Synchronous bone metastasis in lung cancer: retrospective study of a single center of 15,716 patients from Tianjin, China

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Abstract

Background: This study aimed to describe the incidence, clinical characteristics, and prognosis of lung cancer patients with synchronous bone metastasis (SBM) and to analyze the prognostic factors of the lung cancer patients with SBM.

Methods: A total of 15,716 lung cancer patients who were diagnosed between 2009 to 2018 in the Tianjin Medical University Cancer Institute and Hospital were retrospectively reviewed. Among them, patients with SBM were checked. Both the demographic and clinical characteristics were included as follows: age, gender, marital status, history of smoking, alcohol consumption, family history of tumor, Karnofsky score, lymph node metastasis, histological type. Besides, laboratory data such as alkaline phosphatase, lactate dehydrogenase, carcinoembryonic antigen, squamous cell carcinoma antigen, cytokeratin-19 fragment, and neuron specific enolase were also included. The log-rank test and multivariate Cox regression analysis were employed to reveal the potential prognostic predictors. A further analysis using the Kaplan–Meier was employed to demonstrate the difference on the prognosis of LC patients between adenocarcinoma and non-adenocarcinoma.

Results: Among the included patients, 2738 patients (17.42%) were diagnosed with SBM. A total of 938 patients (34.3%) with SBM were successfully followed and the median survival was 11.53 months (95%CI: 10.57–12.49 months), and the 1-, 2-, and 5-year overall survival rate was 51, 17, and 8%, respectively. Multivariable Cox regression results showed history of smoking and high level of NSE were associated with the poor prognosis, while adenocarcinoma histological type was associated with better survival.

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Conclusion: The prevalence of SBM in lung cancer is relatively high with poor survival. The lung cancer patients with SBM showed diverse prognosis. Among all the pathological types, the division of adenocarcinoma suggested different prognosis of the lung cancer patients with SBM. The present study emphasized the importance of pathological diagnosis on prognostic determinants in lung cancer patients with SBM.

Keywords: Lung Cancer, Synchronous bone metastasis, Prognosis, Adenocarcinoma

Background
Lung cancer (LC) has become the most common cancer and the leading cause of cancer-related deaths in the world. Approximately 13% of the estimated new cancers and 24% of estimated deaths were caused by LC in 2019 [1].

Due to a special microenvironment in the bone matrix, bone was accepted to be one of the most common distal metastatic sites, especially for LC [2]. A retrospective cohort study reported a total of 245 patients (19.1%) suffered bone metastasis (BM) among 1283 LC patients [3]. A higher incidence (28.2%) in LC was also reported by Oliveira MB et al. [4] and 36.9% in small cell lung cancer by Conen K [5]. LC patients with BM were usually with frustrating quality of life, resulted by the occurrence of skeletal-related events (SREs), including severe pain, orthopedic surgery interventions, palliative radiation to the bone, hypercalcaemia, pathologic bone fractures, and spinal cord compression. A total of 62.6% of non-small cell lung cancer (NSCLC) patients showed at least one SREs and 16.8% of them showed multiple SREs [6]. The optimal treatment of SREs was accepted to be the early treatment and prevention of BM. Thus, the study looking into BM in LC is warrant.

BM in lung cancer can be found at diagnosis, while minority can be found in their later course after diagnosis [7]. Synchronous bone metastasis (SBM) and metachronous bone metastasis (MBM) were previously defined as different types of BM. Few studies looking into the differences between SBM and MBM in LC were performed. However, SBM and MBM in LC may represent distinct clinico-pathological characteristics, therapeutic sensitivity, and prognostic outcomes [8]. Such difference resulted in the individualized treatment plans.

Compared with the LC patients with MBM, a significant tumor burden and a complicated organism destroy in patients with SBM can usually be found [9]. Thus, the patients with SBM usually suffer more mental stress and financial burden. The accurate prognostic determinants are of significance on generalizing individualized clinical decision.

A series of prognosis prediction models for BM were reported and employed. Ignoring the difference between SBM and MBM, the revised Tokuhashi score system for spinal metastasis classified lung cancer as score 0, indicating the worst prognosis. Such classification neglected the effect of histological type on the survival of LC patients [10, 11]. Lately, Tokuhashi suggested that the system should include serum biomarkers, which can improve the predictive ability and the accuracy of survival estimation [12]. In the revised Katagiri system, lung cancer patients with BM were divided into two groups according to the treatment with molecularly targeted drugs. Those LC patients with molecularly targeted drugs were classified as moderate growth tumor, while those without targeted drugs were classified as rapid growth tumor [13]. However, seldom patients with SBM were diagnosed with molecularly targeted drugs. Our previous study, based on Surveillance, Epidemiology, and End Results (SEER) database, reported different survivals in various histological types of LC patients with BM [14]. The results suggested the histological type was one of the independent prognostic factors for LC patients with SBM. Considering the racial difference between the east and west, we performed the present research to further study SBM in LC.

In the present study, we conducted a comprehensive analysis on the survival and clinical characteristics in a large cohort of LC patients with SBM. We also investigated the factors that being associated with BM occurrence and prognosis, which could help the clinicians predict the prognosis and tailor targeted treatment regimens for lung cancer patients with SBM.

Methods
This retrospective analysis was approved by the Ethics Committee of Tianjin Medical University Cancer Institute & Hospital. The medical records of LC patients were electronically and manually checked. Between January 2009 and December 2018, a total of 15,930 LC patients were initially diagnosed in our hospital. The patients younger than 18 years old or with uncertain bone metastasis were excluded, 15,716 LC patients were retrieved. Among them, LC patients with SBM were chosen for prognostic analysis. The exclusion criteria were (1) those who were diagnosed without BM; (2) those who were diagnosed with MBM in LC; (3) those who were not followed during follow-up. Patients were followed through clinic and telephone. Death was further confirmed by linking the death register system of Tianjin Centers for Disease Control. SBM was defined as BM diagnosis within 3 months with LC diagnosis, while...
MBM was defined as BM diagnosis more than 3 months after LC diagnosis. The flow-chart of the subjects’ selection was shown in Fig. 1.

**Statistical analysis**

Patients’ demographic and clinical characteristics were included as follows: age (18–45 years, 46–65 years or > 65 years), gender (female or male), marital status (married and other status or unmarried), history of smoking (yes or none), alcohol consumption (yes or none), family history of cancer (yes or none), Karnofsky score (10–40, 50–70, or 80–100), lymph node metastasis (yes or none), histological type (small cell lung cancer, adenocarcinoma, squamous cell carcinoma, large cell lung cancer, mixed lung cancer or others). Laboratory data for SBM patients were also investigated. The median level of the data was defined as threshold value, including alkaline phosphatase (ALP: < 102.00 mmol/L or ≥ 102.00 mmol/L), lactate dehydrogenase (LDH: < 215.00 U/L or ≥ 215.00 U/L), carcinoembryonic antigen (CEA: < 15.64 ng/ml or ≥ 15.64 ng/ml), squamous cell carcinoma antigen (SCC: < 0.80 ng/ml or ≥ 0.80 ng/ml), cytokeratin-19 fragment (Cyfra21–1: < 4.93 ng/ml or ≥ 4.93 ng/ml), neuron specific enolase (NSE: < 16.67 ng/ml or ≥ 16.67 ng/ml).

The overall survival was analyzed using the Kaplan–Meier method and the difference was tested by the log-rank test. Multivariable Cox regression model, including significant univariate factors \((P < 0.05)\) was conducted for analyzing the independent prognostic factors for LC patients with SBM. According to the results, a further analysis using the Kaplan–Meier method was employed to demonstrate the LC patients’ prognosis differences between adenocarcinoma and non-adenocarcinoma. All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Armonk, NY) and all charts on

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**Fig. 1** The flow-chart of the selection for lung cancer patients with synchronous bone metastasis
survival were conducted by MedCalc 15.2.2. Two-sided $P < 0.05$ were considered as statistically significant.

**Results**

**Demographic data**

Among the included patients, 2738 (17.42%) were diagnosed with SBM. A total of 938 LC patients with SBM (550 males and 388 females) were with reliable prognosis of follow-up. The mean age of these patients was 61.41 ± 9.94 years. Except the patients without explicit histological type (40.40%), the most common histological type is adenocarcinoma in 331 patients (35.29%), followed by squamous cell carcinoma (13.21%), small-cell lung cancer (SCLC) (7.36%), mixed carcinoma (2.35%), and large-cell carcinoma in 13 patients (1.39%). All detailed information of the included patients was summarized in Table 1.

**Survival rates and prognostic factors**

The median survival time of 938 patients was 11.53 months (95%CI: 10.57–12.49 months). The 1-, 2-, and 5-year overall survival rate was 51, 17, and 8%, respectively. Survival curves for patients was shown in Fig. 2A.

Log-rank test showed the overall survival in subjects with older age (Fig. 2B, $P < 0.001$), male (Fig. 2C, $P = 0.003$), history of smoking (Fig. 2D, $P < 0.001$), KPS = 50–70 (Fig. 2E, $P = 0.010$), with lymph node metastasis (Fig. 2F, $P = 0.020$), higher level of LDH (Fig. 2H, $P < 0.001$), Cyfra21–1 (Fig. 2I, $P < 0.001$) and NSE (Fig. 2J, $P < 0.001$) were worse than that with the counterparts (Table 2). The patients of adenocarcinoma presented significantly better overall median survival (15.67 months, 95%CI: 13.22–18.12) (Fig. 2G, $P < 0.001$).

Multivariable Cox regression results suggested the patients with history of smoking and high level of NSE were associated with poor prognosis. LC Patients with adenocarcinoma were associated with better survival in patients with SBM. The overall median survival of LC adenocarcinoma patients with SBM was 15.67 months (95%CI: 13.22–18.12), while that in non-adenocarcinoma was 9.73 months, (95%CI: 7.62–11.85) (Fig. 3, $P < 0.001$).

**Discussion**

To our knowledge, based on the largest single center population, the present research studied SBM in patients with LC. A total of 2738 LC patients (17.42%) were diagnosed with SBM in 15,716 LC patients. Such incidence was less than our previous reported incidence (20.9%) in a study based on the data from the SEER dataset [14].

The present study suggested the median survival of LC patients with SBM was 11.53 months. Different levels of survival between the patients with synchronous and metachronous bone metastasis were reported [7, 15–17]. It was reported the survival of 18.04 months in LC patients with SBM and 9.12 months in LC patients with MBM [8]. The criteria studying synchronous and metachronous metastasis in cancer was still indefinite. For the cancer patients with metachronous metastasis, the survival can be defined from the initial diagnosis of primary cancer to death, while from the diagnosis of metastasis to death [9, 18, 19]. This may be the main cause of the different results of OS between synchronous and metachronous metastasis in previous studies [8, 9]. The potential explanation for the better survival in cancer patients with synchronous metastasis than those with metachronous metastasis was the occurrence of chemotherapy resistance in the patients with metachronous metastasis [20]. Such resistance significantly limited the treatment choice of the first-line chemotherapy [8]. To get the data standardized, the present study defined OS being within 3 months from BM diagnosis, instead of lung cancer diagnosis. Such standardized definition can make sense to the prediction of prognosis and clinical treatment decisions based on the clinical features in LC patients with SBM.

Three prognostic factors in LC patients with SBM were found, including smoking, high level of NSE and histological type. Recently, Tokuhashi et al. suggested that the predictive model should include serum biomarkers [12]. Some serum factors were reported to be correlated with the prognosis, including the levels of ALP, and LDH [21, 22]. However, in our study with the large population, we did not find the significant correlation between the prognosis and most blood test factors. A series of commonly used indicators were involved, including ALP, LDH, CEA, SCC, Cyfra21–1 and NSE. NSE was proved to be the only indicator with significant effect on the survival of LC patients with SBM. NSE was previously proved to be an important indicator for tumor aggressiveness and bone metastasis development [23, 24]. NSE was found to be one of the prognostic factors in metastatic prostate cancer [25]. Thus, NSE can be a potential prognostic predictor in LC patients with BM.

Another independent prognostic factor of LC patient with SBM was smoking. It was concluded that smoking affected various organs and was a leading cause of premature disease and death [26]. The metabolism of tobacco carcinogens, variations in nicotine receptor-related genes, inflammatory response to the tobacco-induced lung damage and DNA repair were reported to be the consequences of the smoking [27–30]. Smoking was reported to potentially inhibit chemo- and radiotherapy response [31]. Thus, smoking was widely accepted to be a prognostic factor of LC patients [32]. Our study further proved it was one of the prognostic factors of LC patients with SBM.
Table 1 Demographic information of the included patients

| Clinical subjects                        | Number of patients | Proportion (%) |
|------------------------------------------|--------------------|----------------|
| **Age, (years)**                         |                    |                |
| 18–45                                    | 51                 | 5.44           |
| 46–65                                    | 572                | 60.98          |
| > 65                                     | 315                | 33.58          |
| **Gender**                               |                    |                |
| Female                                   | 388                | 41.36          |
| Male                                     | 550                | 58.64          |
| **Marital status**                       |                    |                |
| Married                                  | 933                | 99.47          |
| Unmarried                                | 5                  | 0.53           |
| **History of smoking**                   |                    |                |
| None                                     | 436                | 46.48          |
| Yes                                      | 501                | 53.41          |
| Unknown                                  | 1                  | 0.11           |
| **Alcohol consumption**                  |                    |                |
| None                                     | 703                | 74.95          |
| Yes                                      | 234                | 24.94          |
| Unknown                                  | 1                  | 0.11           |
| **Family history of tumor**              |                    |                |
| None                                     | 754                | 80.38          |
| Yes                                      | 183                | 19.51          |
| Unknown                                  | 1                  | 0.11           |
| **KPS**                                  |                    |                |
| 10–40                                    | 7                  | 0.75           |
| 50–70                                    | 128                | 13.65          |
| 80–100                                   | 395                | 42.11          |
| Unknown                                  | 408                | 43.49          |
| **Lymph node metastasis**                |                    |                |
| None                                     | 368                | 39.23          |
| Yes                                      | 537                | 57.25          |
| Unknown                                  | 33                 | 3.52           |
| **Pathology**                            |                    |                |
| Small-cell                               | 69                 | 7.36           |
| Adenocarcinoma                           | 331                | 35.29          |
| Squamous cell                            | 124                | 13.22          |
| Large cell                               | 13                 | 1.38           |
| Mixed                                    | 22                 | 2.34           |
| Others (unknown)                         | 379                | 40.41          |
| **ALP**                                  |                    |                |
| < 102.00 mmol/L                          | 347                | 36.99          |
| ≥ 102.00 mmol/L                          | 355                | 37.85          |
| Unknown                                  | 236                | 25.16          |
| **LDH**                                  |                    |                |
| < 215.00 U/L                             | 420                | 44.78          |
Table 1 Demographic information of the included patients (Continued)

| Clinical subjects | Number of patients | Proportion (%) |
|-------------------|--------------------|----------------|
| ≥ 215.00 U/L      | 438                | 46.70          |
| Unknown           | 80                 | 8.52           |
| CEA               |                    |                |
| < 15.64 ng/ml     | 404                | 43.07          |
| ≥ 15.64 ng/ml     | 405                | 43.18          |
| Unknown           | 129                | 13.75          |
| SCC               |                    |                |
| < 0.80 ng/ml      | 402                | 42.86          |
| ≥ 0.80 ng/ml      | 404                | 43.07          |
| Unknown           | 132                | 14.07          |
| Cyfra21–1         |                    |                |
| < 4.93 ng/ml      | 401                | 42.75          |
| ≥ 4.93 ng/ml      | 401                | 42.75          |
| Unknown           | 136                | 14.50          |
| NSE               |                    |                |
| < 16.67 ng/ml     | 401                | 42.75          |
| ≥ 16.67 ng/ml     | 402                | 42.86          |
| Unknown           | 135                | 14.39          |

KPS Karnofsky score, ALP Alkaline phosphatase, LDH Lactate dehydrogenase, CEA Carcinoembryonic antigen, SCC Squamous cell carcinoma antigen, Cyfra21–1 Cytokeratin-19 fragment, NSE Neuron specific enolase

Fig. 2 The survival curves for lung cancer patients with synchronous bone metastasis (A, overall), stratified by age (B), gender (C), smoke (D), KPS (E), lymph node metastasis (F), pathology (G), LDH (H), Cyfra21–1 (I) and NSE (J)
The median survival of adenocarcinoma LC with SBM was 15.67 months, while that of non-adenocarcinoma LC was 9.63 months \((P < 0.001)\). Compared with other histological types in LC patients, poor survival of LC patients with non-adenocarcinoma was reported. The frustrating survival might be caused by poor response from the tyrosine kinase inhibitors (TKIs) therapy \([33]\). In previous studies, to properly manage the patients with

| Clinical subjects | Median survival (95%CI), mons | HR (95%CI) | P-value |
|-------------------|-------------------------------|------------|---------|
| **Age, (years)**  |                               |            |         |
| 18–45             | 11.90 (10.08–13.72)           | 1 (Reference) | 1.00    |
| 46–65             | 12.97 (11.65–14.28)           | 0.85 (0.45–1.60) | 0.61    |
| > 65              | 8.13 (6.70–9.57)              | 1.12 (0.58–2.17) | 0.81    |
| **Gender**        |                               |            |         |
| Female            | 13.43 (11.95–14.92)           | 1 (Reference) | 1.00    |
| Male              | 9.63 (8.44–10.83)             | 1.04 (0.75–1.47) | 0.80    |
| **History of smoking** |                         |            |         |
| None              | 14.13 (12.42–15.85)           | 1 (Reference) | 1.00    |
| Yes               | 9.23 (7.92–10.55)             | 1.42 (1.02–1.96) | 0.04    |
| Unknown           | NA                            | NA         |         |
| **KPS**           |                               |            |         |
| 10–40             | 14.47 (0.00–40.30)            | 1 (Reference) | 1.00    |
| 50–70             | 8.30 (4.88–11.72)             | 2.28 (0.77–6.79) | 0.14    |
| 80–100            | 12.43 (11.12–13.74)           | 1.94 (0.67–5.63) | 0.22    |
| Unknown           | NA                            | NA         |         |
| **Lymph node metastasis** |                         |            |         |
| None              | 13.37 (11.33–15.40)           | 1 (Reference) | 1.00    |
| Yes               | 10.77 (9.56–11.98)            | 1.10 (0.81–1.45) | 0.51    |
| Unknown           | NA                            | NA         |         |
| **Pathology**     |                               |            |         |
| Small-cell        | 10.10 (7.48–12.73)            | 1.22 (0.78–1.91) | 0.38    |
| Adenocarcinoma    | 15.67 (13.22–18.12)           | 1 (Reference) | 1.00    |
| Squamous cell     | 9.73 (7.62–11.85)             | 1.42 (0.98–2.05) | 0.06    |
| Large cell        | 8.67 (2.99–14.34)             | 1.85 (0.80–4.30) | 0.15    |
| Mixed             | 7.10 (4.15–10.05)             | 2.09 (1.11–3.94) | 0.02    |
| Unknown           | NA                            | NA         |         |
| **LDH**           |                               |            |         |
| < 215.00 U/L      | 13.43 (11.90–14.96)           | 1 (Reference) | 1.00    |
| ≥ 215.00 U/L      | 8.67 (7.37–9.97)              | 1.12 (0.82–1.51) | 0.48    |
| Unknown           | NA                            | NA         |         |
| **Cyfra21–1**     |                               |            |         |
| < 4.93 ng/ml      | 15.33 (13.36–17.31)           | 1 (Reference) | 1.00    |
| ≥ 4.93 ng/ml      | 8.30 (7.17–9.43)              | 1.26 (0.93–1.71) | 0.13    |
| Unknown           | NA                            | NA         |         |
| **NSE**           |                               |            |         |
| < 16.67 ng/ml     | 15.00 (12.74–17.27)           | 1 (Reference) | 1.00    |
| ≥ 16.67 ng/ml     | 9.23 (7.86–10.61)             | 1.42 (1.06–1.92) | 0.02    |
| Unknown           | NA                            | NA         |         |

*KPS* Karnofsky score, *LDH* Lactate dehydrogenase, *Cyfra21–1* Cytokeratin-19 fragment, *NSE* Neuron specific enolase
cancer, the cancer patients were separated into the slow (estimated survival > 20 months), moderate (estimated survival 10 to 20 months), and rapid (estimated survival < 10 months) growth groups [13, 34, 35]. Therefore, LC adenocarcinoma patients with SBM should be treated as the guideline for moderate growth group, while non-adenocarcinoma with SBM as rapid growth group. Thus, the clarification pathologic diagnosis of LC is of significant importance for the prognostic determinants in LC patients with SBM.

In our previous study using the SEER data, the median survival of LC with SBM was 4.00 months. Histological type and number of the metastatic sites (brain, lung and liver metastasis) were proved to be the independent prognosis factors [14]. When stratified by different histological types, the OS of adenocarcinoma was significantly longer than OS of other histological types, which was consistent with the present study. Survival difference between our previous SEER study and the present study was potentially resulted by the cohort with different regional and ethnic. Another potential explanation for such difference may result in the developed treatment for LC with SBM in recent years. Compared with the present study, SEER public database did not provide the information on performance status, smoking status, and serum biomarkers such as ALP, LDH, CEA, SCC, Cyfra21–1 and NSE. In both studies with SEER database and single center database, histological type was proved to be one of the independent prognostic factors in LC with SBM. However, Tokuhashi and Tomita scores roughly treated lung cancer as rapid growth tumor. Based on the present study, lung cancer should be categorized into different classifications, adenocarcinoma as moderate growth group, and non-adenocarcinoma as rapid growth group.

Several limitations of this study should be mentioned: (1) detailed information on the numbers and locations of bone metastasis were not recorded; (2) the present study was a single-center retrospective study, thus the bias in the program might be exist; (3) external validation was needed to further verify the results.

Conclusions
This study evaluated the incidence of SBM in LC, reported the clinical features and prognosis of LC patients with SBM, and identified a series of prognostic factors in LC patients with SBM. The survival of LC patients with SBM was of significant difference. To properly predict the prognosis, we suggested the importance of clarification pathologic diagnosis of lung cancer in LC patients with SBM. The division of adenocarcinoma patients in LC patients with SBM can significantly guide the management of disease and aid clinicians in properly allocating medical resources to the patients.

Abbreviations
SBM: Synchronous Bone Metastasis; LC: Lung Cancer; BM: Bone Metastasis; SREs: Skeletal-Related Events; NSCLC: Non-Small Cell Lung Cancer; MBM: Metachronous Bone Metastasis; SEER: Surveillance, Epidemiology, And End Results

Acknowledgements
Not applicable.

Authors’ contributions
XW and CZ designed the study. XG, DW and SZ collected the data. YX and ZL analysed the data. XG, WM and HW organized the manuscript. VP, C, KP and JZ reviewed the papers and revised the manuscript. All the authors have read and approved the final manuscript. All authors contributed to the data analysis and the drafting and revising of the paper and agree to be accountable for all aspects of the work.

Funding
The present study was sponsored by Natural Science Foundation of China (82011530050, 81801781, 81903398) and Cangzhou Research and Development Program (172302043).

Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The present study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and the Research Ethics Board of the Tianjin Medical University Cancer Institute and Hospital approved the study (bc2021008). All participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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