Original Article

External validation of the PATHFx decision-support tool on Turkish patients with skeletal metastasis

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Abstract

Objective: Accurate determination of life expectancy becomes very important when determining the treatment of patients with pathologic fractures. We aimed to investigate the predictive role of the PATHFx model in Turkish patients by estimating the area under curve (AUC) of the receiver operator characteristic (ROC) and externally validating the results of PATHFx on the Turkish population.

Methods: The data of 122 patients who presented to one of four orthopaedic oncology referral centres in Istanbul (2010–2017) and underwent surgical management of pathologic fractures were retrospectively collected. Patients were evaluated according to age, sex, type of pathologic fracture, presence of organ metastasis, presence of lymph node metastasis, haemoglobin concentration at presentation, primary oncologic diagnosis, number of bone metastases, and Eastern Cooperative Oncology Group (ECOG) status. Estimations of the PATHFx program by months were statistically evaluated using ROC analysis.

Results: In our study population (122 patients), all survived the first month, 102 survived the third month, 89 were alive at 6 months, and 58 patients survived at 12 months. At 18 and 24 months, 39 and 27 patients were alive, respectively. The AUC value was 0.677 at 3 months, 0.695 at 6 months, 0.69 at 12 months, 0.674 at 18 months, and 0.693 at 24 months. The 3-, 6-, 12-, 18-, and 24-month survival rates were statistically significant ($P < 0.01$ and $P < 0.05$). ECOG performance status was 0–2 points in 33 patients (Memorial Sloan-Kettering Cancer Center (MSKCC) data set: 93 cases, our data set: 33 cases). ECOG performance status was 3–4 points in 89 patients (MSKCC data set: 96 cases, our data set: 89 cases).

Conclusions: The objective data used by PATHFx for prediction provided statistically accurate estimates on Turkish patients, who are presumed to have mixed genomes through history from both Europe and Asia, and demonstrates its applicability to the Turkish population.

Keywords:
Expected survival, metastatic bone disease, PATHFx, pathologic fracture

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Introduction

Cancer has become an increasingly important health issue worldwide. The number of people with carcinoma increases each year.[1] It has been estimated that 50% of all cancer deaths include bone metastasis.[2-4] The risk of pathologic fracture increases because bone biomechanics are impaired due to metastatic events.[3]

The prediction of exact estimated survival is of utmost importance for planning treatment of patients who present to health facilities due to pathologic fractures. Treatment modalities vary depending on estimated survival.[5] A surgeon's subjective estimate of survival generally does not match real survival time.[6] There is a need for the development of prediction tools with greater accuracy based on more objective data. The PATHFx model has been tested in developed countries[7]; however, there is no study on its validation in developing countries.

The aim of this study was to compare a training data set of a Memorial Sloan-Kettering Cancer Center (MSKCC) patient group with our patient population, and to test the PATHFx model in the Turkish population, which establishes a bridge between Europe and Asia.

Subject and Methods

This retrospective chart review study involving human participants was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. An Institutional review board approval was obtained from our University. Between 2010 and 2017, patients with pathologic fractures who present to one of four orthopedic oncology referral centers in our region were retrospectively reviewed. Two hundred thirty-three cases were identified. One hundred eleven patients who had a follow-up of less than 1 year and had incomplete data sets were excluded from the study. The reasons for exclusion of the 111 patients were follow-up of less than 1 year (n = 37), insufficient data to calculate Eastern Cooperative Oncology Group (ECOG) status (n = 23), unavailable data for hemoglobin concentrations (n = 18), visceral metastasis (n = 15), and skeletal metastasis (n = 18).

Data collected included age, sex, type of pathologic fracture, presence of visceral metastasis, lymph node metastasis, hemoglobin, and leucocyte concentrations at initial presentation, primary oncologic diagnosis, number of bone metastases, and ECOG status using the PATHFx model (version 3.0). PATHFx version 3.0 is a software package, supported by international collaborations, which is used to predict the survival time of patients with malignancies through the use of objective data instead of subjective evaluations.

Table 1: Comparison of Turkish population and the MSKCC patient group

	MSKCC	TURKISH
Age	62.4	60.7
Sex		
Male	85	62
Female	104	60
Skeletal metastases		
Solitary	55	42
Multiple	134	80
ECOG performance		
0-2	93	33
3-4	96	89
Oncological diagnosis by grade		
1	52	34
2	34	23
3	103	65
Survival - 3 months		
yes	129	102
no	60	20
Survival - 6 months		
yes	111	89
no	78	33
Survival - 12 months		
yes	79	58
no	110	64
Survival - 18 months		
yes	59	39
no	130	83
Survival - 24 months		
yes	44	27
no	145	95

ECOG: Eastern Cooperative Oncology Group Performance Status; MSKCC: Memorial Sloan Kettering Cancer Center

Table 1 demonstrates the comparison of our data set with the MSKCC patient group based on previous studies.[7] The real survival time was compared with the estimated survival time. Receiver operator characteristic (ROC) curve analysis was performed to determine the 1-, 2-, 3-, 6-, 12-, 18-, and 24-month probability for the survival of patients, who were retrospectively reviewed [Figures 1–5]. Area under the curve (AUC) graphs were generated for each survival time.

Statistical analysis was performed using the Number Cruncher Statistical System (2007, Kaysville, Utah, USA). Values are represented with descriptive analyses (mean, standard deviation, median, frequency, ratio, minimum, maximum). The Chi-square

Key Message

Estimations of the PATHFx program have been used to predict survival in developed countries. This study shows that PATHFx tool can also be used for survival estimates in patients living in developing countries.

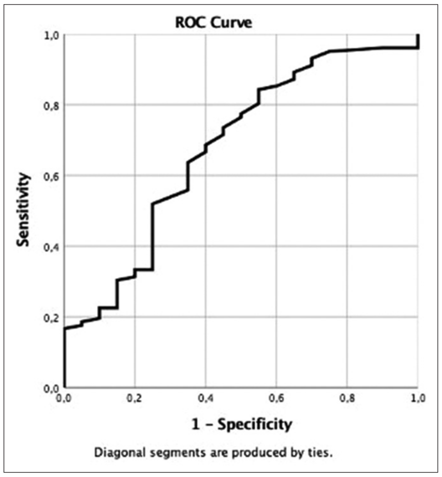

Figure 1: ROC curve (3 months)

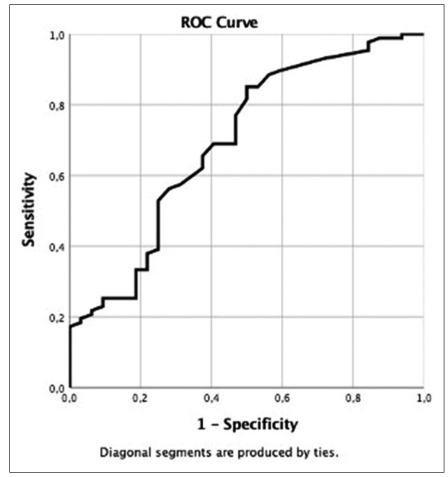

Figure 2: ROC curve (6 months)

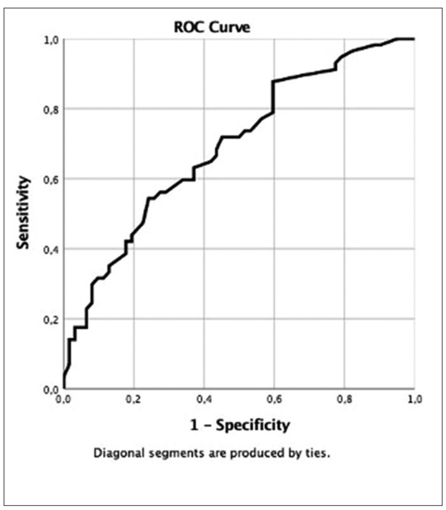

Figure 3: ROC curve (12 months)

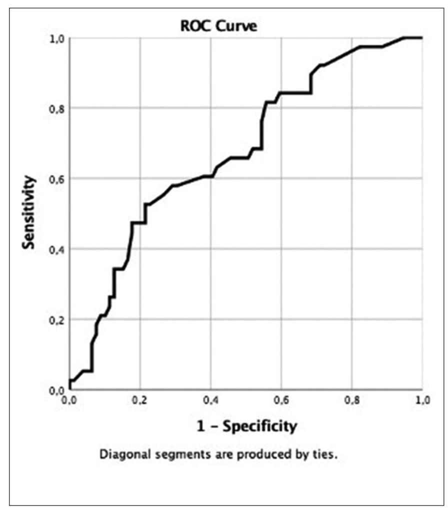

Figure 4: ROC curve (18 months)

test was used to compare qualitative data. ROC curves were used depending on survival time. AUC and cut-off values were calculated. P values less than 0.01 and 0.05 were considered statistically significant.

Results

Our study population included 112 patients (62 females, 60 females; mean age 60.7 years; range 14–85 years). Eighty patients had multiple skeletal metastases. [Table 1] All patients in our study population were alive at the end of first month. Of these 122 patients, 102, 89, 58, 39, and 27 patients were alive at 3, 6, 12, 18, and 24 months, respectively. [Table 1] The 3-, 6-, 12-, 18-, and 24-month survival rates between the MSKCC data set and our study group were statistically significant ($P < 0.01$ and $P < 0.05$).

The AUCs for the 3-, 6-, 12-, 18-, and 24-month models were 0.677, 0.695, 0.69, 0.674, and 0.693, respectively [Table 2]. When the cut-off point at 3 months of survival was taken as 18.5, the sensitivity and specificity were 84.3 and 45%, respectively [Table 2] [Figure 1]. When the cut-off point at 6 months of survival was taken as 14.5, the sensitivity and specificity were 88.5 and 43.76%, respectively [Table 2] [Figure 2]. When the cut-off point at 12 months of survival was taken as 33.5, the sensitivity and specificity were 54.4 and 75.8%,

Table 2: Cut off and AUC values after ROC analysis

Periods	Sensitivity (%)	Specificity (%)	Cut-off value	Area under curve (AUC)
3 months	84.3	45.0	18.5	67.7
6 months	88.5	43.7	14.5	69.5
12 months	54.4	75.8	33.5	69.0
18 months	52.6	78.5	36.5	67.4
24 months	66.7	71.3	23.5	69.3

respectively [Table 2] [Figure 3]. When the cut-off point at 18 months of survival was taken as 36.5, the sensitivity and specificity were 52.6 and 78.5%, respectively [Table 2] [Figure 4]. When the cut-off point at 24 months of survival was taken as 23.5, the sensitivity and specificity were 66.7 and 71.3%, respectively [Table 2] [Figure 5]. There was a statistically important correlation between real survival time and PATHFx results at all time points; at 3 months ($P = 0.006$; $P < 0.05$) [Table 3], at 6 months ($P = 0.006$; $P < 0.05$) [Table 4], at 12 months ($P = 0.001$; $P < 0.05$) [Table 5], at 18 months ($P = 0.001$; $P < 0.05$) [Table 6], and at 24 months ($P = 0.001$; $P < 0.05$) [Table 7].

ECOG performance status was 0–2 points in 33 patients (MSKCC data set: 93 cases, our data set: 33 cases). ECOG performance status was 3–4 points in 89 patients (MSKCC data set: 96 cases, our data set: 89 cases). There was no statistically significant difference between our patient data set and the MSKCC data group in terms of oncologic diagnoses, metastasis rates, and sex distribution ($P < 0.05$); however, there was a significant difference in terms of ECOG status between our patient data set and the MSKCC data group ($P < 0.01$). There was a significant difference between ECOG status at admission to hospital and estimated survival time between our patient data set and the MSKCC data group ($P < 0.01$).

Kaplan–Meier curves obtained after the application of the PATHFx prediction tool demonstrated no statistically significant results in the 3-, 6-, 12-, 18-, and 24-month survival between the estimated and expected survival times. During treatment planning, this clinical decision support tool can aid in the prediction of real survival time based on objective criteria.

Discussion

Visceral metastasis is one of the most frequently metastatic areas of all bone tumors. With the ever-increasing number of cases of carcinoma, there is also an increase in bone metastasis.[1,8,9] In patients with pathologic fractures, treatment modalities may

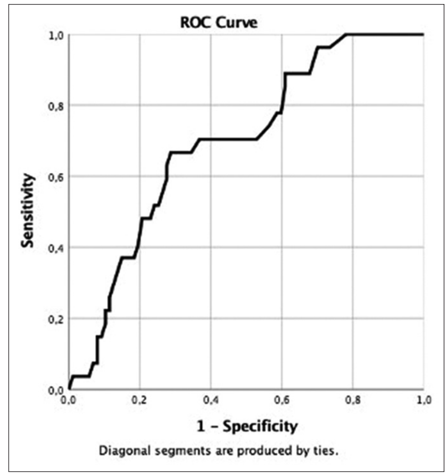

Figure 5: ROC curve (24 months)

vary depending on the expected survival estimate. The aim of treatment is to relieve pain, maintain function with adequate stability, and improve/maintain quality of life.[10] Wide resection and combined adjuvant treatments influence survival in patients with solitary bone metastasis.[11]

After surgery, survival of patients with metastatic disease depends on metastatic burden, type of primary malignancy, and the development of pathologic fractures. Survival time decreases in patients with solitary cranial/visceral metastasis.[12] The type of primary carcinoma represents one of the main important prognostic criteria in solitary bone metastasis.[13] Inadequate surgery in patients with increased expected survival causes implant failure and reoperations.[14] To avoid these problems, an optimal treatment decision should be made for the patient. To determine the most appropriate treatment modality, objective criteria should be used to predict an accurate expected survival time. PATHFX 3.0 is an easily accessible online software. Surgical decision making with the support of this software can help to prevent over or under treatment.[15]

ECOG status is one of the main criteria that directly influence expected survival time in patients with solitary metastasis.[16] When ECOG status and survival time were compared in our study group, ECOG status was shown to directly impact survival time; 18 of 27 patients who were still alive at the end of 2 years had ECOG status of 3-4. Hemoglobin count, ECOG status, presence of visceral metastasis, primary diagnosis, and the number of metastatic lesions are objective criteria that affect expected survival time.[5,13,16] In addition to the objective criteria, PATHFx version 3.0 performs survival time prediction by adding the surgeon's estimated survival as a subjective criterion. PATHFx predicts near-accurate

Table 3: Comparison between the real survival time and 3-month PATHFx results

Survival estimate	Status	Real Survival		
		Death	Alive	P^b
PATHFX results	Death	9 (36.0%)	16 (64.0%)	0.006**
	Alive	11 (11.3%)	86 (88.7%)	

[b]Pearson's Chi-square test; *P<0.05; **P<0.01

Table 4: Comparison between the real survival time and 6-month PATHFx results

Survival estimate	Status	Real Survival		
		Death	Alive	P^b
PATHFX results	Death	16 (53.3%)	14 (46.7%)	0.001**
	Alive	17 (18.5%)	75 (81.5%)	

[b]Pearson's Chi-square test; *P<0.05; **P<0.01

Table 5: Comparison between the real survival time and 12-month PATHFx results

Survival estimate	Status	Real survival		
		Death	Alive	P^b
PATHFX results	Death	48 (64.9%)	26 (35.1%)	0.001**
	Alive	16 (33.3%)	32 (66.7%)	

[b]Pearson's Chi-square test; *P<0.05; **P<0.01

Table 6: Comparison between the real survival time and 18-month PATHFx results

Survival estimate	Status	Real survival		
		Death	Alive	P^b
PATHFX results	Death	64 (78.0%)	18 (22.0%)	0.001**
	Alive	18 (46.2%)	21 (53.8%)	

[b]Pearson's Chi-square test; *P<0.05; **P<0.01

Table 7: Comparison between the real survival time and 24-month PATHFx results

Survival estimate	Status	Real survival		
		Death	Alive	P^b
PATHFX results	Death	62 (87.3%)	9 (12.7%)	0.001**
	Alive	27 (60.0%)	18 (40.0%)	

[b]Pearson's Chi-square test; *P<0.05; **P<0.01

expected survival time using all these objective criteria.[15] We did not include surgeon estimated survival in our model due to variations in these estimations between surgeons and different centers. The PATHFx model predicted accurate survival at 3, 6, 12, 18 and 24 months in our cohort of patients.

Application of PATHFx in various populations have been demonstrated in previous studies. PATHFx has been shown to be an appropriate software to predict expected survival time for use in preoperative treatment planning.[7,17,18] Our investigation was performed in a Turkish population, which constitutes a connection between Europe and Asia. It is unique because such a validation study has never been performed in a Turkish population. Although significant differences exist between our data set and the MSKCC population regarding demographic and patient characteristics, PATHFx was able to make accurate predictions of survival time ($P < 0.01$).

For oncology surgeons, there is a need for objective and accurate evaluation instead of subjective and inaccurate expected survival time. With recent advances, many survival-prediction tools have been introduced.[15,19-21] In a previous study, the prediction rate made by PATHFx was stated as more accurate than other prediction models in all survival times.[22] Anderson *et al*.[23] evaluated PATHFx version 3.0, which is an update, adding more data sets of patients treated surgically or non-surgically. Except for radiotherapy patients with less than 1-month expected survival time, PATHFx version 3.0 was successful in the prediction of survival. Our study group confirmed these findings by making statistically significantly accurate predictions in all survival time periods. Despite these findings, 3- and 6-month expected survival times were more accurate than other time periods.

We realize that although PATHFx's expected survival estimates in the first 12 months were more pessimistic, expected survival estimates at 12–24 months were more optimistic relative to the real survival time. The reasons for these findings could be attributed to the fact that in the first 12 months, patients who were well referred to us for surgical treatment from the medical oncology department, whereas patients with poor health status were referred to radiation oncology or palliative care. Scarce palliative care centers, inadequate supportive care, and the presence of patients with a desire for home living in their last days due to cultural issues could be reasons for the low survival rate in the second year.

Our study has limitations in that it is based on retrospective data set and inherently has the errors and biases associated with retrospectively collected data. Furthermore, our study was limited to those patients who were referred to our centers for surgical treatment for pathological fracture from bone metastasis. It does not include those patients who opted for nonsurgical treatment or refused surgery, thereby adding selection bias. It was not possible to obtain complete information of all orthopedic oncology referrals in Turkey. However, data was collected from four orthopedic oncology referral centers in Istanbul, which constitutes one-quarter of the entire country's population. The tool potentially can be made more accurate by including a larger population subset of patients and including those who were treated nonoperatively with chemotherapy and/or radiation treatment and those who declined all treatments.

In conclusion, our external validation of PATHFx version 3.0 for the Turkish population predicted accurate 3-, 6-, 12-, 18-, and 24-month survivals even though the MSKCC population had statistically different demographic characteristics relative to the Turkish population. Using PATHFx version 3.0, we can determine more appropriate treatment for individual patients with better estimations of survival. This will help avoid exhausting surgical interventions in patients with poor survival and avoid reoperations in those with better medium- to longer-term survival; thereby improving the quality of life for patients with metastatic bone disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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