Ad, but it was not a prognostic factor for Sq for both OS and RFS. For example, Ly factor (HR 2.28, 95%CI 0.97–5.32) may become an independent factor for RFS if the sample size is increased, but invasion diameter had a HR of < 1.00, suggesting that it is not likely to be associated. These findings indicate that the prognosis of early Sq is poorly influenced by tumor size, which could be one of the reasons for the difference in prognosis between early Sq and Ad. Essentially, the stage grouping of the TNM subsets was developed to provide high specificity for identifying patient groups with similar prognoses. However, significant differences in survival between each histopathological cell type were not considered [1]. The TNM classification system contributes to a common understanding worldwide for cancer prognosis prediction and treatment selection. Moreover, the TNM classification is often used as a cutoff value for clinical trial protocols and data analysis [16,17]. As mentioned above, the correlation between tumor size and prognosis differs depending on the histological type, and future studies may need to consider that Sq has a poorer prognosis than Ad after complete resection, especially for cancers with a tumor size of ≤ 2 cm.

Interestingly, there have been recent reports in basic research that the intracellular signaling and surrounding microenvironment involved in tumor growth and suppression, migration and invasion potential, and metastatic potential differ between Ad and Sq [5,6]. These findings provide scientific support for the results in this study regarding the prognostic differences between Ad and Sq histological types and the differential impact of invasion diameter on prognosis. There have also been reports that the speed of preoperative tumor size growth is potentially a greater risk of lung cancer cell metastasis than the clinical tumor invasion diameter [18,19]. The speed of potential tumor growth may explain why the prognosis of smaller Sq was

not relatively better in this study.

This study had some limitations. First, because this was a retrospective cohort analysis, several biases may have existed that could have affected survival, such as the clinical background of the patient. Essentially, Ad and Sq with different clinical backgrounds should be analyzed in cases with various variables matched. This is a single-center study, and there were not enough cases to analyze by strictly matching background factors with respect to cases with clear histological type and clinical background that could be followed up. Although stratified and multivariate analyses were used to minimize the influence of confounding factors as much as possible, it is possible that factors such as the location of occurrence of Ad and Sq were not eliminated. However, as mentioned above, some reports have been published on the differences between Ad and Sq at the cellular level and the impact of tumor growth speed, and it is highly likely that there are prognostic differences that are not dependent only on the clinical characteristics of each histological type.

Second, the study size was not enough to investigate prognosis, especially with regard to stage IA1 Sq (9 patients) and stage IIA cancer (14 Ad patients and 5 Sq patients). Despite combining some groups, the number of cases, especially for Sq, was still not enough and there was a risk of type 2 error. Therefore, it is necessary to study a larger number of cases to validate the results of the present study. We are working on an analysis that includes more cases using a multi-institutional database that shares information with our institution. Third, lung cancer after stage IIB has not been studied. However, in order to evaluate factors such as metastatic potential and invasive potential of the tumor, we decided that cases in which the tumor remained in the primary tumor were more suitable, and limited our analysis to early-stage lung cancer cases without lymph node metastasis. Further analysis is needed for cases with lymph node metastasis.

In conclusion, we identified significant differences, especially regarding the role of tumor

invasion size, in survival and recurrence between patients with Ad and those with Sq in a Japanese cohort. The prognostic impact of invasion diameter in Ad and Sq is significantly different, suggesting that the two histologic types may differ not only in clinical background but also in oncologic characteristics. In particular, stage IA squamous cell carcinoma may not have the same relatively good prognosis as adenocarcinoma, even if the tumor invasion diameter is small, and it may be necessary to consider that the risk is hidden as much as stage IB or IIA in the current 8th edition. These findings may be useful for new staging concepts and optimization of treatment strategies.

Funding statements

none

Conflict of interest statement

none

Acknowledgment

The authors would like to thank Enago (www.enago.jp) for the English language review.

Data Availability Statements

The data underlying this article cannot be shared publicly due to the privacy of the individuals who participated in the study. Data will be shared if the corresponding author has a reasonable request.

References

1. 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. Journal of Thoracic Oncology. 2016;11(1):39-51.
2. Usui S, Minami Y, Shiozawa T et al. Differences in the prognostic implications of vascular invasion between lung adenocarcinoma and squamous cell carcinoma. Lung Cancer. 2013;82(3):407-12.
3. Fukui T, Taniguchi T, Kawaguchi K et al. Comparisons of the clinicopathological features and survival outcomes between lung cancer patients with adenocarcinoma and squamous cell carcinoma. General thoracic and cardiovascular surgery. 2015;63:507-13.
4. Cooke DT, Nguyen DV, Yang Y, Chen SL, Yu C, Calhoun RF. Survival comparison of adenosquamous, squamous cell, and adenocarcinoma of the lung after lobectomy. The Annals of thoracic surgery. 2010;90(3):943-8.
5. Zhang L, Chen J, Cheng T, Yang H, Li H, Pan C. Identification of the key genes and characterizations of tumor immune microenvironment in lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC). Journal of Cancer. 2020;11(17):4965.
6. Anusewicz D, Orzechowska M, Bednarek AK. Lung squamous cell carcinoma and lung adenocarcinoma differential gene expression regulation through pathways of Notch, Hedgehog, Wnt, and ErbB signalling. Scientific reports. 2020;10(1):21128.
7. Rice TW, Patil DT, Blackstone EH. AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. Annals of cardiothoracic surgery. 2017;6(2):119.
8. Asamura H, Goya T, Koshiishi Y et al. A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. Journal of Thoracic Oncology. 2008;3(1):46-52.
9. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years'

observations on male British doctors. Bmj. 2004;328(7455):1519.

10. Sawabata N, Miyaoka E, Asamura H et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. Journal of Thoracic Oncology. 2011;6(7):1229-35.
11. Chansky K, Sculier J-P, Crowley JJ, Giroux D, Van Meerbeeck J, Goldstraw P. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. Journal of thoracic oncology. 2009;4(7):792-801.
12. Maeda R, Yoshida J, Ishii G, Hishida T, Nishimura M, Nagai K. Prognostic impact of histology on early-stage non-small cell lung cancer. Chest. 2011;140(1):135-45.
13. Kawase A, Yoshida J, Ishii G et al. Differences between squamous cell carcinoma and adenocarcinoma of the lung: are adenocarcinoma and squamous cell carcinoma prognostically equal? Japanese journal of clinical oncology. 2011;42(3):189-95.
14. Hattori A, Suzuki K, Takamochi K et al. Prognostic impact of a ground-glass opacity component in clinical stage IA non–small cell lung cancer. The Journal of Thoracic and Cardiovascular Surgery. 2021;161(4):1469-80.
15. Nakamura S, Fukui T, Taniguchi T et al. Prognostic impact of tumor size eliminating the ground glass opacity component: modified clinical T descriptors of the tumor, node, metastasis classification of lung cancer. Journal of Thoracic Oncology. 2013;8(12):1551-7.
16. Hamada C, Tanaka F, Ohta M et al. Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non–small-cell lung cancer. Journal of Clinical Oncology. 2005;23(22):4999-5006.
17. Hamada C, Tsuboi M, Ohta M et al. Effect of postoperative adjuvant chemotherapy with tegafur-uracil on survival in patients with stage IA non-small cell lung cancer: an exploratory analysis from a meta-analysis of six randomized controlled trials. Journal of

376 Thoracic Oncology. 2009;4(12):1511-6.
377 18. Karita R, Suzuki H, Onozato Y et al. A simple nomogram for predicting occult lymph node
378 metastasis of non-small cell lung cancer from preoperative computed tomography findings,
379 including the volume-doubling time. Surgery Today. 2024;54(1):31-40.
380 19. Nakahashi K, Shiono S, Nakatsuka M, Endo M. Prognostic impact of the tumor volume
381 doubling time in clinical T1 non-small cell lung cancer with solid radiological findings.
382 Journal of Surgical Oncology. 2022;126(7):1330-40.
383

Figure legends

Figure 1.

Overall survival (OS) and recurrence-free survival (RFS) curves of patients with adenocarcinoma (Ad) and squamous cell carcinoma (Sq). (A) the 5-year OS rate for Ad and Sq were 90% (95% confidence interval [CI] 86%–92%) and 77% (95% CI 66%–85%), respectively ($p < 0.01$, log-rank test). (B) The 5-year RFS rate for Ad and Sq were 85% (95% CI 81%–88%) and 69% (95% CI 58%–78%), respectively ($p < 0.01$, log-rank test).

Figure 2.

Overall survival (OS) and recurrence-free survival (RFS) curves for the adenocarcinoma (Ad) and squamous cell carcinoma (Sq) histological subtypes according to the 8th edition of the TNM classification. (A) The 5-year OS (95% confidence interval [CI]) rate for Ad patients in pathological (p) Stage IA1, IA2, IA3, and IB was 95% (90%–98%), 91% (84–95%), 96% (86%–99%), and 76% (66%–84%), respectively. (B) The 5-year OS (95% CI) rate for Sq patients in pStage IA1, IA2, IA3, and IB was 100% (–), 71% (51%–85%), 79% (58%–91%), and 75% (53%–89%), respectively. (C) The 5-year RFS (95% CI) rate for Ad patients in pStage IA1, IA2, IA3, and IB was 95% (90%–98%), 88% (81%–92%), 88% (77%–94%), and 61% (50%–71%), respectively. (D) The 5-year RFS (95% CI) rate for Sq patients in pStage IA1, IA2, IA3, and IB were 100% (–), 63% (43%–79%), 69% (47%–85%), and 65% (45%–81%), respectively.

Figure 3.

Overall survival (OS) and recurrence-free survival (RFS) curves for the adenocarcinoma (Ad) with lepidic component (Lp+), Ad without lepidic component (Lp-), and squamous cell carcinoma (Sq) histological subtypes according to pathological (p) stage.

The 5-year OS (95% confidence interval) rate for Lp+, Lp-, and Sq (A) for pStage IA1 + IA2 patients: 94% (90%–96%), 88% (73%–95%), and 77% (59%–88%), respectively; (B) for pStage IA3 patients: 97% (84%–100%), 92% (61%–99%), and 79% (58%–91%), respectively; and (C) for pStage IB + IIA patients: 88% (72%–95%), 69% (54%–80%), and 75% (53%–89%), respectively.

The 5-year RFS (95% confidence interval) rate for Lp+, Lp-, and Sq (A) for pStage IA1 + IA2 patients: 92% (88%–95%), 87% (74%–94%), and 71% (53%–84%), respectively; (E) for pStage IA3 patients: 93% (81%–98%), 73% (49%–89%), and 69% (47%–85%), respectively; and (F) for pStage IB + IIA patients: 73% (56%–85%), 53% (39%–66%), and 66% (45%–81%), respectively.

Table 1. Clinical characteristics

Variables		All n = 628	Ad n = 532	Sq n = 96	*p*
Age	Median (IQR)	69 (63-74)	69 (63-74)	68.5 (65-74.75)	0.31
Sex	Male	361	279 (52%)	82 (85%)	<0.01
	Female	267	253 (48%)	14 (15%)	
Smoke	Smoker	359	265 (50%)	94 (99%)	<0.01
	Never smoker	267	266 (50%)	1 (1%)	
Comorbidity	Heart	48	39 (7%)	9(9%)	0.50
	Lung	121	82 (15%)	39(41%)	<0.01
	Other	246	201 (38%)	45(47%)	0.10
Operative methods	Lobectomy	422	349 (66%)	73 (76%)	0.04
	Segmentectomy	206	183 (34%)	23 (24%)	
pStage	IA1	186	177 (33%)	9 (9%)	
	IA2	212	182 (34%)	30 (31%)	
	IA3	97	69 (13%)	28 (29%)	<0.01
	IB	114	90 (17%)	24 (25%)	
	IIA	19	14 (3%)	5 (5%)	
Lymphovascular invasion	Ly1	91	69 (13%)	22(23%)	0.02
	V1	124	89 (17%)	35(36%)	<0.01
Adenocarcinoma subtype	Minimally invasive		23 (4%)		
	Lepidic		138 (26%)		
	Acinar		27 (5%)		
	Papillary		300 (56%)		
	Micropapillary		9 (2%)		
	Solid		20 (4%)		
	Invasive mucinous		15 (3%)		
Lepidic pattern	+		388 (73%)	-	
	-		144 (27%)	-	
Pleural invasion	+	91	77 (14%)	14 (15%)	0.98
	-	537	455 (86%)	82 (85%)	
Adjuvant chemotherapy	+	196	174 (33%)	22(23%)	0.05
	-	432	358 (67%)	74(77%)	

Ad, adenocarcinoma; Sq, squamous cell carcinoma

420

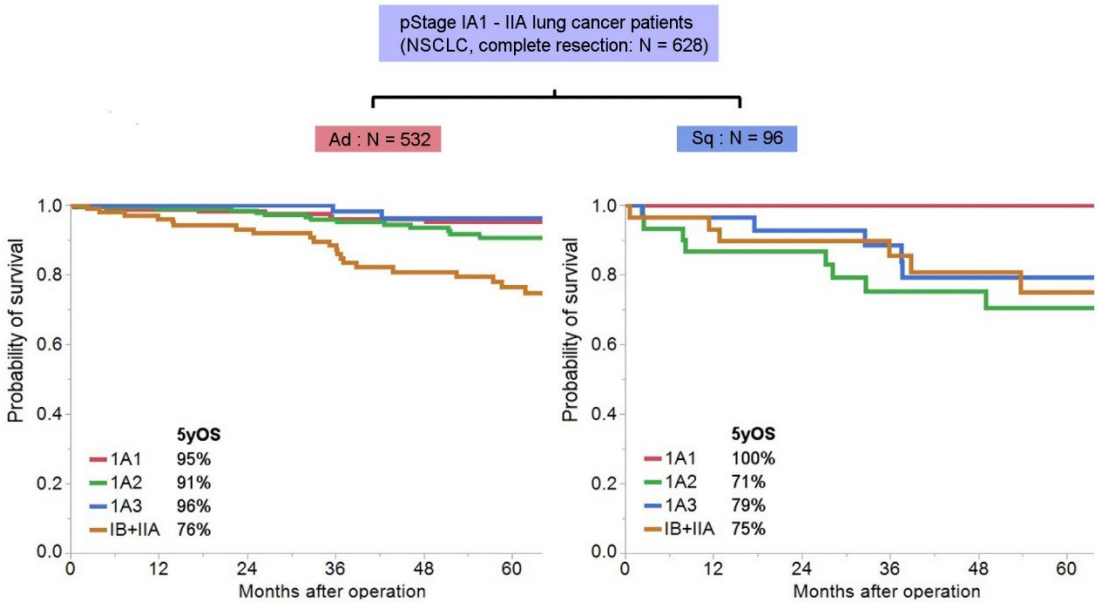
Table 2. Multivariate analysis by Cox's proportional hazard's model

Ad (n = 532)				
Variables	OS		RFS	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (70≦/70＞)	5.45 (2.61 to 11.37)	**<0.01**	2.71 (1.60 to 4.60)	**<0.01**
Sex (M/F)	2.06 (0.85 to 5.02)	0.11	1.38 (0.70 to 2.73)	0.35
Smoke (+/-)	1.21 (0.50 to 2.91)	0.68	0.85 (0.43 to 1.70)	0.65
Pleural invasion (+/-)	2.03 (0.97 to 4.25)	0.06	2.24 (1.27 to 3.95)	**0.01**
Ly (+/-)	0.83 (0.37 to 1.84)	0.64	1.49 (0.83 to 2.68)	0.19
V (+/-)	2.51 (1.27 to 4.97)	**0.01**	2.98 (1.71 to 5.17)	**<0.01**
Adjuvant therapy (+/-)	0.67 (0.34 to 1.33)	0.25	0.82 (0.48 to 1.41)	0.48
Lung disease	4.60 (2.38 to 8.90)	**<0.01**	3.94 (2.30 to 6.75)	**<0.01**
Heart disease	1.76 (0.73 to 4.31)	0.21	1.57 (0.71 to 3.47)	0.27
Other comorbidity	1.40 (0.78 to 2.53)	0.26	1.47 (0.90 to 2.39)	0.12
Subtype Minimally invasive Ad		1.00		1.00
Lepidic	0.25 (0.05 to 1.24)	0.09	0.20 (0.04 to 0.94)	**0.04**
Acinar	0.10 (0.01 to 0.89)	**0.04**	0.38 (0.12 to 1.25)	0.11
Papillary	0.51 (0.21 to 1.28)	0.15	0.60 (0.27 to 1.34)	0.21
Micropapillary	0.76 (0.13 to 4.51)	0.77	0.73 (0.17 to 3.08)	0.67
Solid	0.63 (0.16 to 2.58)	0.52	0.36 (0.95 to 2.39)	0.12
Invasive mucinous	0.92 (0.17 to 5.09)	0.93	0.82 (0.16 to 4.25)	0.82
Invasive size	1.64 (1.22 to 2.23)	**<0.01**	1.62 (1.27 to 2.06)	**<0.01**
Sq (n =96)				
Variables	OS		RFS	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age (70≦/70＞)	1.63 (0.63 to 4.25)	0.31	1.46 (0.64 to 3.33)	0.37
Sex (M/F)	1.02 (0.30 to 3.41)	0.98	1.60 (0.51 to 5.08)	0.40
Smoke (+/-)		1.00		1.00
Pleural invasion (+/-)	2.04 (0.65 to 6.37)	0.23	1.67 (0.61 to 4.59)	0.33
Ly (+/-)	1.74 (0.65 to 4.69)	0.28	2.28 (0.97 to 5.32)	0.06
V (+/-)	1.18 (0.46 to 3.04)	0.73	1.68 (0.72 to 3.94)	0.23
Adjuvant therapy (+/-)	0.97 (0.29 to 3.25)	0.96	1.17 (0.42 to 3.21)	0.77
Lung disease	1.61 (0.59 to 4.39)	0.36	0.98 (0.41 to 2.34)	0.97
Heart disease	0.79 (0.18 to 3.53)	0.75	0.61 (0.13 to 2.74)	0.50
Other comorbidity	1.12 (0.44 to 2.86)	0.81	1.12 (0.50 to 2.53)	0.78
Invasive size	0.70 (0.40 to 1.16)	0.18	0.74 (0.46 to 1.15)	0.19

Ad, adenocarcinoma; Sq, squamous cell carcinoma; OS, overall survival;
RFS, recurrence free survival; HR, hazard ratio CI, confidence interval; M, male; F, female; Le, lepidic

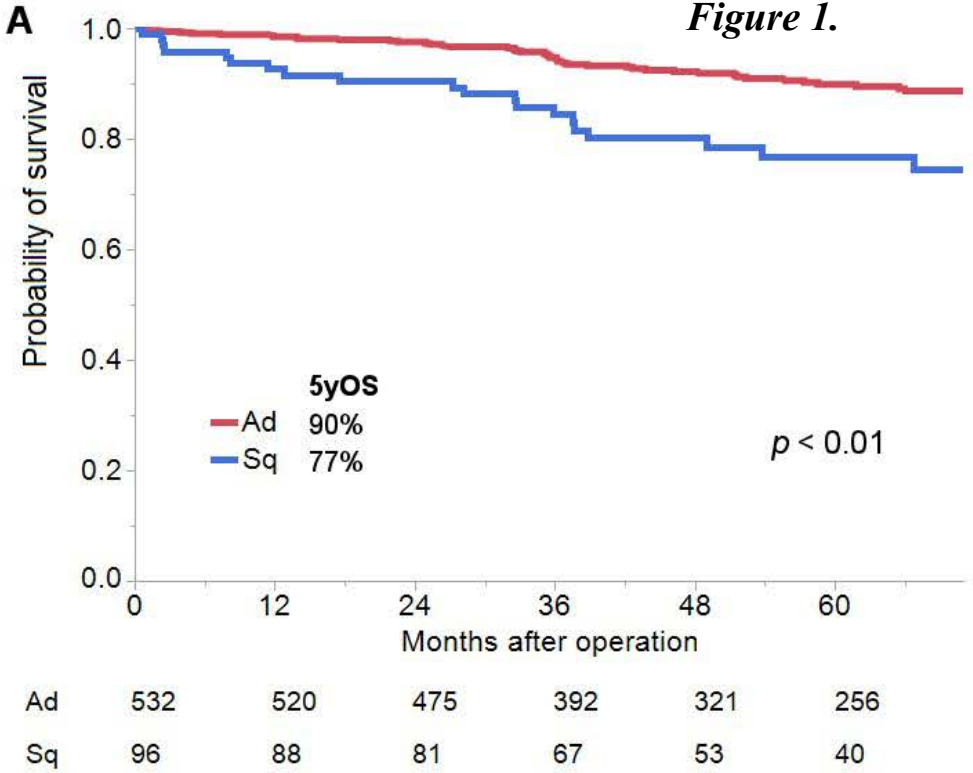
421

Graphical Abstract



The prognostic impact of tumor progression, particularly tumor invasion diameter, differed between the two histologic types.

Figure 1.


A
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yOS
Ad 90%
Sq 77%
p < 0.01
0
12
24
36
48
60
Months after operation
Ad 532 520 475 392 321 256
Sq 96 88 81 67 53 40

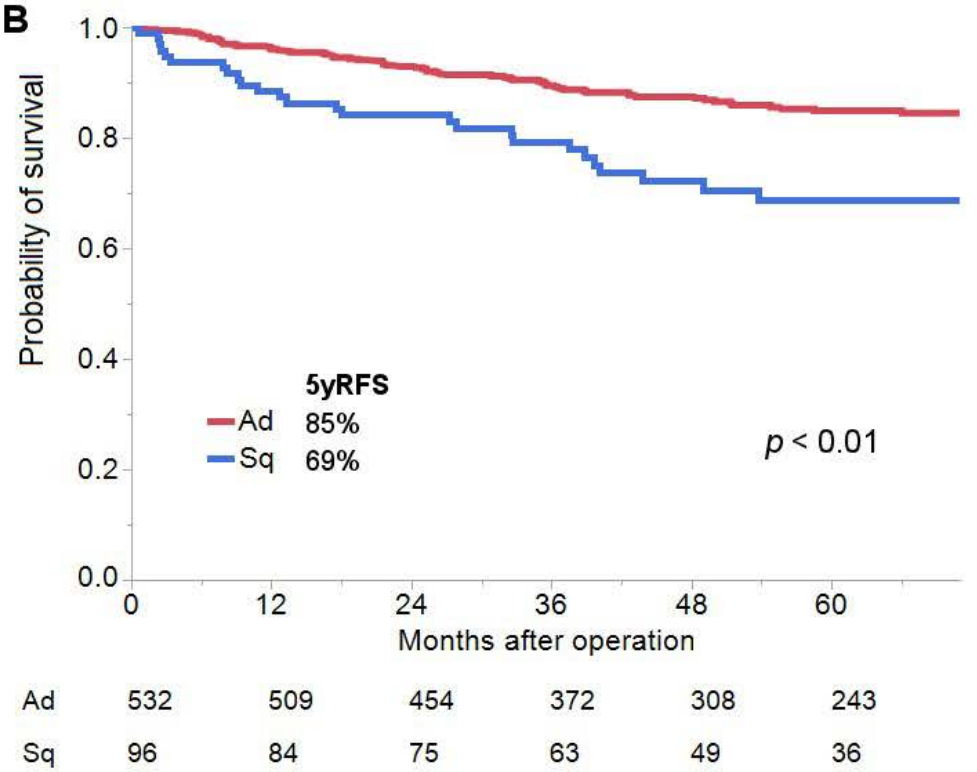
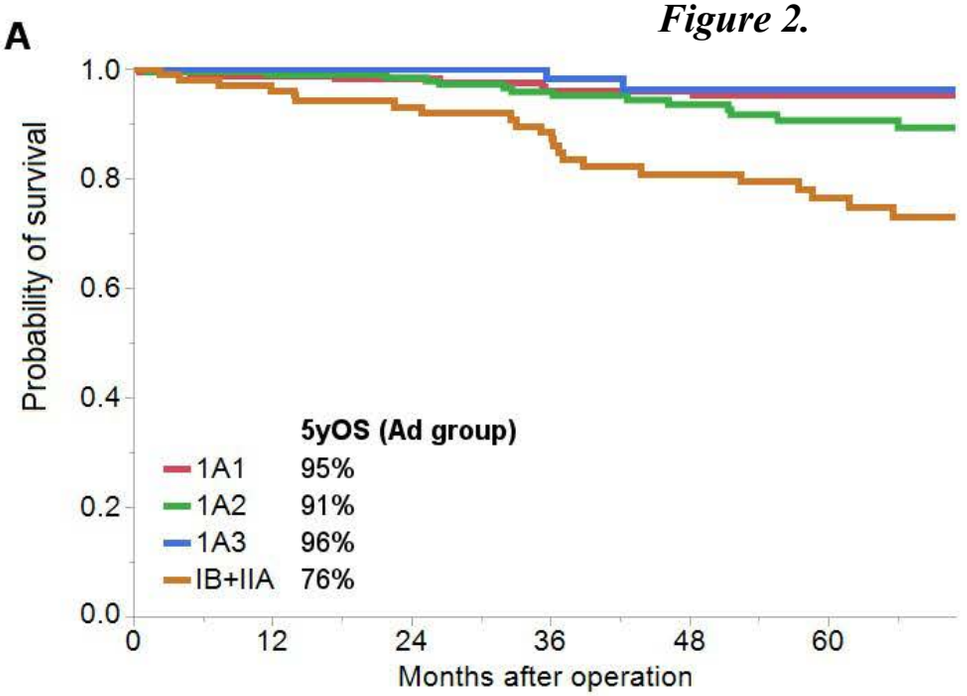
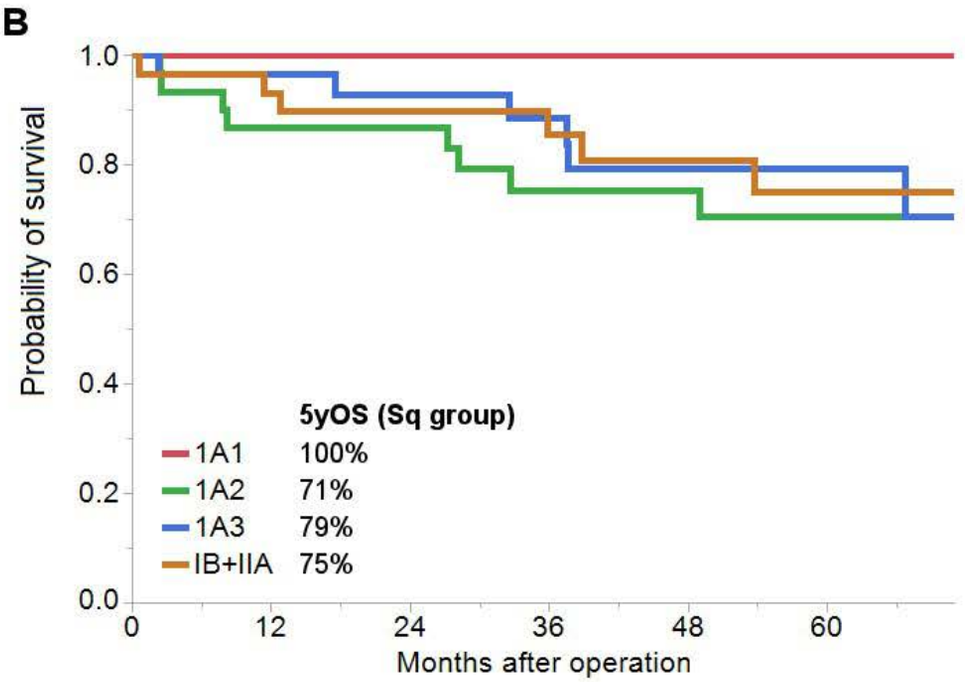

B
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yRFS
Ad 85%
Sq 69%
p < 0.01
0
12
24
36
48
60
Months after operation
Ad 532 509 454 372 308 243
Sq 96 84 75 63 49 36

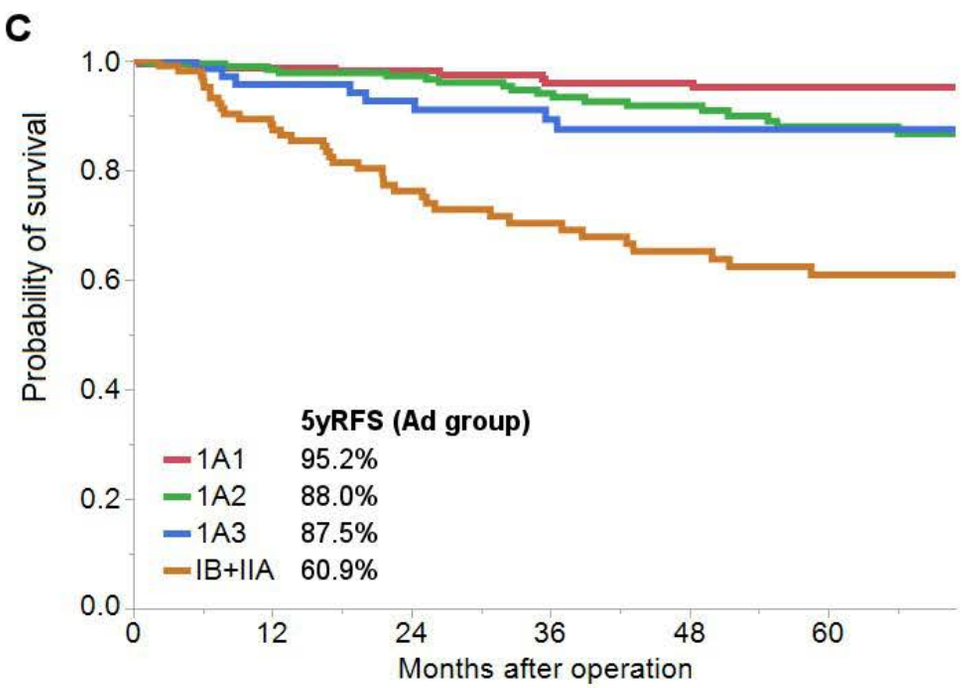
Figure 2.



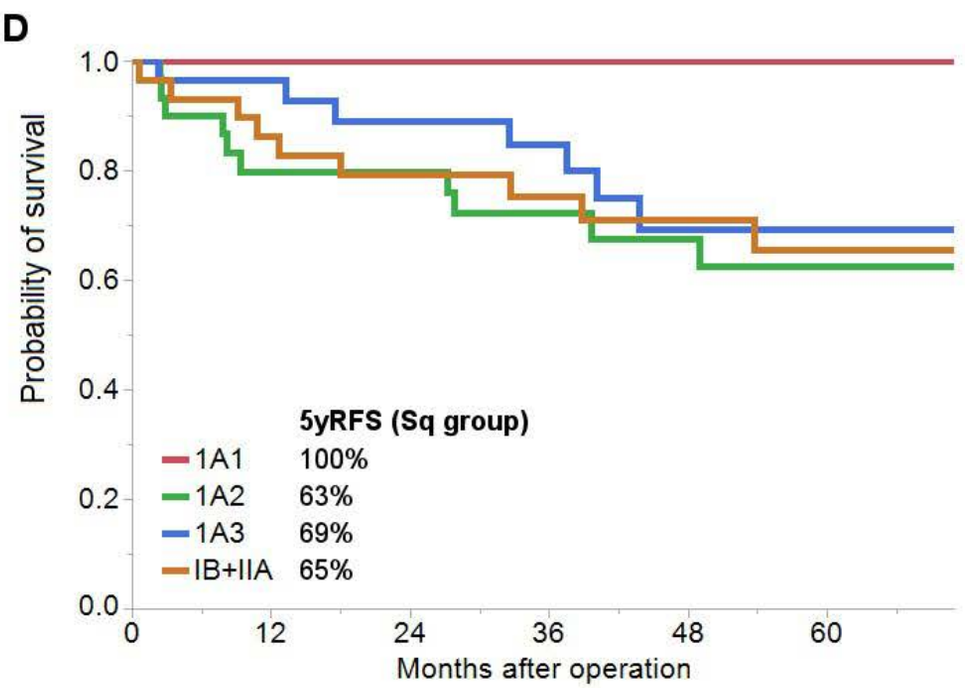
IA1	177	174	38	127	105	83
IA2	182	181	169	140	114	86
IA3	69	69	63	55	46	38
IB+IIA	104	99	90	74	58	52



IA1	9	9	8	7	7	4
IA2	30	26	24	20	17	14
IA3	28	27	26	22	14	12
IB+IIA	29	28	26	21	18	13

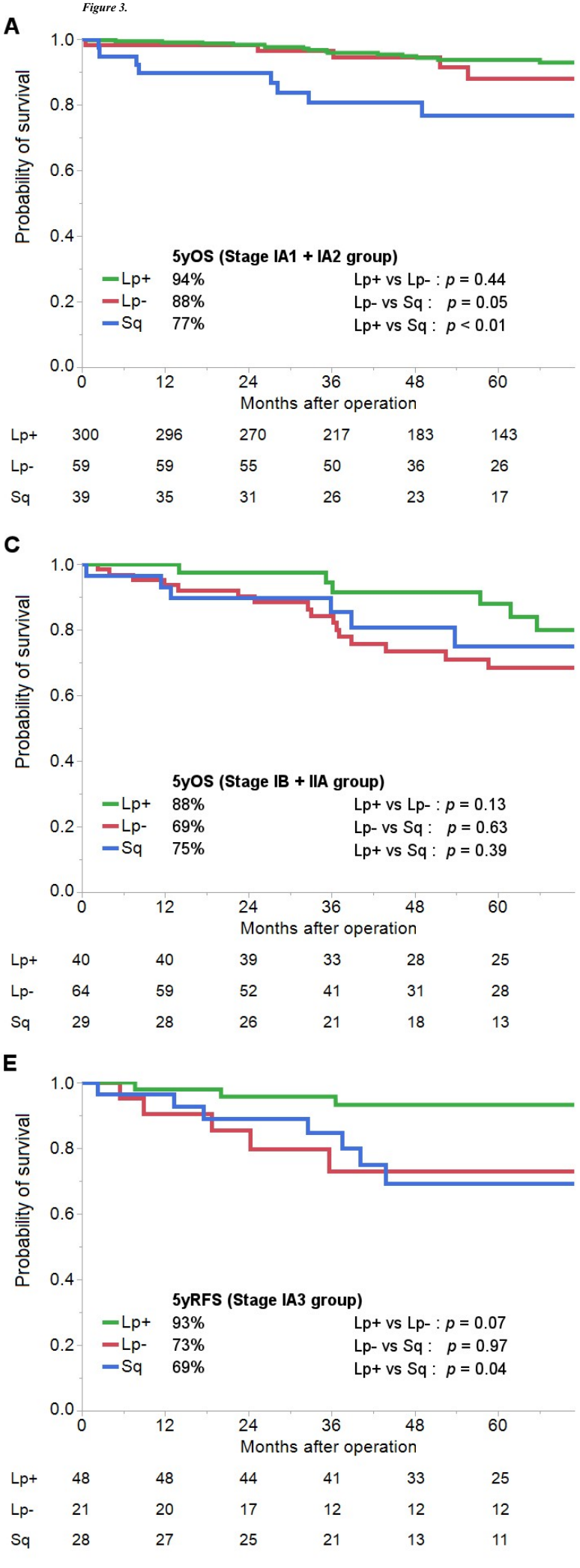


IA1	177	174	156	127	105	83
IA2	182	180	167	138	113	84
IA3	69	67	60	52	44	36
IB+IIA	104	91	74	58	49	43



IA1	9	9	8	7	7	4
IA2	30	23	22	19	15	12
IA3	28	27	25	21	13	11
IB+IIA	29	26	23	19	17	12

Figure 3.


A
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yOS (Stage IA1 + IA2 group)
Lp+ 94%
Lp- 88%
Sq 77%
Lp+ vs Lp- : p = 0.44
Lp- vs Sq : p = 0.05
Lp+ vs Sq : p < 0.01
0 12 24 36 48 60
Months after operation
Lp+ 300 296 270 217 183 143
Lp- 59 59 55 50 36 26
Sq 39 35 31 26 23 17
B
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yOS (Stage IA3 group)
Lp+ 97.4%
Lp- 92.3%
Sq 79.2%
Lp+ vs Lp- : p = 0.79
Lp- vs Sq : p = 0.13
Lp+ vs Sq : p = 0.03
0 12 24 36 48 60
Months after operation
Lp+ 48 48 46 43 35 27
Lp- 21 21 18 13 12 12
Sq 28 27 26 22 14 12
C
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yOS (Stage IB + IIA group)
Lp+ 88%
Lp- 69%
Sq 75%
Lp+ vs Lp- : p = 0.13
Lp- vs Sq : p = 0.63
Lp+ vs Sq : p = 0.39
0 12 24 36 48 60
Months after operation
Lp+ 40 40 39 33 28 25
Lp- 64 59 52 41 31 28
Sq 29 28 26 21 18 13
D
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yRFS (Stage IA1 + IA2 group)
Lp+ 92%
Lp- 87%
Sq 71%
Lp+ vs Lp- : p = 0.39
Lp- vs Sq : p = 0.02
Lp+ vs Sq : p < 0.01
0 12 24 36 48 60
Months after operation
Lp+ 300 296 269 217 183 141
Lp- 59 58 54 48 35 26
Sq 39 33 29 25 21 15
E
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yRFS (Stage IA3 group)
Lp+ 93%
Lp- 73%
Sq 69%
Lp+ vs Lp- : p = 0.07
Lp- vs Sq : p = 0.97
Lp+ vs Sq : p = 0.04
0 12 24 36 48 60
Months after operation
Lp+ 48 48 44 41 33 25
Lp- 21 20 17 12 12 12
Sq 28 27 25 21 13 11
F
Probability of survival
1.0
0.8
0.6
0.4
0.2
0.0
5yRFS (Stage IB + IIA group)
Lp+ 73%
Lp- 53%
Sq 66%
Lp+ vs Lp- : p = 0.03
Lp- vs Sq : p = 0.23
Lp+ vs Sq : p = 0.50
0 12 24 36 48 60
Months after operation
Lp+ 40 39 35 28 23 21
Lp- 64 53 40 31 27 23
Sq 29 26 23 19 17 12