

Relevance of Tokuhashi Score in Spinal Metastases Management in the Era of Molecular Biology: Focus on Lung Cancer

Nicolas Danthez

`nicolas.danthez@ico.unicancer.fr`

Institut de Cancérologie de l'Ouest

Amaury Paumier

Institut de Cancérologie de l'Ouest

Pierre Ingrand

Centre Hospitalier Universitaire de Poitiers

Antoine Berger

Centre Hospitalier Universitaire de Poitiers

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Abstract

Background

The Tokuhashi score is widely used to guide therapeutic strategies in patients with spinal metastases from solid tumors. However, the introduction of targeted therapies and immune checkpoint inhibitors has profoundly modified the prognosis of several malignancies, particularly non-small cell lung cancer (NSCLC). The objective of this study was to evaluate the current prognostic relevance of the Tokuhashi score in lung cancer patients with spinal metastases while integrating molecular biology status.

Methods

A retrospective regional cohort study was conducted including patients discussed in multidisciplinary tumor boards for malignant spinal osteolysis between 2007 and 2019. Overall survival was analyzed according to Tokuhashi score and molecular status using Kaplan–Meier survival analysis, log-rank tests, and multivariate Cox regression models.

Results

Among 804 patients, 220 presented with lung cancer. Molecular alterations were identified in 38 patients. According to the Tokuhashi classification, 91.4% of lung cancer patients were categorized in the poor prognosis group. No significant association was found between Tokuhashi prognostic classes and overall survival. In contrast, molecular positivity was strongly associated with improved survival. Median overall survival reached 10.22 months in molecular-positive patients versus 3.61 months in molecular-negative patients. In multivariate analysis, molecular status remained an independent prognostic factor with a hazard ratio of 0.47.

Conclusion

The Tokuhashi score no longer accurately predicts prognosis in lung cancer patients with spinal metastases in the molecular era. Molecular profiling should be systematically integrated into future prognostic tools for spinal metastases.

Introduction

Spinal metastases represent the third most common metastatic site in solid tumors and are associated with substantial morbidity and mortality [1, 2]. Bone dissemination occurs through chemokine-mediated migration of tumor cells toward the bone microenvironment [3]. Skeletal-related events include pain, pathological fractures, spinal cord compression, hypercalcemia, and the need for surgery or radiotherapy [4, 5]. Approximately fifty percent of patients with bone metastases will develop at least one skeletal-related event during the course of their disease [5].

Lung cancer is one of the primary malignancies most frequently associated with spinal metastases, with nearly seventy percent of patients presenting locally advanced or metastatic disease at diagnosis [6]. Bone metastases occur in approximately thirty to fifty percent of lung cancer patients and predominantly involve the thoracic spine [7–9].

Management of spinal metastases requires a multidisciplinary approach combining systemic therapies and local treatments such as surgery, radiotherapy, and interventional radiology [10]. Surgery may improve spinal stability, neurological outcomes, and quality of life while reducing pain [11–14]. Advances in minimally invasive surgery, vertebroplasty, stereotactic radiotherapy, and ablative techniques have considerably expanded therapeutic possibilities [15–20].

To guide therapeutic decision making, several prognostic scores have been developed. Among them, the Tokuhashi score remains one of the most widely used systems for estimating survival in patients with spinal metastases [21, 22]. The revised Tokuhashi score integrates six parameters including performance status, number of bone metastases, number of vertebral metastases, visceral metastases, primary tumor type, and neurological status [22].

However, this score was established before the advent of precision oncology. In non-small cell lung cancer, the discovery of actionable molecular alterations such as EGFR mutations, ALK and ROS1 rearrangements, MET amplification, and BRAF mutations has dramatically modified survival outcomes [23–27]. Immune checkpoint inhibitors targeting PD-1 and PD-L1 have further improved survival in metastatic NSCLC [28–31].

Despite these major therapeutic advances, the Tokuhashi score still classifies lung cancer as a uniformly poor prognosis tumor without accounting for molecular status. This study aimed to evaluate the prognostic relevance of the Tokuhashi score in lung cancer patients

with spinal metastases in the era of molecular biology.

Materials and Methods

Study Design

A retrospective multicenter cohort study was conducted using data collected from multidisciplinary tumor boards dedicated to malignant spinal osteolysis within the Poitou-Charentes regional oncology pole between June 2007 and October 2019.

Patient Selection

Eligible patients were adults older than eighteen years presenting spinal metastases from solid tumors. Diagnosis was confirmed using computed tomography, magnetic resonance imaging, positron emission tomography, or bone scintigraphy. Patients with multiple myeloma, primary spinal tumors, or isolated extraspinal metastases were excluded.

Data Collection

The revised Tokuhashi score was calculated according to the 2005 classification [22]. Clinical variables included age, sex, Karnofsky performance status, neurological status according to Frankel classification, number of vertebral metastases, extraspinal bone metastases, and visceral metastases.

Molecular status was specifically recorded for lung cancer patients and included EGFR mutations, ALK and ROS1 rearrangements, MET amplification, BRAF mutations, and PD-L1 expression. Molecular analyses were performed using immunohistochemistry, fluorescence in situ hybridization, polymerase chain reaction, or next-generation sequencing depending on the period and available technology.

Overall survival was defined as the interval between diagnosis of spinal metastasis and death or last follow-up. Informed consent was obtained from all subjects and/or their legal guardian. The experimental protocol was approved by the Comité de Protection des Personnes Ouest III (CPP Ouest III). All methods were performed in accordance with the relevant guidelines and regulations.

Statistical Analysis

Survival curves were generated using the Kaplan–Meier method and compared using log-rank tests. Variables with p values lower than 0.20 in univariate analyses were included in multivariate Cox proportional hazards models. Statistical significance was defined as $p < 0.05$.

There was no Funding for this study.

Results

Patient Characteristics

A total of 804 patients were included. Among them, 220 patients presented lung cancer (all histology types). Mean age was 65 years, ranging from 34 to 91 years. One hundred and fifty-one patients were male and sixty-nine were female.

Molecular alterations were identified in 38 patients, corresponding to 17.3% of lung cancer cases. EGFR mutations represented the majority of actionable alterations.

According to the revised Tokuhashi score, 201 patients (91.4%) were classified in the poor prognosis group with scores ranging from 0 to 8. Nineteen patients were classified in the intermediate prognosis group. No patient reached the favorable prognosis category. (Table1)

Table 1
Baseline demographic, clinical, and molecular characteristics of the study population (N = 220).

Variable	N (%)
Age, mean (range), years	65.1 (34–91)
Male sex	151 (69.0)
Epidural disease	147 (66.8)
Karnofsky PS (poor/moderate/good)	27 (12.3) / 54 (24.5) / 139 (63.2)
Extraspinal bone metastases (≥ 3 / 1–2 / 0 / unknown)	110 (50.0) / 39 (17.7) / 67 (30.4) / 4 (1.8)
Affected vertebrae (≥ 3 / 2 / 1)	145 (65.9) / 36 (16.4) / 39 (17.7)
Visceral metastases (non-resectable / resectable / none / unknown)	135 (61.2) / 4 (1.8) / 80 (36.4) / 1 (0.5)
Neurological status (Frankel A–B / C–D / E)	3 (1.5) / 28 (12.7) / 189 (85.9)
Tokuhashi score (0–8 / 9–11)	201 (91.4) / 19 (8.6)
Treatment (en bloc / palliative / RT / supportive care)	1 (0.4) / 20 (9.0) / 172 (78.2) / 42 (19.1)
Molecular status (EGFR / ALK / ROS1 / MET / BRAF / PD-L1 / none / unknown)	20 (9.1) / 6 (2.7) / 1 (0.5) / 1 (0.5) / 1 (0.5) / 9 (4.1) / 134 (60.9) / 48 (21.8)

Survival Analysis

Median overall survival for the entire lung cancer cohort was 4.24 months. Molecular-positive patients demonstrated significantly improved survival compared with molecular-negative patients. Median overall survival was 10.22 months in molecular-positive patients versus 3.61 months in molecular-negative patients. This difference was highly significant with a log-rank p value below 0.0001. (Table 2, Fig. 1)

Table 2
Survival rates at 3, 6, and 12 months according to molecular biomarker status.

Survival Outcome	Biomarker Negative	Biomarker Positive	Biomarker Status Unknown	Overall
Alive at 3 months	76 (56.7%)	30 (78.9%)	25 (52.1%)	131 (59.5%)
Alive at 6 months	43 (32.0%)	22 (57.9%)	14 (29.2%)	79 (35.9%)
Alive at 12 months	13 (9.7%)	17 (44.7%)	7 (14.6%)	37 (16.8%)

No statistically significant association was identified between Tokuhashi prognostic classes and overall survival in lung cancer patients. A log-rank test comparing the Tokuhashi prognostic groups yielded a chi-square value of 2.2 ($p = 0.14$). Conversely, molecular status showed a strong prognostic impact with Chi-square = 23.3 and $p < 0.0001$.

Multivariate Analysis

We studied the association of variables, used for calculating the Tokuhashi score, or selected by us, with patient survival (Table 3).

Table 3

Univariate analysis of prognostic factors associated with survival in patients with lung cancer and spinal metastases Those that were statistically significant were included in multivariate analysis (Table 4).

Variable	Molecular status	Age	Sex	Epidural disease	Performance status	Extraspinal bone metastases	Vertebral metastases	Visceral metastases	Neurological deficit
3-month survival	95% CI [1.39–8.16] p = 0.0071	95% CI [0.39–1.32] p = 0.2899	95% CI [0.95–3.64] p = 0.0681	95% CI [0.80–1.09] p = 0.3862	95% CI [1.39–3.39] p = 0.0007	95% CI [0.98–2.02] p = 0.0675	95% CI [1.14–2.81] p = 0.0117	95% CI [1.35–2.87] p = 0.0004	95% CI [0.66–2.80] p = 0.4006
6-month survival	95% CI [1.50–6.53] p = 0.0023	95% CI [0.49–1.62] p = 0.6914	95% CI [1.06–3.74] p = 0.0326	95% CI [0.83–1.14] p = 0.7167	95% CI [1.21–3.20] p = 0.0065	95% CI [0.87–1.75] p = 0.2301	95% CI [0.73–1.57] p = 0.7357	95% CI [1.29–2.48] p = 0.0005	95% CI [0.52–2.25] p = 0.8347
12-month survival	95% CI [3.44–17.93] p < 0.0001	95% CI [0.60–2.73] p = 0.5253	95% CI [1.23–5.66] p = 0.0125	95% CI [0.85–1.22] p = 0.8619	95% CI [1.23–5.60] p = 0.0128	95% CI [0.96–2.24] p = 0.0757	95% CI [0.73–1.85] p = 0.5265	95% CI [1.61–3.62] p < 0.0001	95% CI [0.61–6.50] p = 0.2515

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Table 4

Multivariate analysis of prognostic factors associated with survival in patients with lung cancer and spinal metastases (Variables remaining independently associated with survival in multivariate analysis are shown in bold).

Variable	Molecular status	Age	Sex	Epidural disease	Performance status	Extraspinal bone metastases	Vertebral metastases	Visceral metastases	Neurological deficit
3-month survival	95% CI [0.90–6.38] p = 0.0789	–	95% CI [0.88–4.12] p = 0.1015	–	95% CI [1.14–3.16] p = 0.0136	95% CI [0.56–1.37] p = 0.5555	95% CI [1.15–3.22] p = 0.0131	95% CI [1.42–3.27] p = 0.0003	–
6-month survival	95% CI [1.07–5.31] p = 0.0345	–	95% CI [0.86–3.52] p = 0.1225	–	95% CI [1.03–2.94] p = 0.0368	–	–	95% CI [1.27–2.52] p = 0.0010	–
12-month survival	95% CI [2.85–21.58] p = 0.0001	–	95% CI [0.79–5.26] p = 0.1400	–	95% CI [0.87–5.23] p = 0.0996	95% CI [0.62–1.81] p = 0.8329	–	95% CI [1.70–4.69] p = 0.0001	–

In multivariate Cox regression analysis adjusted for Tokuhashi score, molecular positivity remained independently associated with improved survival. The hazard ratio for death in molecular-positive patients was 0.47 with a 95% confidence interval ranging from 0.32 to 0.70 and $p = 0.0001$.

Discussion

The present study demonstrates that the Tokuhashi score no longer adequately stratifies prognosis in patients with lung cancer and spinal metastases in the era of precision oncology. Although the score remains associated with overall survival, its prognostic classification appears poorly adapted to modern lung cancer management. More than 90% of our patients were assigned to the poor prognosis group (0–8 points), despite a substantial proportion surviving beyond 6 or even 12 months.

The main limitation of the Tokuhashi score lies in the weighting assigned to the primary tumor. Lung cancer systematically receives the lowest prognostic score (0/5), regardless of molecular characteristics or access to targeted therapies [18]. While this classification was justified when the score was developed, it has become increasingly outdated as the prognosis of advanced non-small cell lung cancer (NSCLC) has improved considerably over the past two decades [22–25].

Our findings highlight the major prognostic role of molecular biology. Patients harboring actionable molecular alterations or predictive biomarkers experienced a median overall survival of more than 10 months, compared with less than 4 months in molecular-negative patients. Furthermore, molecular status remained independently associated with survival after adjustment for the Tokuhashi score. These results are consistent with previous studies demonstrating prolonged survival among NSCLC patients treated with EGFR tyrosine kinase inhibitors [19, 22, 23] and immune checkpoint inhibitors [24, 25]. Similar benefits have also been reported in patients carrying ALK, ROS1, BRAF, or MET alterations, further supporting the growing importance of molecular profiling in metastatic lung cancer.

In contrast, several traditional prognostic factors incorporated into the Tokuhashi score remain clinically relevant. Performance status and visceral metastases were significantly associated with survival in our cohort, in agreement with previous reports and systematic reviews of metastatic spinal disease [26,32].

The clinical implications are substantial. Accurate estimation of life expectancy remains essential when selecting the most appropriate treatment strategy for spinal metastases. Current management relies on multidisciplinary decision-making combining surgery, radiotherapy, stereotactic body radiotherapy (SBRT), and minimally invasive interventional procedures [10–17]. Historically, patients predicted to survive less than three to six months were often excluded from aggressive local treatments [11, 12]. However, our data suggest that many molecular-positive patients classified as poor prognosis by Tokuhashi may actually experience prolonged survival and therefore benefit from more ambitious local approaches. Failure to recognize this subgroup could result in undertreatment and missed opportunities for pain control, neurological preservation, and quality-of-life improvement.

These observations are consistent with the broader evolution of spinal oncology. Contemporary decision-making frameworks such as NOMS increasingly integrate oncological characteristics and treatment responsiveness into therapeutic planning [10]. Nevertheless, most prognostic scores currently used in spinal metastases were developed before the widespread implementation of targeted therapies and immunotherapy and therefore insufficiently account for their impact on survival.

The strengths of this study include its large regional cohort and real-world design. Patients were selected from multidisciplinary meetings specifically dedicated to malignant bone disease, reflecting routine clinical practice and enhancing the external validity of our findings. In addition, the independent prognostic value of molecular status was confirmed through multivariable analysis.

Several limitations should nevertheless be acknowledged. First, the retrospective design may have introduced selection bias. Second, molecular testing was not routinely available during the early years of the study period, resulting in missing molecular data for a subset of patients. Third, systemic treatment strategies evolved substantially between 2007 and 2019, potentially contributing to therapeutic heterogeneity. Finally, the molecular-positive group remained heterogeneous, encompassing distinct oncogenic drivers and PD-L1-positive tumors associated with variable prognoses and treatment responses.

Several contemporary prognostic models, including the New England Spinal Metastasis Score (NESMS) and other machine learning-based approaches, have attempted to improve survival prediction in patients with spinal metastases [26,27,32–35]. However, most currently available scores still insufficiently integrate molecular oncology. Future prognostic systems should incorporate actionable molecular alterations and biomarkers of response to targeted therapies or immunotherapy. Validation of this concept will require larger prospective cohorts reflecting current standards of precision medicine.

Conclusion

The Tokuhashi score is no longer fully adapted to prognostic assessment of patients with lung cancer and spinal metastases in the era of targeted therapies and immunotherapy.

Molecular profiling emerged as a major independent determinant of survival in our cohort and identified a subgroup of patients with outcomes substantially better than those predicted by traditional prognostic classifications. These findings support the systematic integration of molecular data into therapeutic decision-making and prognostic evaluation in spine oncology.

Future prognostic models should combine established clinical factors with molecular characteristics and treatment responsiveness. The development and validation of such a molecularly informed prognostic score represent a promising direction for improving personalized management of patients with spinal metastases.

Declarations

Author Contribution

ND wrote the main manuscript text, did the data collection, and led the global project AB were the supervisor PI were the statistician AP did a proofreading

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to restrictions related to patient confidentiality and data protection, but are available from the corresponding author on reasonable request.

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