What are the Survival Factors in Surgically Resected Synchronous Multiple Primary Lung Cancers: A Retrospective Study

Haichao Li
Shandong University Qilu Hospital https://orcid.org/0000-0002-5086-1357
Kai Wang
Yanzhou Branch of Affiliated Hospital of Jining Medical University
Xingxing Zhang
Taian Maternal Child Health Hospital
Rong Chen
Linyi People's Hospital
Jian Zhao (zhaojianjn@sdu.edu.cn)
Linyi People's Hospital

Research

Keywords: lung cancer, synchronous multiple primary lung cancers, surgery, survival

Posted Date: December 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-117726/v1

Abstract

Background: With the popularization of high-resolution computed tomography (HRCT), the detection rate of synchronous multiple primary lung cancer (SMPLC) is increasing. We retrospectively analyzed the surgical results of SMPLC patients in our hospital to determine the best treatment, surgical prognosis and survival analysis.

Methods: A total of 78 SMPLC patients met the diagnostic criteria underwent complete resection and lymph node dissection or sampling without any preoperative induction therapy in the Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University. We analyzed the postoperative survival rate, and further studied the relationship between survival rates and sex, age, preoperative symptoms, tumor location, tumor number, tumor size, lymph node metastasis, TNM stage, surgical type, surgical frequency, histopathologic types, vascular infiltration, visceral pleural invasion and postoperative therapy.

Results: Among 78 patients, the 1-,2-,3-,4- and 5-year disease free survival (DFS) rates were 93.42%, 86.84%, 77.78%, 62.96%, and 60.00%, respectively, while the 1-,2-,3-,4- and 5-year overall survival (OS) rates were 94.73%, 92.11%, 82.22%, 77.78%, and 65.00%, respectively. TNM stage of the largest tumor (II:HR=7.40,III:9.01,p=0.002) was an independent risk factor for DFS. Smoking history (HR=4.34,p=0.039) and TNM stage of the largest tumor (II:HR=9.38,III:9.42,p=0.003) were independent risk factors for overall survival.

Conclusions: First, SMPLC is different from intrapulmonary metastasis and its clinical stage is also different from the 8th (2015) edition TNM classification for lung cancer. Second, when pulmonary function permits, surgery (complete resection and lymph node dissection) is a significantly beneficial treatment for patients with SMPLC. Third, TNM stage of the largest tumor (II:HR=7.40,III:9.01,p=0.002) was an independent risk factor for DFS. Smoking history (HR=4.34,p=0.039) and TNM stage of the largest tumor (II:HR=9.38,III:9.42,p=0.003) were independent risk factors for overall survival.

Introduction

According to global cancer statistics, lung cancer is one of the malignant tumors with the highest morbidity and mortality in the world [1]. With the popularization of high-resolution computed tomography (HRCT), the detection rate of synchronous multiple primary lung cancer (SMPLC) is increasing but there is no clear clinical stage and clinical guidelines for SMPLC. And the latest 8th (2015) edition TNM classification for lung cancer [2] still classified separate tumor nodules in the same lobe as T3, in the ipsilateral lung but different lobes as T4 and in the contralateral lung as M1a. Obviously, SMPLC is still regarded as intrapulmonary metastasis. However, according to related studies, the prognosis of SMPLC surgery is better than that of patients with high-stage lung cancer [2–7]. So such classification and stage still need to be further studied. In this study, the clinical data of 78 patients with SMPLC who underwent thoracic surgery in the Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine,

Shandong University from January 2013 to November 2018 were collected retrospectively in order to evaluate the surgical effect and related prognosis of SMPLC and to provide reference for clinical practice.

Materials And Methods

Patient selection: All the medical records of SMPLC who underwent thoracic surgery in the Department of Thoracic Surgery, Qilu Hospital, Cheeloo College of Medicine, Shandong University from January 2013 to November 2018 were collected retrospectively. All patients had postoperative pathology as the basis for diagnosis. Informed consent was waived because this was a retrospectively study.

Diagnostic criteria: All patients met the new improved standard of SMPLC [8–9]. The subjects of this study were SMPLC, with more than 2 independent cancers in the lung at the same time. They were also considered after multi-disciplinary discussion and met at least one of the following criteria: (1) tumors with different histology; (2) tumors with similar histology requires that the tumor was located in different lobes or segments of the lung, without common lymph node metastasis and extrapulmonary metastasis; (3) tumors originated from different primary cancers; (4) tumors with different histologic subtypes (such as acinar cell or papillary cell is the main part of the adenocarcinomas, etc.); (5) tumors with different molecular genetic characteristics (such as epidermal growth factor receptor [EGFR], k-ras, etc.) [10, 11].

Preoperative evaluation: All patients with lung cancer in our hospital underwent relevant preoperative examinations, including thoracic and abdominal Computed Tomography (CT), cranial magnetic resonance image (MRI) or CT, bone scintigraphy, electrocardiogram, cardiac ultrasonography, pulmonary function and so on. Some patients were examined by PET/CT scan. The appropriate operation method was chosen carefully according to the preoperative examination, the patient's physical condition and the situation during the operation.

Surgical strategy: The principle of surgery was to remove the tumor as thoroughly as possible and preserve lung function as much as possible. And the following strategies should be followed: (1) when pulmonary function permits, the lobes of all lesions should be removed; (2) when pulmonary function did not allow multi lobectomy, the lobe of major lesion (the tumor with central type or the highest TNM stage) should be removed, then the secondary lesions should be removed locally, otherwise local resection of multiple lesions should be performed; (3) when the lesions were on different sides, if the patient's physical quality permits, the tumors should be removed at the same time. If the physical quality of the patient was not allowed, the main lesions should be removed first and then remove the secondary lesions in another time. According to the preoperative discussion and intraoperative conditions, thoracotomy or video-assisted thoracoscopic surgery (VATS) was selected. No matter which operation method was chosen, all patients underwent radical pneumonectomy and lymph node dissection or sampling.

Postoperative pathological stages: We staged every lesion independently using the 8th edition TNM classification [2] for each patient. Each tumor was staged and the highest stage was taken as the final stage of the patient.

Postoperative follow-up: The patients were checked every 3 months within 2 years, every 6 months within 2–5 years, and every 1 year after 5 years. The follow-up items included tumor markers, thoracic CT, abdominal ultrasound, cranial MRI, and bone scintigraphy (if necessary).

Statistical analysis: Disease-free survival (DFS) was defined as the time from the first operation to postoperative recurrence or distant metastasis or the last follow-up. Overall survival (OS) was defined as the time from the first operation to death or the last follow-up. The follow-up time at the end of this study was August 4, 2020. The Kaplan-Meier method was used to estimate the survival curve, and log-rank test was used to compare the survival curve of each group. The cox proportional hazard regression model was used to analyze the prognostic factors for survival. The data were analyzed by SPSS20.0 statistical software, and the value of $P < 0.05$ was considered statistically significant.

Results

General clinical characteristic data: The general clinical features of all the researched 78 patients with SMPLC were shown in Table 1. A total of 78 patients were included in the study, including 30 (38.46%) males and 48 (61.54%) females. The median age was 62 years (28–76 years). There were 21(26.92%) patients with smoking history and 57 (73.08%) patients without. 55 (70.51%) patients had clinical symptoms (fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.) and 23 (29.49%) had no clinical symptoms before operation. There were 4 (5.13%) patients with a family history of malignant tumor and 74 (94.87%) without. 19 (24.36%) patients had elevated tumor markers before surgery (first surgery), 12 (15.38%) had no increased.

Operation and tumor characteristics: The operation, tumor features and pathological data of 78 patients were shown in Table 2. Of all the patients, 72(92.31%) had the single-stage operation and 6(7.69%) had the two-stage operation (bilateral tumors). There were 69 (88.46%) people with tumors on the same side and 9 (11.54%) people with tumors on both sides. Among the 78 SMPLC patients, 21 (26.92%) had all tumors located in the same lobe, and 52 (66.67%) had tumors located in different lobes, and 5(6.41%) had tumors located in mixed lobes (3 or more primary lung cancers with at least 2 lesions located in the same lung lobe and the other lesions were located in different lung lobes). There were 65 (83.33%) patients with double primary lung cancers, 12 (15.38%) patients with triple primary lung cancers, and 1 (1.28%) patients with four or more primary lung cancers. In terms of surgical methods, 32(41.03%) patients underwent lobectomy alone, 35(44.87%) patients underwent lobectomy plus sublobectomy (segmentectomy or wedge resection), and 11(14.10%) patients underwent sublobectomy alone. Among all pathological diagnoses, adenocarcinoma was the most common type of pathology. There were 66 (84.62%) patients suffering from adenocarcinoma and 12 (15.38%) patients with non-total adenocarcinoma (including squamous cell carcinoma, neuroendocrine carcinoma, mucoepidermoid carcinoma, sarcoma, etc.). According to the highest pT stage of every SMPLC, 64(82.05%) patients were at T1 ($d \leq 3$ cm) stage, 15(19.23%) patients were at T2 ($3 < d \leq 5$ cm) stage and 2(2.56%) patients were at T3 + 4 ($d > 5$ cm) stage. Among 78 patients with SMPLC, 5(6.41%) had positive lymph node metastasis (N1), 1(1.28%) had positive lymph node metastasis (N2) and 72(92.31%) had no lymph node metastasis.

After the operation, 2(2.56%) people had tumor pathology showing vascular infiltration, and 76(97.44%) had no vascular infiltration. 5(6.41%) people showed pathologically visceral pleura invasion, and 73(93.59%) had no visceral pleura invasion. In postoperative treatments, 33(42.31%) received adjuvant postoperative anti-tumor therapy (including chemotherapy, targeted therapy and radiotherapy), while 38(48.72%) did not receive anti-tumor therapy.

Prognostic survival analysis:

In the whole group, the median follow-up time was 35.0 months, and a total of 76 patients were followed up, with a follow-up rate of 97.44%. 15 patients finally experienced recurrence, metastasis or death during the follow-up. Among 78 patients, the 1-,2-,3-,4- and 5-year DFS rates were 93.42%, 86.84%, 77.78%, 62.96%, and 60.00%, respectively, while the 1-,2-,3-,4- and 5-year OS rates were 94.73%, 92.11%, 82.22%, 77.78%, and 65.00%, respectively.

The results of univariate analysis of prognostic factors related to OS and DFS were showed in Table 1. The results showed that male patients (HR = 5.46,p = 0.001), smoking history (HR = 5.00,p = 0.001), preoperative symptoms (HR = 3.45,p = 0.015), advanced pT stage of the largest tumor (T2:HR = 5.46,T3:HR = 8.57,p = 0.006), metastasis in the lymph node (HR = 8.78,p = 0.000), advanced TNM stage of the largest tumor (II:HR = 16.12,III:22.30,p = 0.001), non - total adenocarcinoma (HR = 4.76,p = 0.005) and postoperative adjuvant chemotherapy (HR = 54.61,p = 0.001) were adverse prognostic factors affecting the DFS rates of patients with SMPLC. And male patients (HR = 9.06,p = 0.001), smoking history (HR = 8.81,p = 0.001), preoperative symptoms (HR = 5.06,p = 0.015), advanced pT stage of the largest tumor (T2:HR = 3.58,T3:HR = 10.00,p = 0.025), metastasis in the lymph node (HR = 8.34,p = 0.000), advanced TNM stage of the largest tumor (II:HR = 12.40,III:9.33,p = 0.000), non - total adenocarcinoma (HR = 8.17,p = 0.001) and postoperative adjuvant chemotherapy (HR = 53.10,p = 0.003) were adverse prognostic factors affecting the OS rates of patients with SMPLC. There were no statistically significant differences in age, family history of malignant tumors, preoperative tumor markers, tumor laterality, tumor location, surgical methods, number of operations, number of tumors, tumor pathology with or without vascular invasion and visceral pleural invasion The clinical characteristics with statistical differences in univariate analysis were classified into multivariate analysis (Table 2) and the results showed that advanced TNM stage of the largest tumor (II:HR = 7.40,III:9.01,p = 0.002) was the independent risk factor affecting the DFS rate, while Smoking history (HR = 4.34,p = 0.039) and advanced TNM stage of the largest tumor (II:HR = 9.38,III:9.42,p = 0.003) were independent risk factors affecting the OS rate of SMPLC patients.

Discussion

At present, according to the latest t 8th (2015) edition TNM classification for lung cancer[2], same as the 7th edition [12], SMPLC is still regarded as intrapulmonary metastasis in T and M stages. Multiple tumor nodules in the same lobe were classified as T3, in the different lobe but ipsilateral as T4 and in the bilateral lobe were classified as M1a (8th and 7th edition). In our study, the 1-,2-,3-,4- and 5-year disease free survival (DFS) rates were 93.42%, 86.84%, 77.78%, 62.96%, and 60.00%, respectively, while the

1-,2-,3-,4- and 5-year overall survival (OS) rates were 94.73%, 92.11%, 82.22%, 77.78%, and 65.00%, respectively. These were basically consistent with other researches [2–7]. The research of Shintani, T. et al [13] and Chang JY.et al [14]found that in SMPLC patients only treated with stereotactic body radiotherapy (SBRT), The 2-year and 4-year OS rates were 73.2% and 47.5%, respectively; DFS rates were 67% and 58%, far lower than the surgical-based comprehensive therapy. Other studies also supported this conclusion [15–16].Comprehensive studies had shown that the prognosis of patients with SMPLC was better than that of patients with lung cancer recurrence or metastasis [2–7]. Therefore, whether to treat multiple primary lung cancer as intrapulmonary metastasis for clinical staging remains to be further studied and discussed. At present, there is no systematic and authoritative treatment guideline for SMPLC, but our study showed that surgery can bring a great survival benefit. Therefore, for patients with SMPLC, it should never treat them as lung cancer recurrence or metastasis and give up surgery. Further research and discussion of clinical guidelines for SMPLC are still needed.

In the choice of surgical methods, the principle was radical resection of tumor and maximum preservation of pulmonary function at the same time. In our study, there was no significant difference in prognosis among patients who underwent multi lobectomy, lobectomy + sublobectomy and sublobectomy alone. The results may be due to the popularity of early screening in recent years, the early diagnosis and treatment of SMPLC make the prognosis difference small. Some literatures [17–18] suggested that sublobectomy was acceptable for patients with SMPLC at an early stage, with the equivalent prognosis to the standard resection and better pulmonary function preservation. While the study of Ishikawa, Y. et al [19] suggested that lobectomy was an independent risk factor for poor prognosis. In our study, there were 32 patients who underwent lobectomy only. Their 2-, 4-, and 5-year DFS survival rates were 84.38%, 61.54%, and 60.00%, and 2-, 4-, and 5-year OS survival rates were 84.38%., 69.23% and 70.00%. Another 46 patients underwent sublobectomy (sublobectomy and lobectomy + sublobectomy), their 2-, 4-, and 5-year DFS rates were 86.63%, 64.29%, and 60.00% and the 2-year, 4-year and 5-year OS rates were 97.73%, 85.71%, and 70.00%, which were all higher than the above-mentioned stereotactic radiotherapy (2-year and 4-year OS rates were 73.2% and 47.5%, respectively, and DFS rates were 67% and 58%, respectively). Although the survival rate of sublobectomy is higher than the rate after simple lobectomy, the latter has more patients in the middle and late stages, so more samples and evenly staged patients were still needed to compare the two surgical methods impact on the prognosis, but for patients who cannot tolerate simple lobectomy, sublobectomy (simple sublobectomy and lobectomy + sublobectomy) can bring a significant prognosis. In order to study the impact of surgical methods on patients with the same TNM stage, the author analyzed the stage I patients in this sample separately, but the surgical method had not been found to be an independent prognostic risk factor.

It was also found that the number of operations was not an adverse factor for DFS and OS in SMPLC patients. In our study, most of the unilateral tumors were removed with a single operation, and 5 of the 9 bilateral tumors were operated in different time. The treatment method was to first remove the tumor which was large, central, quick-progressing or with positive lymph node metastasis, and then remove the tumor which was small, peripheral, slow-progressing or no positive lymph node metastasis. The general principle was to deal with the main lesions with late stage and high malignancy first. And the remaining

lesions of the patients were closely followed up and treated in time for the second-stage operation. The study of Peng Y. et al [4] showed that simultaneous operation of bilateral lesions was feasible. There was no significant statistical difference in postoperative hospital stay between synchronous surgery and non-synchronous surgery. However, the study did not mention other postoperative conditions, such as extubation time and postoperative complications and the study was more based on clinical experience with no more significant statistical studies.

For DFS, the TNM stage of largest tumor was the only independent risk factor. For OS, smoking history and the TNM stage of largest tumor were independent risk factors. This study found that the 3-year survival rate of DFS and OS in patients whose largest tumor was TNM stage I were 84.85% and 87.88%, which were significantly higher than those of patients whose largest tumor was TNM stage > I (50.00% and 64.29%, respectively). In univariate analysis, T stage, N stage and TNM stage were all risk factors for DFS and OS. However, in multivariate analysis, only TNM stage was an independent risk factor for prognosis. Considering that TNM stage includes T stage and N stage, they were still closely related to the prognosis of patients, which is basically consistent with the results of other studies [3, 6–7, 20–21].

Smoking history was one of the independent prognostic risk factors for OS. Among 21 patients in our study, 18 were heavy smokers (smoker index > 400). The 5-year DFS rate and 5-year OS rate of heavy sMPLC smokers were only 33.3% and 44.44%, which were much lower than the overall 5-year rate of the patients in this study (DFS: 60.00%, OS: 65.00%). For patients with mild to moderate smoking, whether smoking history was an independent prognostic factor remained to be studied, but the existing study showed that smoking did harm to the human health, especially the lungs, and it was inseparable from the occurrence of lung cancer. The risk of lung cancer in smokers was 30 times higher than that of non-smokers. Tobacco smoke can lead to gene mutations, DNA damage, abnormal DNA methylation, DNA adduct formation, lung inflammation, oxidative stress, abnormal proliferation, abnormal differentiation, epithelial-mesenchymal transition (EMT) and so on[22–26].

In univariate analysis, postoperative adjuvant therapy was not conducive to the patients' DFS and OS. This should be due to the synergy with the independent risk factor TNM stage. Obviously, the prognosis of patients with high TNM stage was bad to the patients with low TNM stage and all the patients with high TNM stage in our study had adjuvant treatment after surgery, so in the univariate analysis, postoperative adjuvant therapy was a risk factor but not in the multivariate analysis. Some literatures showed that postoperative adjuvant chemotherapy can bring survival benefits [6, 27–28]. Based on the relevant research subjects, we found that it may be beneficial to the patients with late TNM stage and positive lymph node metastasis.

In clinical practice, there was no unified opinion on whether adjuvant therapy should be given to sMPLC patients whose largest tumor was TNM stage I. In order to study whether postoperative adjuvant therapy affects the prognosis of those patients, we separated them to carry out survival analysis. The univariate survival analysis found that smoking history and postoperative adjuvant therapy were risk factors for DFS. Gender, smoking history and postoperative adjuvant therapy were risk factors for OS. However, in

multivariate analysis, no independent survival risk factors were found in DFS and OS (P > 0.05). Considering that in the univariate analysis, postoperative adjuvant therapy in patients with TNM stage I of the largest tumor was a risk factor for DFS and OS, whether postoperative adjuvant therapy increased recurrence or death and whether it prolonged prognostic survival rate remained to be further studied. However, it was certain that during the operation, the relevant lymph nodes should be removed as radically as possible so that accurate lymph node staging can guide the follow-up treatment.

This study had found that age, preoperative symptomatic, family history of cancer, preoperative tumor markers, tumor laterality, tumor location, surgical type, surgical frequency, pathological types, vascular infiltration, and visceral pleural invasion had no significant impact on the prognosis of sMPLC, which still need further study.

Limitations: First of all, the sample size was insufficient, and there was a bias in the selection of patients. Patients with high pT stage and high pN stage were not enough in the study. Secondly, we did not include patients who only received non-surgical treatment (such as chemotherapy, radiotherapy, targeted therapy, etc.) and no rigorous comparison was operated. Thirdly, there was still a need for more sample sizes and evenly staged patients to compare the influence of surgical method and times on prognosis. Finally, no independent prognostic risk factors were found in SMPLC patients whose largest tumor was TNM stage I.

Conclusion

First, SMPLC is different from intrapulmonary metastasis and its clinical stage is also different from the 8^{th} (2015) edition TNM classification for lung cancer. Second, when pulmonary function permits, surgery (R0 resection and lymph node dissection) is a significantly beneficial treatment for patients with SMPLC. Third, heavy smoking and high TNM stage are not conducive to the prognosis of SMPLC patients

Abbreviations

SMPLC: synchronous multiple primary lung cancer; HRCT: high-resolution computed tomography; pT: tumor. pN: lymph node.; d: maximum diameter; HR, Hazard ratio; CI, confidence interval.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of Qilu Hospital, Cheeloo College of Medicine, Shandong University (KYLL-202008-179). Informed consent was waived because this was a retrospectively study. We obtained patient data from the Medical Records and Statistics Room. We analyzed the data anonymously and would abide by the confidentiality agreement. The use of the raw data was permitted by the Ethics Committee of Qilu Hospital, Cheeloo College of Medicine, Shandong University.

Consent for publication

Not applicable; no personal information is presented in this article.

Availability of data and materials

The data supporting our findings can be found by contacting us (zhaojianjn@sdu.edu.cn).

Competing interests

The authors declare that they have no competing interests.

Funding

1. Natural Science Foundation of Shandong Province No.ZR2018MH025
2. Primary Research & Development Plan of Shandong Province No.2019GSF108076

Authors' contributions

Haichao Li was majored in the study design, data extraction, data analysis, statistical analysis and was the major author of writing the manuscript. Kai Wang, Xingxing Zhang, Rong Chen and Jian Zhao all contributed to the study and the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank all people who responded to our screening and analysis.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and INT J CANCER. 2019;144(8):1941-53. doi:10.1002/ijc.31937.
2. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE 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. doi:10.1016/j.jtho.2015.09.009.
3. Yu YC, Hsu PK, Yeh YC, Huang CS, Hsieh CC, Chou TY et al. Surgical results of synchronous multiple primary lung cancers: similar to the stage-matched solitary primary lung cancers? ANN THORAC SURG. 2013;96(6):1966-74. doi:10.1016/j.athoracsur.2013.04.142.
4. Peng Y, Wang H, Xie H, Ren W, Feng Z, Li M et al. Surgical Treatment and Prognosis for Patients with Synchronous Multiple Primary Lung Adenocarcinomas. Zhongguo Fei Ai Za Zhi. 2017;20(2):107-13. doi:10.3779/j.issn.1009-3419.2017.02.05.

5. Peng Y, Ren W, Wang H, Li M, Feng Z, Peng Z. Surgical treatment is an effective approach for patients with synchronous multiple primary lung cancers. J CANCER RES THER. 2017;13(4):702-6. doi:10.4103/jcrt.JCRT_140_17.
6. Zhang Z, Gao S, Mao Y, Mu J, Xue Q, Feng X et al. Surgical Outcomes of Synchronous Multiple Primary Non-Small Cell Lung Cancers. Sci Rep. 2016;6:23252. doi:10.1038/srep23252.
7. Lv J, Zhu D, Wang X, Shen Q, Rao Q, Zhou X. The Value of Prognostic Factors for Survival in Synchronous Multifocal Lung Cancer: A Retrospective Analysis of 164 Patients. ANN THORAC SURG. 2018;105(3):930-6. doi:10.1016/j.athoracsur.2017.09.035.
8. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg. 1975;70(4):606-12
9. Kozower BD, Larner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. CHEST. 2013;143(5 Suppl):e369S-e399S. doi:10.1378/chest.12-2362.
10. Wu C, Zhao C, Yang Y, He Y, Hou L, Li X et al. High Discrepancy of Driver Mutations in Patients with NSCLC and Synchronous Multiple Lung Ground-Glass Nodules. J THORAC ONCOL. 2015;10(5):778-83. doi:10.1097/JTO.0000000000000487.
11. Fan J, Dai X, Wang Z, Huang B, Shi H, Luo D et al. Concomitant EGFR Mutation and EML4-ALK Rearrangement in Lung Adenocarcinoma Is More Frequent in Multifocal Lesions. CLIN LUNG CANCER. 2019;20(4):e517-30. doi:10.1016/j.cllc.2019.04.008.
12. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J THORAC ONCOL. 2007;2(8):706-14. doi:10.1097/JTO.0b013e31812f3c1a.
13. Shintani T, Masago K, Takayama K, Ueki K, Kimino G, Ueki N et al. Stereotactic Body Radiotherapy for Synchronous Primary Lung Cancer: Clinical Outcome of 18 Cases. CLIN LUNG CANCER. 2015;16(5):e91-6. doi:10.1016/j.cllc.2014.12.011.
14. Chang JY, Liu YH, Zhu Z, Welsh JW, Gomez DR, Komaki R et al. Stereotactic ablative radiotherapy: a potentially curable approach to early stage multiple primary lung cancer. CANCER-AM CANCER SOC. 2013;119(18):3402-10. doi:10.1002/cncr.28217.
15. Creach KM, Bradley JD, Mahasittiwat P, Robinson CG. Stereotactic body radiation therapy in the treatment of multiple primary lung cancers. RADIOTHER ONCOL. 2012;104(1):19-22. doi:10.1016/j.radonc.2011.12.005.
16. Griffioen GH, Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Treatment of multiple primary lung cancers using stereotactic radiotherapy, either with or without surgery. RADIOTHER ONCOL. 2013;107(3):403-8. doi:10.1016/j.radonc.2013.04.026.
17. Chen TF, Xie CY, Rao BY, Shan SC, Zhang X, Zeng B et al. Surgical treatment to multiple primary lung cancer patients: a systematic review and meta-analysis. BMC SURG. 2019;19(1):185.

'doi:'10.1186/s12893-019-0643-0.

18. Toufektzian L, Attia R, Veres L. Does the extent of resection affect survival in patients with synchronous multiple primary lung cancers undergoing curative surgery? Interact Cardiovasc Thorac Surg. 2014;19(6):1059-64. doi:10.1093/icvts/ivu295.
19. Ishikawa Y, Nakayama H, Ito H, Yokose T, Tsuboi M, Nishii T et al. Surgical treatment for synchronous primary lung ANN THORAC SURG. 2014;98(6):1983-8. doi:10.1016/j.athoracsur.2014.07.006.
20. Zhang ZR, Mao YS, Gao SG, Mu JW, Xue Q, Wang DL et al. [Survival after surgical treatment of bilateral synchronous multiple primary non-small cell lung cancers]. Zhonghua Zhong Liu Za Zhi. 2016;38(6):460-5. doi:10.3760/cma.j.issn.0253-3766.2016.06.011.
21. Chang YL, Wu CT, Lee YC. Surgical treatment of synchronous multiple primary lung cancers: experience of 92 patients. J Thorac Cardiovasc Surg. 2007;134(3):630-7. doi:10.1016/j.jtcvs.2007.06.001.
22. Yoshida K, Gowers K, Lee-Six H, Chandrasekharan DP, Coorens T, Maughan EF et al. Tobacco smoking and somatic mutations in human bronchial epithelium. NATURE. 2020;578(7794):266-72. doi:10.1038/s41586-020-1961-1.
23. Pfeifer GP. Smoke signals in the DNA of normal lung cells. NATURE. 2020;578(7794):224-6. doi:10.1038/d41586-020-00165-7.
24. Vaz M, Hwang SY, Kagiampakis I, Phallen J, Patil A, O'Hagan HM et al. Chronic Cigarette Smoke-Induced Epigenomic Changes Precede Sensitization of Bronchial Epithelial Cells to Single-Step Transformation by KRAS Mutations. CANCER CELL. 2017;32(3):360-76. doi:10.1016/j.ccell.2017.08.006.
25. Ahluwalia IB, Smith T, Arrazola RA, Palipudi KM, Garcia DQI, Prasad VM et al. Current Tobacco Smoking, Quit Attempts, and Knowledge About Smoking Risks Among Persons Aged 5 Years - Global Adult Tobacco Survey, 28 Countries, 2008-2016. MMWR Morb Mortal Wkly Rep. 2018;67(38):1072-6. doi:10.15585/mmwr.mm6738a7.
26. Goldkorn T, Filosto S, Chung S. Lung injury and lung cancer caused by cigarette smoke-induced oxidative stress: Molecular mechanisms and therapeutic opportunities involving the ceramide-generating machinery and epidermal growth factor receptor. Antioxid Redox Signal. 2014;21(15):2149-74. doi:10.1089/ars.2013.5469.
27. Kocaturk CI, Gunluoglu MZ, Cansever L, Demir A, Cinar U, Dincer SI et al. Survival and prognostic factors in surgically resected synchronous multiple primary lung cancers. Eur J Cardiothorac Surg. 2011;39(2):160-6. doi:10.1016/j.ejcts.2010.05.037.
28. Trousse D, Barlesi F, Loundou A, Tasei AM, Doddoli C, Giudicelli R et al. Synchronous multiple primary lung cancer: an increasing clinical occurrence requiring multidisciplinary management. J Thorac Cardiovasc Surg. 2007;133(5):1193-200. doi:10.1016/j.jtcvs.2007.01.012.

Tables

Table 1

Clinical characteristics and Univariate analysis of disease free survival and overall survival in 78 SMPLC patients

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	P value	HR	95%CI	P value
Sex				0.001			0.001
Female	48	1.00	Reference		1.00	Reference	
Male	30	5.46	1.76–16.96		9.06	1.98–41.39	
Age, yrs				0.213			0.258
< 60	39	1.00	Reference		1.00	Reference	
>=60	39	0.49	0.16–1.54		0.49	0.13–1.81	
Symptom†,				0.015			0.007
No	55	1.00	Reference		1.00	Reference	
Yes	23	3.45	1.19–9.99		5.06	1.36–18.84	
Smoking				0.001			0.000
No	57	1.00	Reference		1.00	Reference	
Yes	21	5.00	1.81–13.79		8.81	2.38–32.57	
Family history of cancer ‡				0.900			0.712
No	74	1.00	Reference		1.00	Reference	
Yes	4	1.14	0.15–8.73		1.51	0.19–11.82	

Abbreviations: No, number. ADC, adenocarcinoma. pT, tumor; pN, lymph node; d, maximum diameter.

†: Including fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.

‡: First degree relatives.

§: Squamous cell carcinoma antigen (SCCA) > 1.5 ng/ml; alpha-fetoprotein (AFP) > 20 ng/ml; carcinoembryonic antigen(CEA) > 5 ng/ml; ferritin (Ferr) > 400 ng/ml; carbohydrate antigen 199 (CA-199) > 39 U/ml; carbohydrate antigen 125 (CA-125) > 35 U/ml; carbohydrate antigen 724 (CA-724) > 6.9 U/ml; sialic acid (SA) > 75.4 mg/dl.

#: The new revision of T stage in the forthcoming 8th TNM system.

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	P value	HR	95%CI	P value
Preoperative tumor marker				0.947			0.804
No-rise	12	1.00	Reference		1.00	Reference	
Rise§	19	1.05	0.25–4.40		1.24	0.23–6.77	
Laterality				0.431			0.229
Unilateral	69	1.00	Reference		1.00	Reference	
Bilateral	9	1.71	0.49–6.02		2.39	0.64–8.89	
Location of lobe				0.261			0.429
Same lobe	21	1.00	Reference		1.00	Reference	
Different lobe	52	1.64	0.47–5.76		1.19	0.32–4.40	
Combined lobe†	5	0.00	0.00–0.00		0.00	0.00–0.00	
No. of tumors				0.764			0.798
2	65	1.00	Reference		1.00	Reference	
>=3	13	0.80	0.18–3.56		1.23	0.26–5.80	
Surgical types				0.659			0.431
Lobectomy	32	1.00	Reference		1.00	Reference	
Lobectomy + sublobectomy	35	0.64	0.22–1.85		0.50	0.15–1.72	
Multi-sublobectomy	11	0.61	0.13–2.87		0.40	0.05–3.22	
Staging Operation				0.344			0.217

Abbreviations: No, number. ADC, adenocarcinoma. pT, tumor; pN, lymph node; d, maximum diameter.

†: Including fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.

‡: First degree relatives.

§: Squamous cell carcinoma antigen (SCCA) > 1.5 ng/ml; alpha-fetoprotein (AFP) > 20 ng/ml; carcinoembryonic antigen(CEA) > 5 ng/ml; ferritin (Ferr) > 400 ng/ml; carbohydrate antigen 199 (CA-199) > 39 U/ml; carbohydrate antigen 125 (CA-125) > 35 U/ml; carbohydrate antigen 724 (CA-724) > 6.9 U/ml; sialic acid (SA) > 75.4 mg/dl.

#: The new revision of T stage in the forthcoming 8th TNM system.

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	P value	HR	95%CI	P value
Single-stage	72	1.00	Reference		1.00	Reference	
Two-stage	6	2.21	0.50–9.85		2.98	0.64–13.81	
Histology type				0.005			0.001
All ADCs	66	1.00	Reference		1.00	Reference	
Not all ADCs	12	4.76	1.73–13.09		8.17	2.51–26.58	
Highest pT stage#(d, cm)				0.006			0.025
T1(d ≤ 3)	60	1.00	Reference		1.00	Reference	
T2(3 < d ≤ 5)	15	4.45	1.53–12.96		3.58	1.02–12.57	
T3 + 4(d > 5)	3	8.57	1.69–43.40		10.00	1.88–53.24	
pN stage#				0.000			0.000
N0	72	1.00	Reference		1.00	Reference	
N1 + 2	6	8.78	3.16–24.37		8.34	2.62–26.54	
TNM stage#				0.000			0.000
I	64	1.00	Reference		1.00	Reference	
II	12	16.12	5.00-51.98		12.40	3.55–43.30	

Abbreviations: No, number. ADC, adenocarcinoma. pT, tumor; pN, lymph node; d, maximum diameter.

†: Including fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.

‡: First degree relatives.

§: Squamous cell carcinoma antigen (SCCA) > 1.5 ng/ml; alpha-fetoprotein (AFP) > 20 ng/ml; carcinoembryonic antigen(CEA) > 5 ng/ml; ferritin (Ferr) > 400 ng/ml; carbohydrate antigen 199 (CA-199) > 39 U/ml; carbohydrate antigen 125 (CA-125) > 35 U/ml; carbohydrate antigen 724 (CA-724) > 6.9 U/ml; sialic acid (SA) > 75.4 mg/dl.

#: The new revision of T stage in the forthcoming 8th TNM system.

Variables	Total	Disease free survival			Overall survival		
		HR	95%CI	P value	HR	95%CI	P value
III	2	22.30	4.00-124.1		9.33	1.03–84.51	
Vascular invasion				1.000			1.000
No	76	1.00	Reference		1.00	Reference	
Yes	2	small quantity, not analyze			small quantity, not analyze		
Visceral pleural invasion				0.926			0.893
No	73	1.00	Reference		1.00	Reference	
Yes	5	0.91	0.12–6.91		1.15	0.15–8.93	
Adjuvant therapy				0.001			0.003
No	38	1.00	Reference		1.00	Reference	
Yes	33	54.61	0.74->1000		53.10	0.41->1000	

Abbreviations: No, number. ADC, adenocarcinoma. pT, tumor; pN, lymph node; d, maximum diameter.

†: Including fever, cough, expectoration, hemoptysis, chest tightness, shortness of breath, chest pain, etc.

‡: First degree relatives.

§: Squamous cell carcinoma antigen (SCCA) > 1.5 ng/ml; alpha-fetoprotein (AFP) > 20 ng/ml; carcinoembryonic antigen(CEA) > 5 ng/ml; ferritin (Ferr) > 400 ng/ml; carbohydrate antigen 199 (CA-199) > 39 U/ml; carbohydrate antigen 125 (CA-125) > 35 U/ml; carbohydrate antigen 724 (CA-724) > 6.9 U/ml; sialic acid (SA) > 75.4 mg/dl.

#: The new revision of T stage in the forthcoming 8th TNM system.

Table 2

Clinical characteristics and multivariate analysis of disease free survival and overall survival in 78 SMPLC patients

Variables	**Total**	**Disease free survival**		
		HR	**95%CI**	**P value**
TNM stage#				0.002
I	64	1.00	Reference	
II	12	7.4	2.26–24.16	
III	2	9.01	1.62–50.05	
Variables	Total	Overall survival		
		HR	95%CI	P value
Smoking				0.039
No	57	1.00	Reference	
Yes	21	4.34	1.08–17.55	
TNM stage#				0.003
I	64	1.00	Reference	
II	12	9.38	2.25–39.17	
III	2	9.42	0.95–93.96	
#: The new revision of T stage in the forthcoming 8th TNM system				

Figures

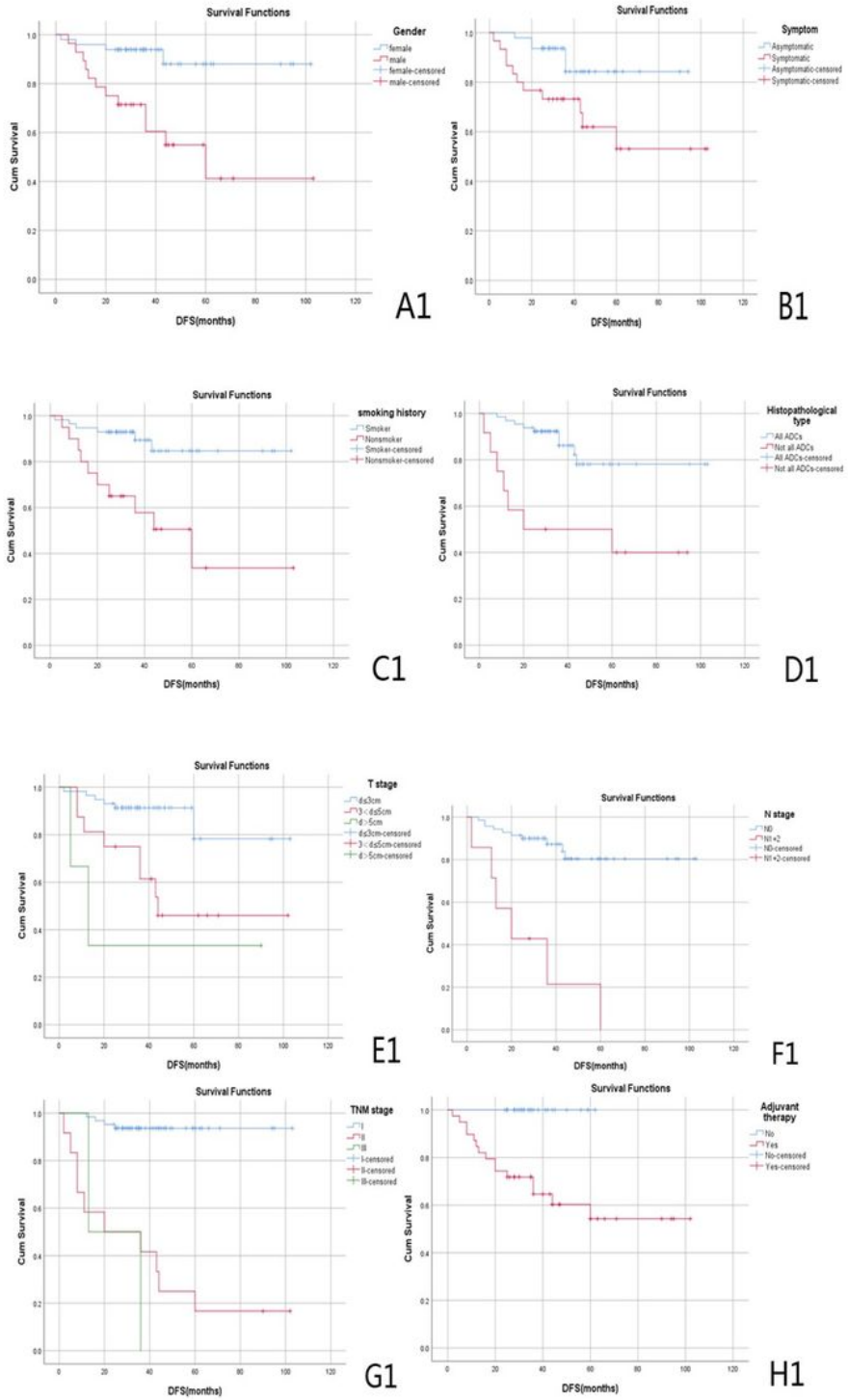

Figure 1

Kaplan-Meier survival estimates of the disease-free survival (DFS) stratified by (A1) Gender, (B1) Symptom, (C1) Smoking history, (D1) Histopathological type, (E1) T stage, (F1) N stage, (G1)TNM stage and (H1) Adjuvant therapy

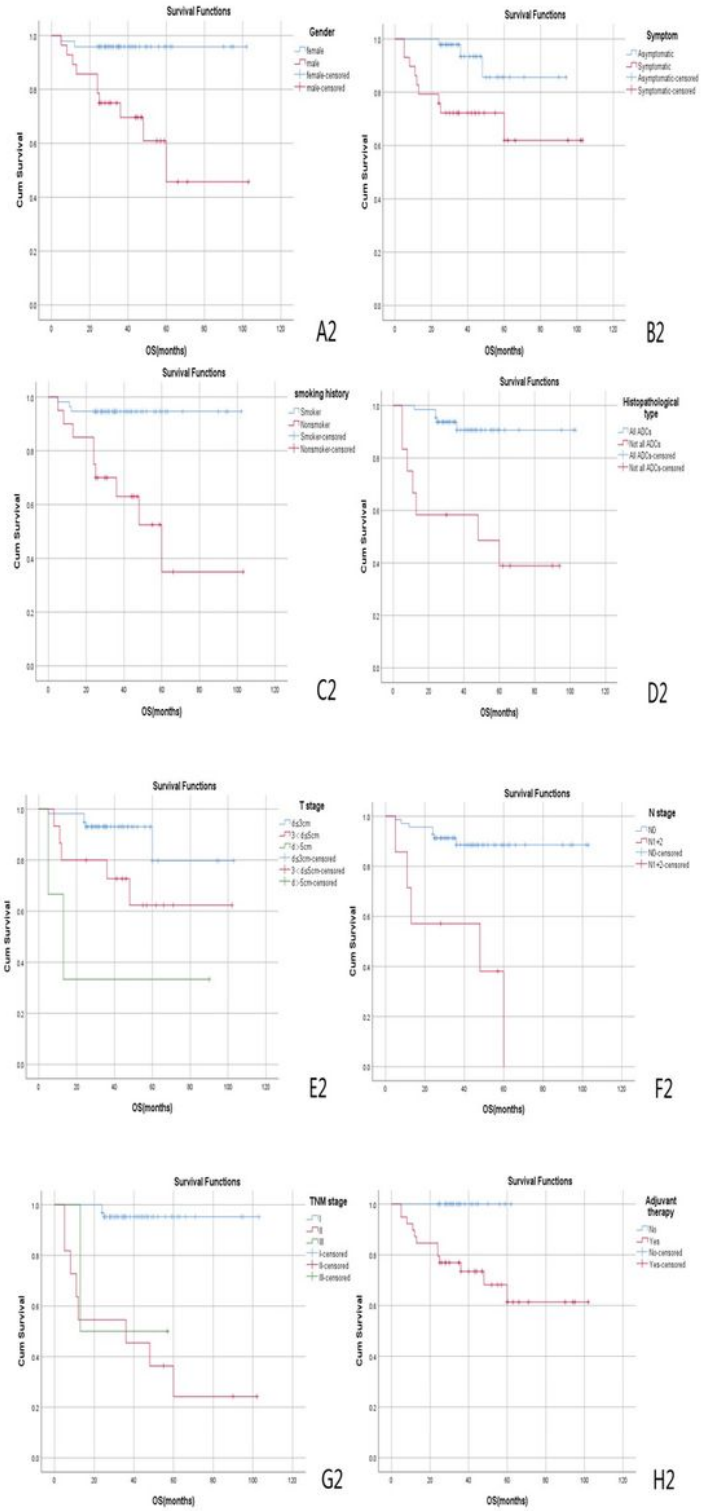

Figure 2

Kaplan-Meier survival estimates of the overall survival (OS) stratified by (A2) Gender, (B2) Symptom, (C2) Smoking history, (D2) Histopathological type, (E2) T stage, (F2) N stage, (G2)TNM stage and (H2) Adjuvant therapy