

RESEARCH ARTICLE

Clinical Predictors of Survival for Patients with Stage IV Cancer Referred to Radiation Oncology

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OPEN ACCESS

Citation: Kao J, Gold KD, Zarrili G, Copel E, Silverman AJ, Ramsaran SS, et al. (2015) Clinical Predictors of Survival for Patients with Stage IV Cancer Referred to Radiation Oncology. PLoS ONE 10(4): e0124329. doi:10.1371/journal.pone.0124329

Academic Editor: Qing-Yi Wei, Duke Cancer Institute, UNITED STATES

Received: January 20, 2015

Accepted: March 2, 2015

Published: April 20, 2015

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Data Availability Statement: To ensure compliance with the existing IRB approval letter and HIPAA compliance for patients, the full deidentified dataset cannot be made available without prior written approval from the Good Samaritan Hospital Institutional Review Board. Requests for deidentified data can be made to Dr. William Engellener, Chairman of the Good Samaritan Hospital Medical Center Institutional Review Board.

Funding: The author(s) received no specific funding for this work.

Abstract

Background

There is an urgent need for a robust, clinically useful predictive model for survival in a heterogeneous group of patients with metastatic cancer referred to radiation oncology.

Methods

From May 2012 to August 2013, 143 consecutive patients with stage IV cancer were prospectively evaluated by a single radiation oncologist. We retrospectively analyzed the effect of 29 patient, laboratory and tumor-related prognostic factors on overall survival using univariate analysis. Variables that were statistically significant on univariate analysis were entered into a multivariable Cox regression to identify independent predictors of overall survival.

Results

The median overall survival was 5.5 months. Four prognostic factors significantly predicted survival on multivariable analysis including ECOG performance status (0–1 vs. 2 vs. 3–4), number of active tumors (1 to 5 vs. ≥6), albumin levels (≥3.4 vs. 2.4 to 3.3 vs. <2.4 and primary tumor site (Breast, Kidney or Prostate vs. Other). Risk group stratification was performed by assigning points for adverse prognostic factors resulting in very low, low, intermediate and high risk groups. The median survival was >31.4 months for very low risk patients compared to 14.5 months for low risk, 4.1 months for intermediate risk and 1.2 months for high risk ($p < 0.001$).

Competing Interests: The authors have declared that no competing interests exist

Conclusions

These data suggest that a model that considers performance status, extent of disease, primary tumor site and serum albumin represents a simple model to accurately predict survival for patients with stage IV cancer who are potential candidates for radiation therapy.

Introduction

Approximately half of cancer patients referred for radiotherapy evaluation have stage IV cancer [1]. An accurate estimation of life expectancy of patients with metastatic cancer remains a difficult challenge for clinicians [2]. When using intuition and experience alone, clinicians systematically overestimate survival in patients with incurable cancer [3,4]. A more accurate estimate of survival can reduce the administration of unnecessarily protracted courses of palliative radiotherapy [5,6]. Conversely, it is important for clinicians to identify a subset of patients with metastatic cancer that can benefit from improved local control and disease-free survival with aggressive local and systemic therapy [7,8]. Therefore, there is a clear need for robust models of predicted survival in stage IV cancer.

Patients with metastatic cancer are heterogeneous and with the exception of performance status, there has not been uniform agreement on predictors of survival [9]. Performance status alone only accounts for less than half of the variability in survival observed in terminally ill cancer patients [10]. A recent review by the European Association for Palliative Care of published studies attempted to identify favorable and unfavorable subgroups and showed that prognostic factors evaluated were highly variable [11]. In general, performance status and clinical signs and symptoms of organ failure, including dyspnea, dysphagia, weight loss, anorexia and altered mental status, were the strongest predictors of survival [11]. Although not yet widely used in radiation oncology, the Palliative Performance Scale Score augments performance status with measures of extent of disease, self-care, oral intake and level of consciousness [12,13]. In recent studies investigating patients who were still candidates for anticancer therapy, there was additional value in incorporating tumor type, extent of metastatic disease and select laboratory values to further refine the prognostic model [14,15].

With the goal of improving estimates of survival among patients with stage IV cancer referred to radiation oncology, we performed a comprehensive analysis that systematically evaluates possible clinical, imaging, laboratory and pathologic predictors of survival.

Materials and Methods

Inclusion Criteria

This study included consecutive patients older than 18 years with metastatic stage IV solid tumor who were referred to a single physician in a large community hospital-based radiation oncology department. This minimal risk study was approved by the Good Samaritan Hospital Institutional Review Board with waiver of informed consent.

Data Collection

The history, physical examination, radiologic studies, pathology and laboratory tests were documented by review of electronic medical record (EPIC). Confirmation of survival was performed by review of most recent office visit or confirmed activity in the hospital electronic medical record. Confirmation of survival status and date of death was performed using review

of the Social Security Death Index. Patients who were lost to follow-up were censored at the last clinic visit.

The following patient-related factors were collected: age, gender, race, ECOG performance score, weight loss, marital status, Charlson comorbidity score and symptoms (dyspnea, pain, altered mental status, symptoms of anorexia/cachexia syndrome) [1,9,16,17]. Altered mental status is defined as change in brain function from baseline including confusion, drowsiness, delirium, dementia or coma. Laboratory examination included leukocyte count, percentage of lymphocytes, serum albumin and total bilirubin [18,19,20]. Lactate dehydrogenase and C reactive protein were not routinely performed at our institution. The following tumor related factors were analyzed: primary tumor site, histology, metastasis site(s), number of active tumors, number of involved organs, disease status (newly diagnosed with stage IV vs. prior diagnosis of stage IV cancer) and disease-free interval >12 months [1,9]. Number of active tumors was quantified by identifying tumors measuring > 1 cm in short axis on CT or MRI or increased radiotracer activity on PET or bone scan. Oligometastases were defined as 1 to 5 active tumors on whole body imaging [21]. Breast, prostate and kidney cancers have previously been associated with a more favorable prognosis in patients with metastatic disease receiving radiotherapy [15,22]. There was no missing data with the exception of marital status and laboratory values in $\leq 20\%$ of the patient population.

Statistical Methodology

Statistical analysis was performed with Stata 8.0. The primary outcome was overall survival, defined as time from initial radiation oncology consultation to date of death. Survival data was analyzed using the Kaplan-Meier method and summarized by median and 6-month survival. The log-rank method was used to compare the effect of patient and tumor-related variables on overall survival. Continuous variables were categorized into two or three classes using cut points suggested by literature review.

To adjust for the effects of multiple comparisons, variables that were significant at a p value of 0.02 after univariate analysis were entered into a Cox multivariable analysis. The proportional hazards assumption were graphically checked by examining $\log[-\log(\text{probability})]$ plot over time. To determine the prognostic value of each covariate in the final model, a linear regression was performed on 6-month survival. The proportion of variability in observed survival that was explained by the predicative model was measured by the multiple correlation coefficient R^2 .

Results

Patient-Specific Prognostic Factors

Between May 2012 to September 2013, 143 patients with distant metastases were referred for radiation oncology evaluation with 57% inpatient consultations and 43% outpatient consultations. The median survival was 5.5 months. The median follow-up for surviving patients was 19.1 months (range 0.5 to 32.1 months). The mean age was 67 years \pm 13 years (range 33 to 97). Women accounted for 59% of the patient population and the majority of patients were white (80%). With respect to performance status, 29% were ECOG 0–1, 32% were ECOG 2 and 40% were ECOG 3–4. The incidence of moderate to severe dyspnea was 15% and the incidence of moderate to severe pain was 48%. Altered mental status was observed in 14%, extensive comorbidity was noted in 8% and significant weight loss, anorexia or dysphagia was noted in 34% (Table 1).

We performed univariate analysis on the effect of patient factors on survival. Gender, race, dyspnea, pain and serum bilirubin did not predict survival. Nine factors strongly predicted short survival including age ≥ 80 , ECOG 3–4, not married status, altered mental status,

Table 1. Univariate analysis of patient characteristics on survival in patients with advanced cancer.

Variable	Number (%)	P	Median Survival (months)	6 month survival
Overall population			5.5	48%
Age		<0.001		
<60	37 (26%)		10.2	66%
60 to 79	74 (52%)		5.7	49%
≥80	32 (22%)		1.5	26%
Gender		0.93		
Male	58 (41%)		4.2	46%
Female	85 (59%)		5.7	50%
Race				
White	114 (80%)	0.07	6.5	53%
Non-white	29 (20%)		4.2	28%
ECOG performance				
0–1	41 (29%)	<0.001	21.6	90%
2	44 (31%)		5.7	48%
3	45 (31%)		1.7	23%
4	13 (9%)		0.5	8%
Marital status		0.002		
Married	64 (45%)		9.7	65%
Not married	58 (41%)		4.1	37%
Unknown	21(15%)			
Dyspnea		0.33		
Borg 0 to 2	122 (85%)		5.2	48%
Borg ≥3	21 (15%)		5.5	51%
Pain		0.82		
Pain scale 0 to 4	74 (52%)		5.2	46%
Pain ≥5	69 (48%)		5.2	51%
Altered mental status		<0.001		
No	123 (86%)		6.5	55%
Yes	20 (14%)		1.4	10%
Charlson comorbidity score		0.001		
0 to 3	132 (92%)		6.1	52%
≥4	11 (8%)		0.7	9%
Weight loss ≥ 10% or Anorexia or Dysphagia		<0.001		
No	94 (66%)		8.2	61%
Yes	49 (34%)		1.7	27%
Elevated WBC		0.003		
≤11	88 (62%)		6.2	52%
>11	39 (27%)		2.7	28%
Unknown	16 (11%)			
Lymphopenia		<0.001		
≥12%	69 (48%)		8.2	59%
<12%	53 (37%)		1.8	25%
Unknown	21 (15%)			
Albumin		<0.001		
≥3.4	54 (47%)		9.7	61%
2.4 to 3.3	52 (45%)		2.7	26%
<2.4	10 (9%)		1.5	10%

(Continued)

Table 1. (Continued)

Variable	Number (%)	P	Median Survival (months)	6 month survival
Overall population			5.5	48%
Unknown	27 (19%)			
Bilirubin		0.12		
Normal	104 (73%)		4.6	41%
Elevated	11 (8%)		1.7	36%
Unknown	28 (20%)			

doi:10.1371/journal.pone.0124329.t001

Charlson comorbidity score ≥ 4 , weight loss, anorexia or dysphagia, white blood cell count > 11 , percent lymphocytes $< 12\%$, serum albumin 2.4 to 3.3 and serum albumin < 2.4 .

Tumor-Specific Prognostic Factors

The most common primary tumor sites were lung (45%), breast (13%), colorectal (10%), prostate (6%), endometrial (5%), kidney (4%) and gastroesophageal (4%). The majority of tumors were adenocarcinoma (57%) followed by small cell carcinoma (11%) and squamous cell carcinoma (8%). One quarter of patients (25%) had 1 to 5 active tumors and 29% had only 1 involved organ. Cerebral metastases were present in 40% of patients, 50% had bone metastases, 20% had liver metastases, 47% had lung or pleural metastases, 39% had distant lymph nodes, 10% had adrenal metastases, 8% of patients had spinal cord compression or involvement, 5% had skin or muscle metastases and 9% had abdominal carcinomatosis or serosa/omental metastases.

The results of univariate analysis of tumor factors are listed in [Table 2](#). Newly diagnosed cancer and time from initial diagnosis of cancer did not predict for survival while tumor size was a relatively weak predictor of survival ($p = 0.02$). Breast, prostate and kidney primary tumor, adenocarcinoma, 1 to 5 active tumors, single involved organ and absence of liver or spinal cord involvement were associated with longer survival. Bone only metastases weakly predicted survival ($p = 0.03$).

Multivariable Analysis

Among 16 variables that were significant on univariate analysis, 4 remained significant on Cox multivariable analysis ([Table 3](#)). The strongest predictors of longer survival were ECOG performance status 0 to 1 (HR 1.95), fewer than 6 active tumors (HR 2.70), favorable primary tumor site (HR 3.33) and normal serum albumin (HR 2.09). There was a trend towards improved survival with normal mental status and adenocarcinoma histology, although these covariates did not reach statistical significance.

Development of a Predictive Model

To obtain a composite score, we incorporated variables that were statistically significant on Cox multivariable analysis into a logistical regression to predict 6-month survival ([Table 4](#)). Evaluation of the regression coefficient for each covariate informed weighting of the final model. The relative magnitude of regression coefficients suggested that the two covariates with 2 subgroups (number of active tumors and favorable primary tumor site) should be weighed equally assigning 1 point for an unfavorable risk factor. For the two covariates with 3 subgroups (ECOG performance status and serum albumin), ECOG performance status had twice

Table 2. Univariate analysis of tumor characteristics on overall survival of patients with advanced cancer.

Variable	Number (%)	P	Median Survival (months)	
Primary tumor site				
Lung	65 (45%)		4.6	43%
Breast	19 (13%)	0.003 (Breast vs. non-breast)	Not reached	77%
Colorectal	14 (10%)		6.3	70%
Prostate	9 (6%)		8.0	78%
Uterus	7 (5%)		3.8	43%
Kidney	6 (4%)		11.6	83%
Esophagus/Gastric	5 (4%)		1.5	0%
Pancreas	4 (3%)		1.5	25%
Unknown Primary	4 (3%)		0.7	25%
Other (Melanoma, Vulva, Cervix, Ovary, Sarcoma, Bladder, Salivary Gland, Thyroid)	10 (7%)		0.7	0%
Favorable Primary Site		<0.001		
Breast, Prostate or Kidney	34 (24%)		16.5	78%
Others	109 (76%)		4.1	39%
Histology				
Adenocarcinoma	81 (57%)	0.001 (Adenocarcinoma vs. Other)	8.0	60%
Small Cell Carcinoma	16 (11%)		2.9	38%
Squamous Cell Carcinoma	12 (8%)		2.7	33%
Poorly Differentiated or Carcinoma NOS	11 (8%)		1.7	27%
Other (Renal Cell Carcinoma, Papillary Serous Carcinoma, Melanoma, Sarcoma, Urothelial Carcinoma, Adenoid Cystic Carcinoma, Mucinous Carcinoma, Carcinoid)	16 (11%)		2.3	47%
No Biopsy	7 (2%)		0.6	0%
Largest Tumor Size		0.02		
≤5 cm	73 (51%)		6.3	55%
5.1 to 10 cm	59 (41%)		4.1	42%
≥10.1 cm	11 (8%)		2.1	36%
Number of Active Tumors		<0.001		
1	10 (7%)		21.6	69%
2 to 5	26 (18%)		12.7	79%
≥6	107 (75%)		3.9	38%
Number of Organs Involved		0.001		
1	41 (29%)		13.2	70%
≥2	102 (71%)		4.2	40%
Newly Diagnosed with Cancer		0.99		
Yes	87 (61%)		4.6	48%
No	56 (39%)		5.7	49%
Time from Initial Diagnosis of Cancer >12 Months		0.91		
Yes	43 (30%)		5.7	50%
No	100 (70%)		4.6	48%
Brain Metastases		0.13		
Yes	57 (40%)		4.2	40%
No	86 (60%)		6.3	54%
Liver Metastases		0.004		
Yes	29 (20%)		3.7	41%

(Continued)

Table 2. (Continued)

Variable	Number (%)	P	Median Survival (months)	
No	114 (80%)		6.0	50%
Spinal Cord Compression or Leptomeningeal Spread		<0.001		
Yes	11 (8%)		0.9	9%
No	132 (92%)		6.2	52%
Bone only metastases		0.03		
Yes	12 (9%)		Not reached	75%
No	130 (91%)		5.1	46%

doi:10.1371/journal.pone.0124329.t002

the weight of albumin. Therefore, 1 point was assigned for ECOG 2, 2 points were assigned for ECOG 3 to 4, 0.5 points for serum albumin 2.4 to 3.3 and 1 point for serum albumin <2.4. Favorable covariates were assigned 0 points.

Performance of the predictive model

Composite scores ranged from 0 to 5. Composite scores were used to classify patients into 4 groups with clearly distinct median survivals (Table 5). There was a very low risk cohort with a composite score of 0 to 1 had a median survival of >31.4 months (95% confidence interval 15.5 months to not reached). The low risk cohort with a composite score of 1.5 to 2 had a median survival of 14.5 months (95% confidence interval 8.0 to 21.4 months). The intermediate risk group had a composite score of 2.5 to 3.5 had a median survival of 4.1 months (95% confidence interval 2.6 to 5.7 months). The high risk group had a composite score of 4 to 5 and had a median survival of 1.2 months (95% confidence interval 0.7 to 1.5 months). Risk group strongly predicted overall survival with a p value of <0.001 (Fig 1).

Comparison of actual survival with predicted survival gave an R² value of 0.50 compared to 0.34 for ECOG performance status alone, 0.15 serum albumin, 0.11 for number of active tumors and primary tumor site.

Discussion

After a comprehensive review of contemporary patients evaluated in a hospital-based radiation oncology center, we identified numerous predictors of survival on univariate and multivariate analysis. Importantly, we identified fairly common key subgroups of patients with a median survival of less than 2 months including age ≥80, ECOG 3–4, lymphopenia and symptoms of anorexia/cachexia syndrome. Further, we identified less common subgroups of patients with median survival of less than 2 months including altered mental status, Charlson comorbidity score ≥4, serum albumin <2.4, elevated bilirubin, esophagus/gastric/pancreatic or unknown primary tumor, poorly differentiated carcinoma and spinal cord compression. For instance, a patient with ECOG 3–4 and ≥6 active tumors has a grave prognosis with a median survival of

Table 3. Cox multivariable analysis of predictors of overall survival.

Variable	Hazard Ratio	95% Confidence Interval	P value
ECOG Performance Status (0–1 vs. 2 vs. 3–4)	1.95	1.25 to 3.03	0.003
Number of Active Tumors (1 to 5 vs. ≥6)	2.70	1.40 to 5.19	0.003
Serum albumin (≥3.4 vs. 2.4 to 3.3 vs. <2.4)	2.09	1.25 to 3.48	0.005
Tumor Site (Breast, Kidney or Prostate vs. Other)	3.33	1.27 to 8.76	0.015

doi:10.1371/journal.pone.0124329.t003

Table 4. Linear regression of predictors of 6-month survival.

Variable	Regression Coefficient	95% Confidence Interval	P value
ECOG Performance Status (0–1 vs. 2 vs. 3–4)	0.26	0.17 to 0.36	<0.001
Number of Active Tumors (1 to 5 vs. ≥6)	0.29	0.13 to 0.45	0.001
Serum albumin (≥3.4 vs. 2.4 to 3.3 vs. <2.4)	0.14	0.02 to 0.25	0.017
Tumor Site (Breast, Kidney or Prostate vs. Other)	0.31	0.12 to 0.50	0.002

doi:10.1371/journal.pone.0124329.t004

1.2 months and survival beyond 6 months is highly unlikely. Unfavorable risk patients may be best classified as far advanced metastatic disease.

Conversely, these data confirm that oligometastases are not uncommon, representing 25% of stage IV patients referred to radiation oncology [23]. Patients with ECOG 0–1, breast or kidney cancer, 1 to 5 active tumors and single organ involvement were associated with median survival greater than 12 months. Along with recently published biological and genetic studies, these data support the notion that patients with oligometastases are a distinct subset of stage IV cancers that can have prolonged disease-free survival [24]. Recent research suggests that stereotactic body radiotherapy with or without concurrent systemic therapy holds promise for further improving progression-free survival with an acceptable toxicity profile for selected patients with oligometastases [21,25,26].

In our study, we identified 4 robust predictors of survival on multivariable analysis. Consistent with prior studies, ECOG performance status was a strong predictor of survival but accounts for only a fraction of observed survival. Number of active tumors was also a strong predictor of survival that is also included in the Palliative Performance Scale Scores [12]. Anorexia/cachexia syndrome is a strong predictor of terminal cancer. In this study, low serum albumin strongly predicted for short survival. Somewhat surprising was that brain metastases did not strongly impact survival. In our series, 27% of patients with brain metastases survived over 12 months. There has been increasing interest in reducing the late toxicity of whole brain radiotherapy in long-term survivors of brain metastases [27]. However, since only 41% of brain metastases survive 6 months, careful selection using criteria such as ECOG 0–2, limited extracranial disease, no weight loss and no altered mental status for surgery and/or stereotactic radiosurgery.

The group from Toronto-Sunnybrook Regional Cancer Centre has published landmark studies on prognostic factors for a large population of patients with stage IV cancer referred to a palliative radiotherapy service [15]. With the goal of simplicity, they demonstrated that breast cancer, bone only metastases and KPS ≥ 70 was associated with improved survival. However, the authors acknowledged that their statistically significant model explained less than 30% of the observed variability. A second study from University of Minnesota identified performance status as the strongest predictor of survival with some contribution from primary site and solitary metastasis for longer survivors ≥ 8 month [28]. In our analysis, patients with either primary breast, prostate or kidney primary tumors had better survival than other primary tumors.

Table 5. Median and 6-month survival stratified by risk group.

Risk Score	Number (%)	Median survival	6 month survival (95% confidence interval)
Very Low Risk (0 to 1)	22 (15%)	Not reached	100% (n/a)
Low Risk (1.5 to 2)	30 (21%)	14.5 months	89% (69 to 96%)
Intermediate Risk (2.5 to 3.5)	49 (34%)	4.1 months	37% (23 to 50%)
High risk (4 to 5)	42 (29%)	1.2 months	7% (2 to 17%)

doi:10.1371/journal.pone.0124329.t005

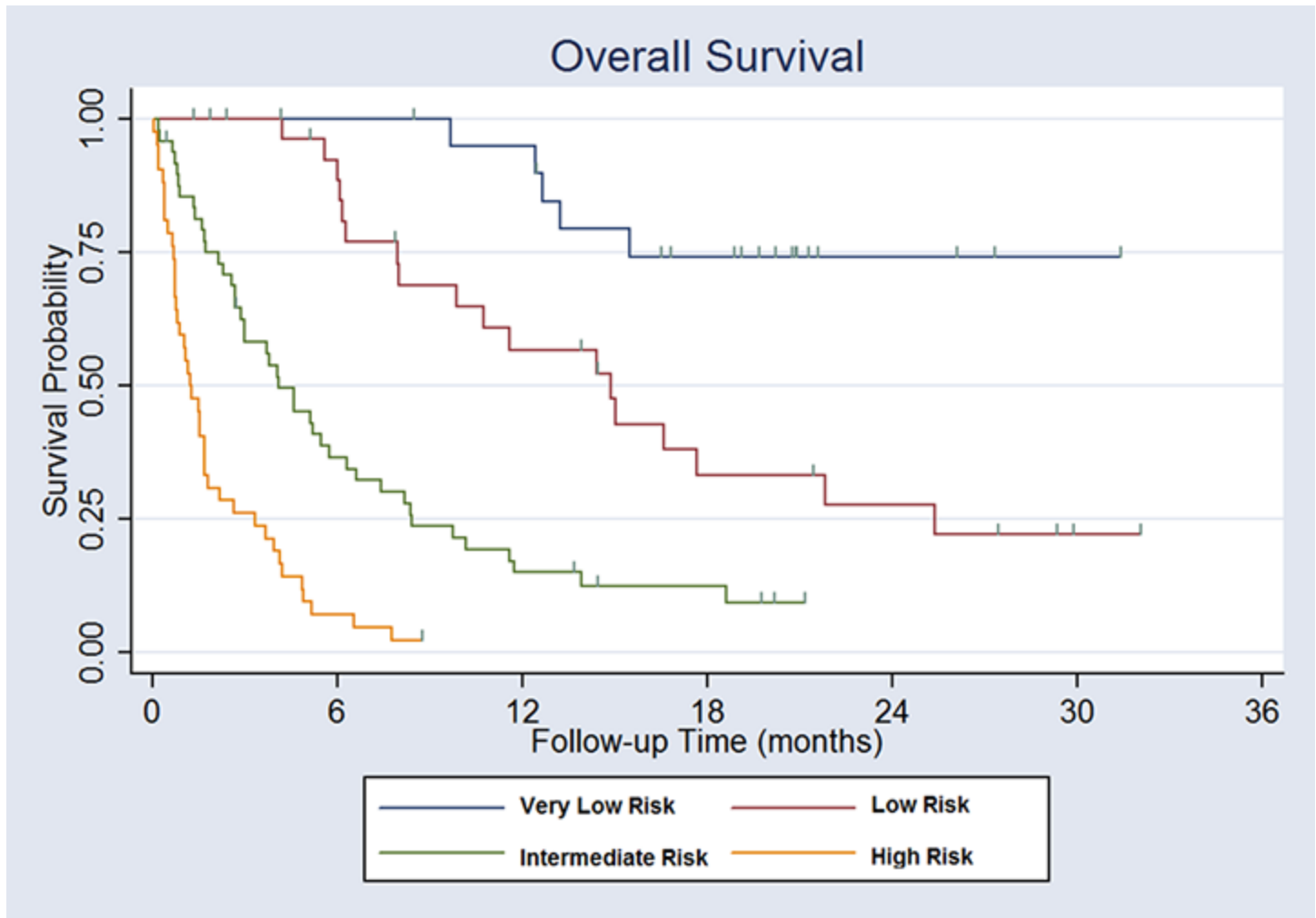


Fig 1. Overall Survival Stratified by Risk Score. Very low risk patients have a risk score of 0 to 1. Low risk patients have a risk score of 1.5 to 2. Intermediate risk patients have a risk score of 2.5 to 3.5. High risk patients have a risk score of ≥ 4 . Patients receive 1 point for serum albumin < 2.4 , ECOG performance status 2, ≥ 6 active tumors or primary site other than breast, kidney or prostate. Patients receive 2 points for ECOG performance status 3 to 4 and 0.5 points for serum albumin 2.4 to 3.3.

doi:10.1371/journal.pone.0124329.g001

The recently published TEACHH model from Harvard Medical School supplemented primary site and performance status with prior chemotherapy, prior hospitalization and liver metastases but did not include laboratory values, weight loss or clinical symptoms [29].

Likely explanations for the variance in prognostic factors identified in studies of stage IV disease include the different patient populations and significant differences in parameters collected. Some studies focused only on far advanced hospice or palliative care patients that deemphasized the contribution of tumor characteristics [30,31]. Prognostic factors identified among hospitalized stage IV cancer patients may not be generalizable to outpatients that tend to have better function and higher activity levels [14,29,30]. A unique strength of this study is that patients in this study were uniformly evaluated by a single physician rather than aggregated data from multiple providers. Therefore, our database evaluated more clinically relevant parameters than prior efforts in the field of survival prognostication in radiation oncology. Our predictive model had a robust R^2 coefficient of 0.50, which was significantly higher than performance status alone or the published three variable Toronto model of 0.23 [15]. Potential weaknesses of

this study are the retrospective study design, heterogeneous patient population and the relatively low ratio of events to variables analyzed. Multi-institutional prospective validation of this model relative to competing models, such as the Toronto and Harvard models is ongoing. Moreover, the performance of various predictive models should be tested in specific primary tumor types, specific metastatic sites and should include additional biomarkers, including genomics. Further use and development of predictive models could allow clinicians to better tailor supportive care and treatment for patients with stage IV cancer.

Author Contributions

Conceived and designed the experiments: JK. Performed the experiments: JK KDG GZ. Analyzed the data: JK EC AJS SSR DY. Contributed reagents/materials/analysis tools: JK KDG GZ. Wrote the paper: JK EC SR.

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