Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Machine Learning Algorithm Guiding Local Treatment Decisions For Lung Cancer Patients With Bone Metastases

Zhiyu Wang
Shanghai 6th Peoples Hospital Affiliated to Shanghai Jiaotong University
Jing Sun
Shanghai Sixth Peoples Hospital
Yi Sun
Shanghai Sixth Peoples Hospital
Yifeng Gu
Shanghai Sixth Peoples Hospital
Yongming Xu
Shanghai Sixth Peoples Hospital
Bizeng Zhao
Shanghai Sixth Peoples Hospital
Mengdi Yang
Shanghai Sixth Peoples Hospital
Guangyu Yao
Shanghai Sixth Peoples Hospital
Yiyi Zhou
Shanghai Sixth Peoples Hospital
Yuehua li
Shanghai Sixth Peoples Hospital
Dongping Du
Shanghai Sixth Peoples Hospital
Hui Zhao (zhao-hui@sjtu.edu.cn)
Shanghai Jiao Tong University Affiliated 6th People's Hospital

Research

Keywords: multidisciplinary team, local treatment, bone metastases, quality of life, machine learning model

Posted Date: December 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-117709/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Abstract

Background: As life expectancy increases for lung cancer patients who develop bone metastases, the need for personalized local treatment for bone metastases is expanding.

Methods: Lung cancer patients with bone metastases were treated by a multidisciplinary team via surgery, percutaneous osteoplasty, or radiation. The pre- and post-treatment visual analog scale (VAS) and Quality of Life (QoL) scores were analyzed. QoL at 12 weeks was the main outcome. Treatment-related costs and overall survival time (OS) were collected. We used machine learning to develop and test models to predict which patients should receive local treatment. Models discrimination were evaluated by the area under curve (AUC), and the best one was used for validation in clinical use.

Results: Under the direction of a multidisciplinary team, 161 patients in the training set, and 32 patients in the test set underwent local treatment. A decision tree model included VAS scale, bone metastases character, Frankel classification, Mirels score, age, driver gene, aldehyde dehydrogenase 2, and enolase 1 expression had a best AUC of 0.92 (95%CI 0.89 to 0.94), and 36 patients in a validation set underwent local treatment guided by the model. Improved QoL and VAS scores were observed at 12 weeks after local treatment in training, test, and validation sets ($p < 0.05$), with no significant differences among the three datasets. There were no significant differences in mean costs among the three datasets in the four treatment groups. OS was 18.03±0.45 months and did not significantly differ among treatment groups or the three datasets.

Conclusions: Local treatment not only had no negative influence on OS but also provided significant pain relief and improved QoL. QoL, OS or costs did not significantly differ between patients whose treatment was guided by a multidisciplinary team or machine learning model. Our machine learning model using clinical data can help guide clinicians to make local treatment decisions to improve patients' QoL.

Trial registration: No. ChiCRT-ROC-16009501

Background

Bone metastases develop in 36% of patients with advanced lung cancers [1]. Bone metastases can lead to skeletal-related events (SREs) such as pathologic fracture (PF), spinal cord compression (SCC), required radiation, bone surgery, and hypercalcemia [2], significantly reducing lung cancer patients' quality of life (QoL) [3].

Although systemic medical treatments can control lung tumor growth [2], they are not sufficient to restore the integrity of bones and allow a return to light weight-bearing [4]. Recent progression in lung cancer treatments, such as development of molecular-targeted agents, has improved patient survival [5]. With increasing life expectancy, there is growing need for effective local treatment for bone metastases to improve QoL. Surgery can restore the integrity of bones, but the decision of whether to perform surgery can be difficult, as the risks may outweigh benefits of pain reduction and improved function [6]. Alternatively, percutaneous osteoplasty (POP) is an effective and safe palliative therapy to reduce pain and improve QoL [7]. Further, radiation can improve reduced QoL caused by painful bone metastases [8]. In addition, previous work has emphasized the requirement of a multidisciplinary team (MDT) approach involving a team of specialists in oncology to improve patients' QoL [9].

Local treatment indications have been controversial, and local treatment for lung cancer patients with bone metastases must be individually tailored to each patient with consideration for multiple factors. As there is increasing need for automatic and accurate analysis for clinical use, machine learning offers a solution to generate reasonable generalizations, discover patterns, and enable more accurate decision-making [10]. Machine learning may facilitate more effective assessments by physicians [11]. We previously built machine learning models to predict SREs risk [12]. The purpose of this study was: 1) to evaluate the feasibility and effectiveness of applying our local treatment algorithm to improve patients' QoL, and 2) to develop and validate machine learning models for local treatment decision-making in lung cancer patients with bone metastases.

Materials

Patient Selection

This study was approved by the ethics committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University in October 20, 2016 and was registered in the Chinese Clinical Trial Registry (No. ChiCRT-ROC-16009501) in October 20, 2016. Principles of the Declaration of Helsinki were followed.

Inclusion criteria were: (1) age > 18 years, (2) pathology-proven diagnosis of lung cancer and radiographical/pathological evidence of bone metastases, (3) no previous treatment for bone metastases, and (4) good general condition, as measured by Eastern Cooperative Oncology Group (ECOG) performance scores of 0–2 with an estimated survival time of > 3 months.

Management Algorithm

Indications for systemic treatments, including chemotherapy, target therapy, and bone-targeting agents (BTAs), as well as local treatment, including surgery, POP, and radiation, were evaluated by an MDT of medical oncologists, radiation oncologists, interventional radiologists, orthopedic oncologists, and pain specialists. The algorithm is shown in Fig. 1.

Spinal stability was ascertained using Spinal Instability Neoplastic Scores (SINS) [13], and the risk of pathological fracture for the appendicular skeleton was ascertained using the Mirels scoring system [14]. Surgical procedures followed guidelines of the Global Spine Tumor Study Group and Italian Orthopedic Society [15–18]. Procedures for POP were introduced by our MDT in 2012 [7]. Radiation was performed mainly with 6-MV photons using linear accelerators. Dose fractionation schedules included multi-fraction radiation, such as 30 Gy in 10 fractions. Adjuvant therapy-like radiation [19] was used after surgery or POP to prevent tumor recurrence.

Informed consent was obtained for all patients in the study. If local treatment was performed, informed consent by the patient or a legal guardian was obtained 24 hours before initiation and after thorough explanation of the methods, potential complications, and alternative treatments.

Data Collection and Follow-up

Medical records were reviewed to collect clinical data. The driver gene of lung cancer (primary lung tissue or bone metastases tissue) and five differentially expressed proteins of bone metastases (bone metastases tissue)—enolase 1 (ENO1), ribosomal protein lateral stalk subunit P2 (RPLP2), calcyphosine (CAPS1), NME/NM23 nucleoside diphosphate kinase 2 (NME1-NME2), and aldehyde dehydrogenase 2 (ALDH2) [20]—were also collected.

Patients were asked to complete a questionnaire that assessed severity of pain using the visual analog scale (VAS) [21] and QoL using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases Module (EORTC QLQ-BM22) [22–23] 1 day before and at 1, 6, 12, and 24 weeks after local treatment or enrollment. QoL at 12 weeks was the main outcome. Patients were followed for survival every 3 months.

Cost Valuation

Cost analyses of individual patients were estimated from a payer perspective using health resource utilization data from patient charts. Costs of procedures performed during an inpatient stay were assumed to be captured in diagnosis-related group costs.

Model Development

Decision trees (DT) (eXtreme Gradient Boosting, XGBoots), support vector machine (SVM), and Bayesian neural networks (BNN) were used to build local treatment decision-making models. Based on our previous research [12], we selected the following predictor variables: sex, age, ECOG score, VAS score, bone metastases character, extent of bone metastases, visceral metastases, Frankel classification, and Mirels scale. As additional predictor variables, we selected lung cancer pathology, lung cancer driver gene, and five differentially expressed bone metastasis proteins. The model output was: 0, no local treatment; or 1, local treatment. The training set including patients who had improved VAS and QoL measures after local treatment.

Model Performance

In the training set, we used 10-fold cross validation. The test set consisted of data not associated with the training set. Model discrimination was evaluated by area under the receiver operator characteristic curves (AUC). Sensitivity, specificity, and accuracy were used to evaluate model performance.

Model Validation

In the validation set, we used the model to make a decision regarding local treatment. The MDT made the final decision about which local treatment to provide to patients and could reject the model's decision.

Statistical Analysis

Stata Corp 2013 (Stata Statistical Software: Release 13; StataCorp LP, College Station, TX, USA) and Python Version 3.6 (Python Software Foundation, Wilmington, DE, USA) were used to analyze data and build the model. Median values and ranges were determined for descriptive statistics. Chi-square and Fisher's exact tests were used for categorical variables. Student's t-tests and Mann-Whitney tests were used for continuous and ordinal variables. Wilcoxon signed-rank tests were used to compare paired outcomes at various follow-up times. The Kaplan-Meier method was used to estimate survival. A $p < 0.05$ was considered statistically significant.

Results

Demographic and Clinical Characteristics

We enrolled 746 patients: the training set included 513 patients enrolled from October 24, 2016 to June 30, 2018; the test set included 108 patients enrolled from July 1, 2018 to October 31, 2018; and the validation set included 125 patients enrolled from November 1, 2018 to February 25, 2019. Of these, 161 patients in the training set, 32 patients in the test set, and 36 patients in the validation set underwent local treatment. A flow chart of the study is shown in Fig. 2A. Patient demographics and clinical characteristics did not significantly differ among the three datasets as shown in Table 1. Treatments in training, test, and validation sets are shown in Fig. 2B–D.

Table 1
Demographics and clinical characteristics for patients

Characteristics	Training	Test	Validation	*P* Value
	N (%)	N (%)	N (%)	
Sex (Males/Females)	262/251	57/51	63/62	.93
	(51.07/48.93)	(52.78/47.22)	(50.40/49.60)	
Age	60.70 ± 10.34	59.80 ± 12.03	59.87 ± 11.45	.60
ECOG Scores (0–1/2)	412/101	91/17	103/22	.59
	(80.31/19.69)	(84.26/15.74)	(82.40/17.60)	
VAS scores* (Grade 1/2/3)	183/271/59	40/56/12	46/67/12	.90
	(35.67/52.83/11.50)	(37.04/51.85/11.11)	(36.80/53.60/9.60)	
Bone metastases character (Lytic/Blastic/Mixed)	292/80/141	64/17/27	69/20/36	.79
	(56.92/15.59/27.49)	(59.26/15.74/25.00)	(55.20/16.00/28.80)	
Extent of bone metastases [24] (Soloway 1/2/3–4)	183/218/112	41/45/22	43/56/26	.88
	(35.67/42.50/21.83)	(37.96/41.67/20.37)	(34.40/44.80/20.80)	
Visceral metastases** (Without/With)	315/198	64/44	80/45	.76
	(61.40/38.60)	(59.26/40.74)	(64.00/36.00)	
Frankel classification*** (0/1/2/3/4/5)	151/3/6/10/35/308	33/1/2/3/7/62	35/1/1/2/9/77	.82
	(29.43/0.58/1.17/1.95/6.82/60.04)	(30.56/0.93/1.85/2.78/6.48/57.41)	(28.00/0.80/0.80/1.60/7.20/61.60)	
Mirels scale**** (0/1/2/3)	172/211/102/28	39/42/20/7	40/54/24/7	.93
	(33.53/41.13/19.88/5.46)	(36.11/38.89/18.52/6.48)	(32.00/43.20/19.20/5.60)	
Pathology***** (1/2/3/4/5)	242/97/132/20/22	54/18/26/5/5	57/25/32/6/5	.90
	(47.17/18.91/25.73/3.90/4.29)	(50.00/16.67/24.07/4.63/4.63)	(45.60/20.00/25.60/4.80/4.00)	
Driver gene (Negative/EGFR(+)/ALK (+)/Unkown)	202/278/17/16	42/57/4/5	49/70/4/2	.87
	(39.38/54.19/3.31/3.12)	(38.89/52.78/3.70/4.63)	(39.20/56.00/3.20/1.60)	
ENO1 (+/-)	112/401	25/83	26/99	.91
	(21.83/78.17)	(23.15/76.85)	(20.80/79.20)	
RPLP2 (+/-)	82/431	19/89	22/103	.86
	(15.98/84.02)	(17.59/82.41)	(17.60/82.40)	
CAPS1 (+/-)	260/253	56/52	62/63	.94
	(50.68/49.32)	(51.85/48.15)	(49.60/50.40)	
NMEI-NME2 (+/-)	227/286	43/65	58/67	.59
	(44.25/55.75)	(39.81/60.19)	(46.40/53.60)	
ALDH2 (+/-)	175/338	34/74	46/79	.69
	(34.11/65.89)	(31.48/68.52)	(36.80/63.20)	

* Pain level on a 10-point scale, with 0 representing no pain and 10 representing maximum pain intensity imaginable. Grade 1: 0–3, Grade 2: 4–6, Grade 3: 7–10.

** Visceral metastases defined as distant metastases, except for BM, including brain metastases.

***Frankel classification defined as: 0: Without spine metastasis, 1: A, 2: B, 3: C, 4: D, 5: E.

****Mirels scale defined as: 0: Without extremity metastasis, 1: 4–6, 2: 7–9, 3: 10–12.

*****Pathology defined as: 1: Adenocarcinoma, 2: Squamous cell carcinoma, 3: Poorly differentiated cancer, 4: Large cell carcinoma, 5: Small cell carcinoma.

Post-Treatment Pain

VAS scores before treatment for all 746 patients in surgery, POP, radiation, and no local treatment groups were 5.70 ± 1.22, 5.53 ± 1.34, 6.62 ± 1.48, and 3.37 ± 1.38, respectively; scores were highest in the radiation group and lowest in the no local treatment group ($p < 0.05$). VAS scores in surgery, POP, and radiation groups decreased significantly to 4.78 ± 1.28, 4.37 ± 1.36, and 5.39 ± 1.31, respectively, at 12 weeks after local treatment ($p < 0.05$). VAS scores for patients in the no local treatment group did not significantly differ 12 weeks after enrollment. Detailed scores are showed in Fig. 3A.

VAS scores in training, test, and validation sets all decreased significantly at 12 weeks after surgery, POP, or radiation ($p < 0.05$), with no significant differences among the three sets. Detailed scores are showed in Fig. 3B–D.

Post-Treatment QoL

Pain sites (PS) and pain characteristic (PC) scores of the QLQ-BM22 before treatment for all 746 patients were highest in the radiation group and lowest in the no local treatment group ($p < 0.05$), while functional interference (FI) and psychosocial aspects (PA) scores were highest in the no local treatment group and lowest in the radiation group ($p < 0.05$). Patients had improved QoL scores 12 weeks after surgery, POP, or radiation ($p < 0.05$). PS and PC scores decreased significantly while FI and PA scores increased significantly at 12 weeks after local treatment in surgery, POP, and radiation groups ($p < 0.05$). PS, PC, FI, and PA scores for patients in the no local treatment group did not significantly differ 12 weeks after enrollment. Pre-treatment and post-treatment subscores in pain and functional domains in QLQ-BM22 are shown in Fig. 3A.

In training, test, and validation sets, PS and PC scores decreased significantly while FI and PA scores increased significantly at 12 weeks after surgery, POP, or radiation ($p < 0.05$), with no significant differences among the three sets. Detailed scores are showed in Fig. 3B–D.

Cost Valuation

Mean costs during 24 weeks for all 746 patients in surgery, POP, radiation, and no local treatment groups were $21,172 ± 8,626, $16,142 ± 5,078, $15,899 ± 5,527, and $13,526 ± 5,685, respectively; costs were highest in the surgery group and lowest in the no local treatment group ($p < 0.05$). There were no significant differences in mean costs among training, test, and validation sets in the four treatment groups. Detailed costs are showed in Fig. 4A, B.

Survival

Median follow-up was 15 months (range: 6–41 months). The end-point of analyses was overall survival time (OS), and a total of 548 patients died. The OS was 18.03 ± 0.45 months in all 746 patients, and the one-year survival rate was 65.55%. OS was 15.50 ± 1.08, 16.72 ± 1.04, 16.90 ± 1.08, and 18.25 ± 0.54 months in surgery, POP, radiation, and no local treatment groups, respectively, with no significant differences. One-year survival rates were 61.11%, 60.68%, 63.38%, and 66.73% in surgery, POP, radiation, and no local treatment groups, respectively, with no significant differences. OS did not significantly differ among the three datasets.

Model Development and Validation

The DT model included VAS scores, bone metastases character, Frankel classification, Mirels scale, age, driver gene, and ALDH2 and ENO1 expression. Compared with the MDT, the DT model was superior to the other two machine learning models in predicting whether patients would receive local treatment, with an AUC of 0.89 for DT model (95% CI: 0.86–0.93), 0.77 for SVM model (95% CI: 0.72–0.82), and 0.71 for BNN model (95% CI: 0.66–0.76) ($p > 0.05$). DT model had 89.44% sensitivity, 90.34% specificity, and 90.06% accuracy.

The DT model was also superior to the other two machine learning models in the test set, with an AUC of 0.85 for DT model (95% CI: 0.77–0.94), 0.78 for SVM model (95% CI: 0.68–0.80), and 0.68 for BNN model (95% CI: 0.57–0.80) ($p > 0.05$). DT model had 83.87% sensitivity, 87.01% specificity, and 86.11% accuracy.

The DT model was used for further validation in clinical use. In the validation set, the MDT rejected the DT model decision to provide local treatment for 9 patients and not provide local treatment for 5 patients. The AUC for DT was 0.88 (95% CI: 0.81–0.96), with 86.11% sensitivity, 89.89% specificity, and 88.80% accuracy.

Discussion

Management of bone metastases has been considered palliative and unassociated with patient prognosis and thus has not been given much importance in the past. Recently, however, it has become necessary to initiate bone management programs concurrently with cancer treatment to effectively prevent serious complications of bone metastases. Mechanical stability, neurological risk, oncological parameters, and preferred treatment (MNOP) algorithms [25] have been used to manage bone metastases since 2017. The algorithm used at our center since 2016 accounts for tumor histology (EGFR mutation is considered an indicator for good prognosis), tumor burden (extent of bone metastases and visceral metastases), patient performance (life expectancy), and technical difficulty (complication).

Similar to previous studies, surgery, POP, or radiation provided significant pain relief and improved QoL [6, 26–30]. The MNOP algorithm suggests surgery or radiation as the main treatment for spinal metastases. Minimally invasive approaches such as POP are also recommended by our algorithm. We have treated hundreds of spinal PF and instabilities with POP instead of high-risk surgery. We find that patients recover spinal stability after POP with low morbidity, and our results here show that mean costs for spine metastases in the POP group were much lower than the surgery group. However, we note that POP does not easily restore structural integrity and weight-bearing for the appendicular skeleton and that surgery can quickly restore these functions

with less risk. To prevent PF, we have used preventive surgery or POP, and our algorithm shows that surgery and POP are complementary. We prefer POP for spinal metastases and surgery for appendicular skeleton metastases. In this study, we found that our algorithm was effective in providing treatment decisions that provided significant pain relief and improved QoL.

Our results show that local treatment did not negatively influence OS for lung cancer patients with bone metastases. According to some studies, patients surgically treated for bone metastases survive < 10 months [27]. Recently, Tang et al reported OS of 14 months in lung cancer patients with spinal metastases, and patients who underwent surgery had longer survival [28]. However, our study excluded patients with a life expectancy of < 3 months, 92.6% patients received systemic medical treatments (57.9% for targeted agents), and Frankel classification in the no local treatment group was almost E, while in Tang's study it was A–D, possibly accounting for the longer survival in our study.

Machine learning models can help guide treatment decisions. Although the MDT approach is an effective method to manage bone metastases, it can be difficult to manage patients who may develop serious SREs in a timely manner by holding weekly meetings. Alternatively our machine learning models based on routinely available clinical parameters were constructed for local treatment decision-making. XGBoost is a novel boosting tree-based ensemble algorithm that has gained wide popularity in the machine learning community [31]. The DT model showed greater accuracy than SVM and BNN models, and it included driver genes and that ALDH2 and ENO1 expression had higher accuracy, which is in line with current needs for precision medicine. For ethical reasons, the final decision was still left to the MDT. However, QoL, mean cost, and OS of the four treatment groups did not significantly differ between MDT and DT model decisions. Feasibility, stability, and economic efficiency of the DT model were satisfying, and the DT model was good at determining whether patients should receive local treatment. Thus, this tool may help clinicians decide on local treatment for individual patients.

To the best of our knowledge, this is the first attempt to use machine learning techniques for local treatment decision-making models in lung cancer patients with bone metastases. However, the algorithm cannot completely solve the problem of patient classification, and the machine learning model could only guide decisions about whether to apply local treatment or not. However, as more patients receive local treatment, thus increasing data availability, we will be able to develop additional models that can better guide types of local treatment. However, some treatments have not been carried out in our study, which represents a weakness. For example, stereotactic body radiation therapy for painful spine metastasis shows better results in local control and pain relief than standard 2D or 3D techniques [30], and recent development of immune checkpoint inhibitors has fundamentally changed how patients with metastatic lung cancer are treated [5]. Further, this study is limited in that it involved a single center. Multi-center trials would provide additional evidence, although standardizing and homogenizing use of local treatment in different centers are challenging problems that remain to be solved.

Conclusions

Local treatment not only had no negative influence on OS but provided significant pain relief and improved QoL in patients in our study. There were no significant differences between MDT and DT model decisions in QoL, mean costs, and OS for local treatment patients. Our machine learning model using clinical data can help guide clinicians to make local treatment decisions to improve patients' QoL.

Abbreviations

SREs: skeletal-related events, PF: pathologic fracture, SCC: spinal cord compression, QoL: quality of life, POP: percutaneous osteopilasty, MDT: multidisciplinary team, ECOG: Eastern Cooperative Oncology Group, BTAs: bone-targeting agents, SINS: Spinal Instability Neoplastic Scores, ENO1: enolase 1, RPLP2: ribosomal protein lateral stalk subunit P2, CAPS1: alcyphosine, NME1-NME2: ME/NM23 nucleoside diphosphate kinase 2, ALDH2: aldehyde dehydrogenase 2, VAS: visual analog scale, EORTC QLQ-BM22: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Bone Metastases Module, DT: decision tree, SVM: support vector machine, BNN: Bayesian neural networks, AUC: area under the receiver operator characteristic curves, PS: pain sites, PC: pain characteristic, FI: functional interference, PA: psychosocial aspects, OS: overall survival time, MNOP: Mechanical stability, neurological risk, oncological parameters, and preferred treatment.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiaotong University in October, 20, 2016 and the TRN is 2016-162.

Consent for publication

All authors have approved to publish this manuscript.

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.

Competing interests

There are no financial or other relationships that might lead to a conflict of interest. The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (81602519, 81672852), Shanghai Municipal Health Commission (20164Y0099), Peak Plateau Project of Shanghai Jiao Tong University (20172024), and Shanghai Shen Kang three-year plan of action project (16CR2007A).

Authors' contributions

WZY and SJ: study concept, design, analysis, and manuscript drafting. SY, GYF, XYM, ZBZ, and LYH: local treatment perform. YMD, YGY, and ZYY: patient followup, data collection. DDP and ZH: study concept, design, and manuscript editing. All authors have read and approved the final manuscript.

Acknowledgements

We appreciate the help of data analyst Ms. Yiru Shen from PerkinElmer for preliminary data during the study.

References

1. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res. 2006;12(20 Pt 2):6243 s-9s.
2. Coleman RE. Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27(3):165 – 76.
3. Cetin K, Christiansen CF, Jacobsen JB, Nørgaard M, Sørensen HT. Bone metastasis, skeletal-related events, and mortality in lung cancer patients: a Danish population-based cohort study. Lung Cancer. 2014;86(2):247 – 54.
4. Fairchild A. Palliative radiotherapy for bone metastases from lung cancer: Evidence-based medicine? World J Clin Oncol. 2014;5(5):845 – 57.
5. Arbour KC, Riely GJ. Systemic Therapy for Locally Advanced and Metastatic Non-Small Cell Lung Cancer: A Review. JAMA. 2019;322(8):764 – 74.
6. Wedin R. Surgical treatment for pathologic fracture. Acta Orthop Scand Suppl. 2001;72(302):2**p**.,1–29.
7. Wang Z, Zhen Y, Wu C, Li H, Yang Y, Shen Z, **et al**. CT fluoroscopy-guided percutaneous osteoplasty for the treatment of osteolytic lung cancer bone metastases to the spine and pelvis. J Vasc Interv Radiol. 2012;23(9):1135-42.
8. Pin Y, Paix A, Le Fèvre C, Antoni D, Blondet C, Noël G. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. Crit Rev Oncol Hematol. 2018;123:132-7.
9. Bongiovanni A, Recine F, Fausti V, Foca F, Casadei R, Falasconi MC, **et al**.Ten-year experience of the multidisciplinary Osteoncology Center. Support Care Cancer. 2019;27(9):3395 – 402.
10. Hosseinzadeh F, Kayvanjoo AH, Ebrahimi M, Goliaei B. Prediction of lung tumor types based on protein attributes by machine learning algorithms. Springer Plus. 2013;2(1):238.
11. Duda RO, Hart PE, Stork DG. **Pattern Classification**. 2. **John Wiley and Sons**. 2000.
12. Wang Z, Wen X, Lu Y, Yao Y, Zhao H. Exploiting machine learning for predicting skeletal-related events in cancer patients with bone metastases. Oncotarget. 2016;7(11):12612-22.
13. Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, **et al**. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. Spine (Phila Pa 1976). 2010;35(22):E1221-9.
14. Mirels H. Metastatic disease in long bones: a-proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop Relat Res. 1989;(249):256 – 64.
15. Choi D, Crockard A, Bunger C, Harms J, Kawahara N, Mazel C, **et al**. Global Spine Tumor Study Group. Review of metastatic spine tumour classification and indications for surgery: the consensus statement of the Global Spine Tumour Study Group. Eur Spine J. 2010;19(2):215 – 22.
16. Rodolfo C, Domenico A. Campanacci. The treatment of metastases in the appendicular skeleton. J Bone Joint Surg Br. 2001;83(4):471 – 81.
17. Gasbarrini A, Boriani S, Capanna R, Casadei R, Di Martino A, Silvia Spinelli M, **et al**. Management of patients with metastasis to the vertebrae: recommendations from the Italian Orthopaedic Society (SIOT) Bone Metastasis Study Group. Expert Rev Anticancer Ther. 2014;14(2):143 – 50.
18. Capanna R, Piccioli A, Di Martino A, Daolio PA, Ippolito V, Maccauro G, **et al**. Management of long bone metastases: recommendations from the Italian Orthopaedic Society bone metastasis study group. Expert Rev Anticancer Ther. 2014;14(10):1127-34.
19. Siegel GW, Biermann JS, Calinescu AA, Spratt DE, Szerlip NJ. Surgical Approach to Bone Metastases. Current Osteoporosis Reports. 2018;16(4):512-8.
20. Yang M, Sun Y, Sun J, Wang Z, Zhou Y, Yao G, **et al**. Differentially expressed and survival-related proteins of lung adenoarcinoma with bone metastasis. Cancer Medicine. 2018, 7(4):1081-92.
21. Joyce CR, Zutshi DW, Hrubes V, Mason RM. Comparison of fixed interval and visual analogue scales for rating chronic pain. Eur J Clin Pharmacol. 1975;8(6):415 – 20.
22. McDonald R, Ding K, Brundage M, Meyer RM, Nabid A, Chabot P, **et al**. Effect of Radiotherapy on Painful Bone Metastases A Secondary Analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23. JAMA Oncol. 2017;3(7):953-9.

23. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol. 1998;16(1):139 – 44.
24. Soloway MS, Hardeman SW, Hickey D, Raymond J, Todd B, Soloway S, **et al**. Stratification of patients with metastatic prostate cancer based on extent of disease on initial bone scan. Cancer. 1988;61(1):195–202.
25. Spratt DE, Beeler WH, de Moraes FY, Rhines LD, Gemmete JJ, Chaudhary N, **et al**. An integrated multidisciplinary algorithm for the management of spinal metastases: an International Spine Oncology Consortium report. Lancet Oncol. 2017; 18(12):e720-30.
26. Anselmetti GC, Marcia S, Saba L, Muto M, Bonaldi G, Carpeggiani P, **et al**. Percutaneous vertebroplasty: multi-centric results from EVEREST experience in large cohort of patients. Eur J Radiol. 2012;81(12):4083-6.
27. Wood TJ, Racano A, Yeung H, Farrokhyar F, Ghert M, Deheshi BM. Surgical management of bone metastases: quality of evidence and systematic review. Ann Surg Oncol. 2014;21(13):4081-9.
28. Tang Y, Qu J, Wu J, Liu H, Chu T, Xiao J, **et al**. Effect of Surgery on Quality of Life of Patients with Spinal Metastasis from Non-Small-Cell Lung Cancer. J Bone Joint Surg Am. 2016;98(5):396–402.
29. Nooh A, Goulding K, Isler MH, Mottard S, Arteau A, Dion N, **et al**. Early improvement in pain and functional outcome but not quality of life after surgery for metastatic long bone disease. Clin Orthop Relat Res. 2018;476(3):535 – 45.
30. Pin Y, Paix A, Le Fèvre C, Antoni D, Blondet C, Noël G. A systematic review of palliative bone radiotherapy based on pain relief and retreatment rates. Crit Rev Oncol Hematol. 2018;123:132-7.
31. Chen T, Guestrin, C. Xgboost: **A scalable tree boosting system**. **In Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining.2016;KDD'16 785 – 94**.

Figures

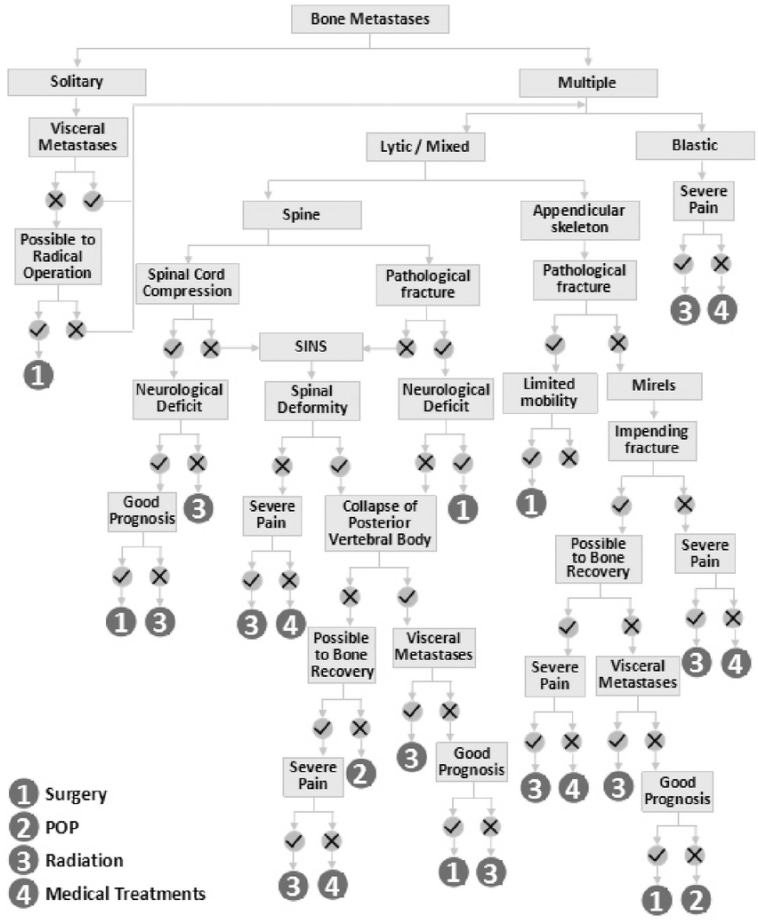

Figure 1

Flow chart of local treatment algorithm for lung cancer patients with bone metastases.

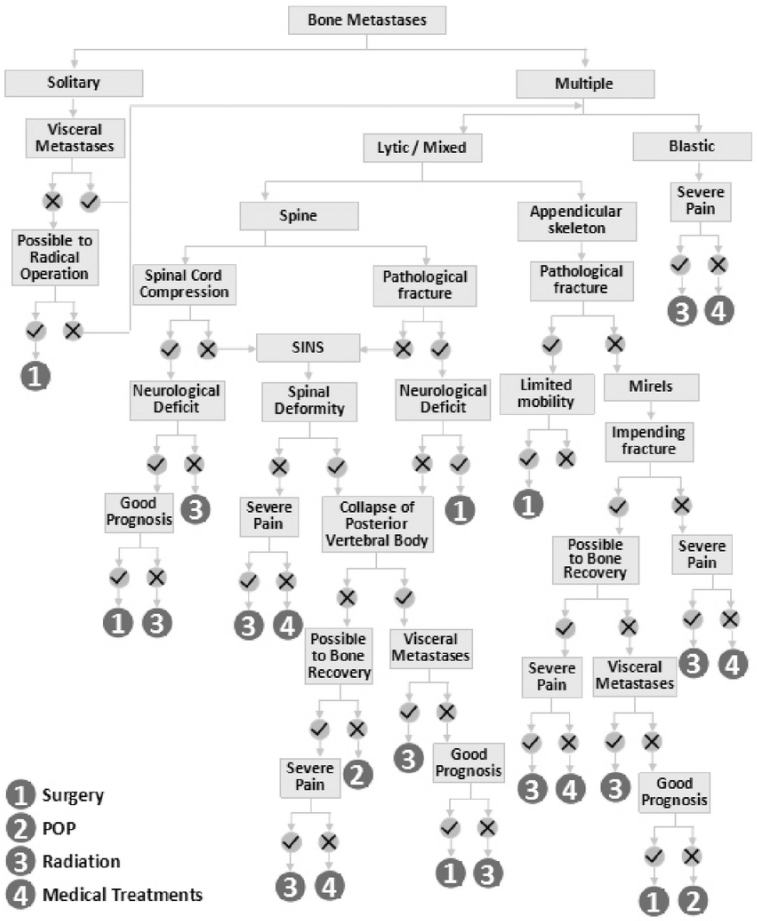

Figure 1

Flow chart of local treatment algorithm for lung cancer patients with bone metastases.

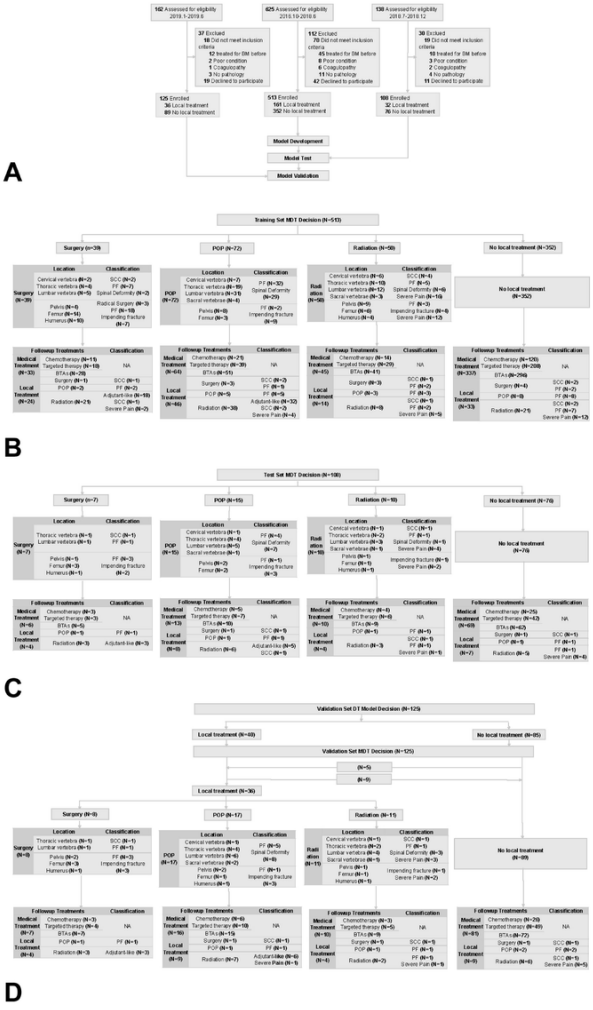

Figure 2

Flow diagram of the study (A). Treatments in training (B), test (C), and validation (D) sets.

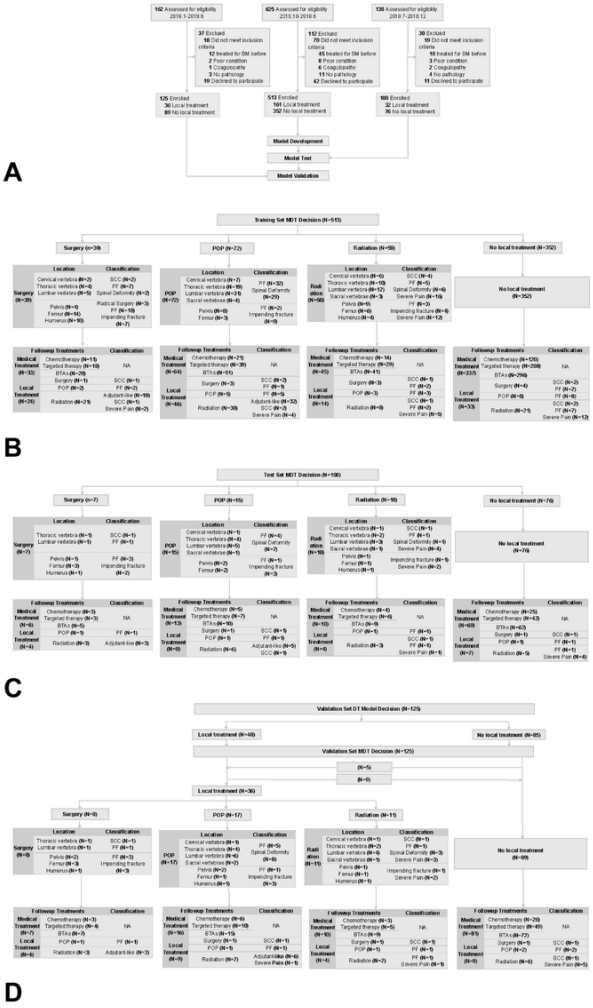

Figure 2

Flow diagram of the study (A). Treatments in training (B), test (C), and validation (D) sets.

Figure 3

Pre-treatment and post-treatment visual analog scale (VAS) scores and Quality of Life Questionnaire Bone Metastases Module (QLQ-BM22) subscores in all patients (A) and in training (B), test (C), and validation (D) sets. ○ Not significantly different from pre-treatment score ($p > 0.05$). ● Significantly different from pre-treatment score ($p < 0.05$). No LT: No local treatment.

Figure 3

Pre-treatment and post-treatment visual analog scale (VAS) scores and Quality of Life Questionnaire Bone Metastases Module (QLQ-BM22) subscores in all patients (A) and in training (B), test (C), and validation (D) sets. ○ Not significantly different from pre-treatment score ($p > 0.05$). ● Significantly different from pre-treatment score ($p < 0.05$). No LT: No local treatment.

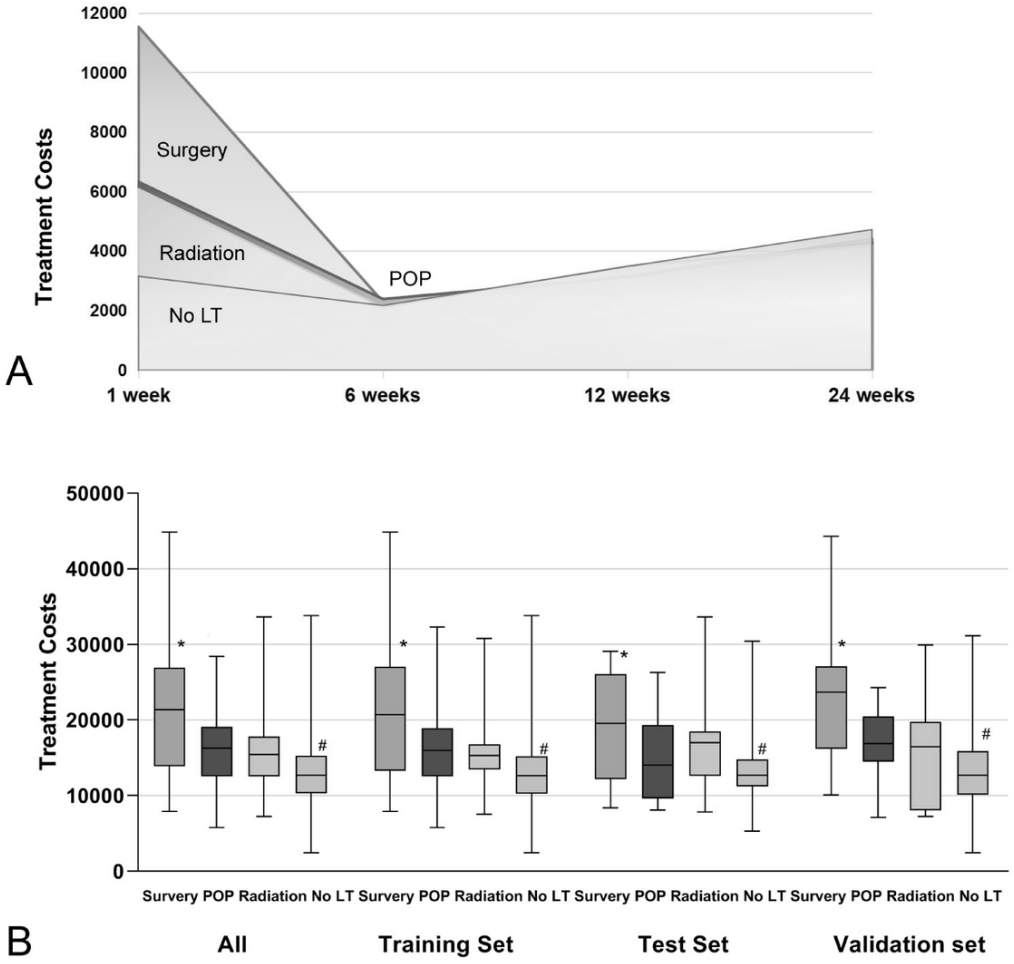

Figure 4

Mean costs during 24 weeks in surgery, POP, radiation, and no local treatment groups (A). Mean costs during 24 weeks in all patients and in training, test, and validation sets (B). * Significantly higher cost compared to other three group ($p < 0.05$). # Significantly lower cost compared to other three group ($p < 0.05$). No LT: No local treatment.

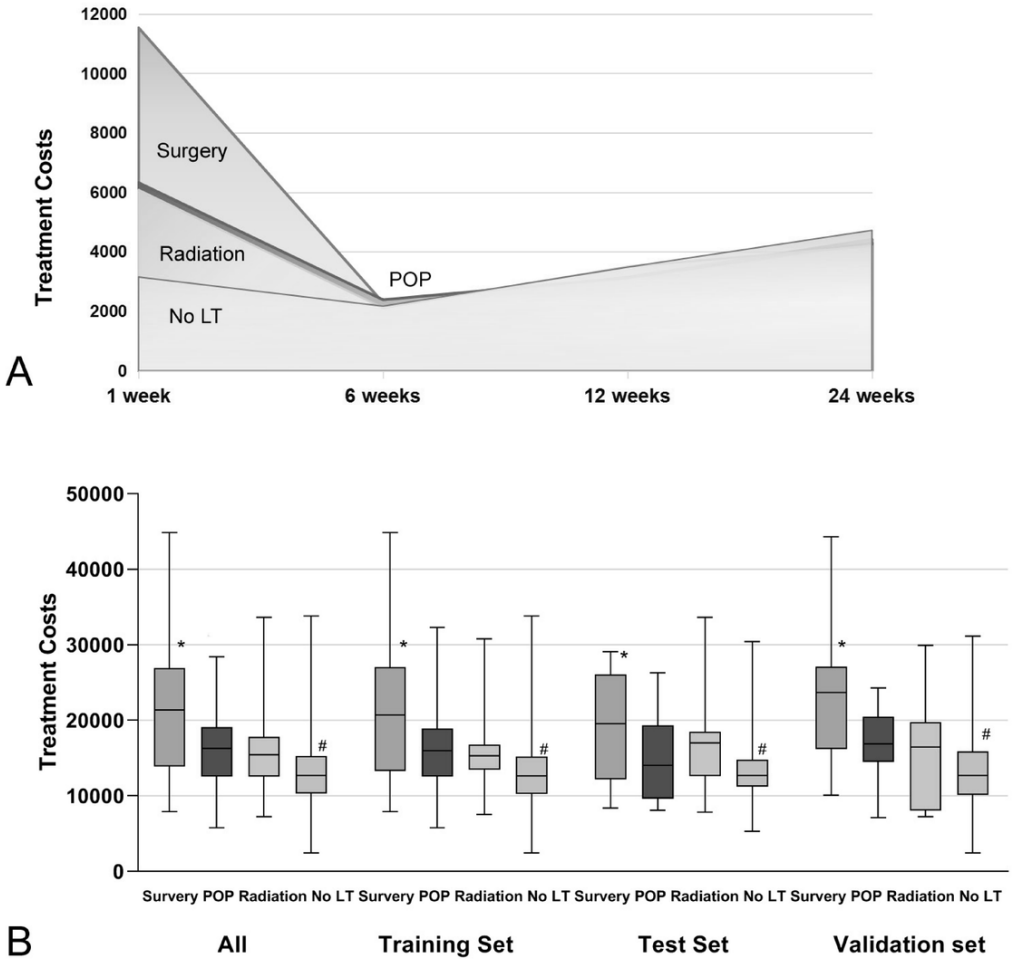

Figure 4

Mean costs during 24 weeks in surgery, POP, radiation, and no local treatment groups (A). Mean costs during 24 weeks in all patients and in training, test, and validation sets (B). * Significantly higher cost compared to other three group ($p < 0.05$). # Significantly lower cost compared to other three group ($p < 0.05$). No LT: No local treatment.