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Prognostic Models to Predict Survival in Non-Small Cell Lung Cancer Patients Treated with First-Line Paclitaxel and Carboplatin with or without Bevacizumab

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Abstract

Purpose—Determine prognostic factors and build a model to predict one-year overall survival (1Y-OS) and six-month progression free survival (6M-PFS) in advanced non-small cell lung cancer (NSCLC) patients treated with first-line paclitaxel and carboplatin (PC) with or without bevacizumab.

Materials and Methods—We analyzed 26 pretreatment clinical variables in 850 NSCLC patients treated in the randomized study ECOG 4599. Univariate and multivariate analyses were performed to identify prognostic factors. Cox regression with 50% randomly sampled data was used to build nomograms with a prognostic score assigned to each factor. The model was validated with the remaining 50% of data.

Results—Eleven poor factors for OS (hazard ratio) were: skin metastasis (4.49), body mass index <18.5 (2.09), increased serum LDH (1.74), adrenal metastasis (1.52), performance status >0 (1.45), low serum albumin (1.45), male (1.39), bone metastasis (1.39), large cell/not other wise specified histology (1.29), mediastinal nodal metastasis (1.23) and treatment without bevacizumab (1.18). Seven poor factors for PFS were: skin metastasis (3.13), treatment without bevacizumab (1.52), bone metastasis (1.41), liver metastasis (1.40), low serum albumin (1.39), performance status >0 (1.21) and mediastinal nodal metastasis (1.14). Based on these factors, we built and validated two nomograms predicting 1Y-OS and 6M-PFS.

Conclusion—Using our proposed models, the probability of survival with first-line paclitaxel and carboplatin with or without bevacizumab in non-squamous NSCLC patients can be estimated. These prognostic models provide a tool for research design and clinical decision making, such as patient stratification and therapy selection.

Keywords

Prognostic Models; Nomograms; Non-Small Cell Lung Cancer; Chemotherapy; Bevacizumab

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INTRODUCTION

In 2005, we reported a clinical model to predict survival in chemo-naïve patients with advanced non-small cell lung cancer (NSCLC) treated with third-generation platinum-based chemotherapy doublets.[1] Six clinical prognostic factors were determined and a nomogram was built based on data of the two randomized phase III studies ECOG 5592 and ECOG 1594.[2,3] Since then, ECOG investigators have published the pivotal randomized study ECOG 4599 which demonstrated the benefit of adding the VEGF targeted monoclonal antibody bevacizumab to the standard regimen of paclitaxel and carboplatin (PC) in non-squamous NSCLC.[4] Patients receiving the triplet regimen of paclitaxel, carboplatin and bevacizumab (PCB) lived significantly longer than those treated PC alone with a hazard ratio (HR) of 0.79 (p=0.003). Based on these results, bevacizumab was approved for use in combination with PC as first-line therapy for non-squamous NSCLC.

In spite of proven survival benefits, bevacizumab is associated with certain specific, sometimes fatal adverse events, including hemorrhages, organ perforation, hypertension, and proteinuria. In addition, significant neutropenia and thrombocytopenia are seen more often in those treated with the triplet PCB. Therefore, it is critical to identify patients who may benefit the most, and conversely those who may benefit the least, with bevacizumab. Unfortunately, despite extensive investigation on several potential biomarkers for anti-angiogenic therapy, to date no biomarkers for bevacizumab have been validated for clinical use. Instead, the decision to use bevacizumab in NSCLC is based upon clinical features such as histology and history of hemoptysis.

Therefore, we retrospectively analyzed ECOG 4599 data to identify clinical and laboratory characteristics which would predict survival of NSCLC patients receiving first-line treatment with PC with or without bevacizumab. We used this data to build a nomogram to estimate the probability of survival in this patient population.

MATERIALS AND METHODS

Patients

We retrospectively analyzed data of 850 eligible patients with advanced NSCLC who were randomized to receive first-line therapy of PCB or PC in the study ECOG 4599. The inclusion/exclusion criteria and treatment regimens was previously described in the original report by Sandler et al.[4] In short, patients were randomly assigned to receive paclitaxel 200 mg/m^2 and carboplatin at AUC of 6, with or without bevacizumab 15 mg/kg every 3 weeks for up to 6 cycles. Patients with at least stable disease in the PCB arm continued bevacizumab until disease progression or unacceptable toxicity.

Statistical Analysis Methods

The primary objectives of this analysis are to determine prognostic factors to predict survival of NSCLC patients treated with first-line PC with or without bevacizumab, and to build nomograms to predict one-year survival (1Y-OS) and six-month progression free survival (6M-PFS). Based on our prior clinical model[1] as well as other analyses on prognosis in lung cancer,[5–8] we selected 26 pretreatment clinical and laboratory variables recorded in the database for this study, including (Table 1): treatment with or without bevacizumab, patient demographics, disease stage, performance status, histology subtypes, metastatic sites/organs, number of metastatic sites, prior radiation therapy, body mass index or BMI (underweight < 18.5, normal weight 18.5–24.9, overweight 25–29.9, and obesity ≥ 30); body surface area BSA (</≥ 2 m^2), and baseline laboratory tests including serum albumin level (</≥ lower limit of normal LLN), serum lactate dehydrogenase LDH (≤/>

upper limit of normal ULN), and proteinuria by urinary analysis (negative, trace or 1+/ higher).

A univariable Cox regression analysis was used to assess the association between each variable and outcome. Multivariable stepwise Cox models were then fitted for final variable selection of prognostic factors. Using 50% randomly sampled data (test set), we built the two nomograms predicting 1Y-OS and 6M-PFS. Prognostic scores used in each nomogram are derived from the absolute values of the estimated log hazard ratios (from the multivariate Cox model built on the test set) multiplied by ×100. The prediction models were then validated with the remaining 50% of data (validation set).

RESULTS

As reported in the original ECOG 4599 paper by Sandler et al, PCB significantly prolonged survival in comparison to chemotherapy alone, with median OS of 12.3 months vs. 10.3 months, 1Y-OS of 51% vs. 44%, with a death HR of 0.79 (p=0.003), and median PFS of 6.2 months vs. 4.5 months, with a HR for disease progression of 0.66 (p<0.001).[4] A summary of baseline clinical and laboratory variables of 850 patients included in this analysis is presented in Table 1. Patients were randomized equally to PC and PCB arms. One out of four patients were 70 years or older. More than two-thirds had adenocarcinoma and almost half were women. A small number of patients had adenocarcinoma with lepidic pattern (formerly bronchioalveolar carcinoma) (3%) or large cell carcinoma (5%), while 19% had not otherwise specified (NOS) NSCLC. Of all metastatic organs, the most common site was mediastinal nodes (52%). Other common metastatic sites included ipsilateral (45%) or contralateral (33%) lung, pleura (20% reported as malignant effusion and 26% pleural metastasis), and bone (31%). The least reported metastatic organ was skin (1.4%). More than half of patients were overweight (36%) or obese (20%), while only 4% were considered underweight with BMI <18.5. Serum albumin was low in 28% of patients, serum LDH was high in 32%, and proteinuria (trace or higher) was seen in 20%.

Prognostic Factors and Nomogram Predicting One-Year Overall Survival

To determine independent prognostic factors predicting OS, univariate and multivariate Cox models were fitted. Out of 26 variables analyzed in univariate analysis, 15 are associated with poor survival. The Cox multivariate regression model further identified 11 independent poor prognostic factors (Table 2).

Based on those 11 independent prognostic markers, we built a nomogram to predict 1Y-OS using 50% randomly sampled data (Figure 1A). In this model, each poor prognostic factor is “assigned” a prognostic score (P/S) correlating with 1Y-OS prognosis. A higher score implies a poorer survival outcome. The factor with the poorest prognosis is skin metastasis (HR = 4.49, P/S = 130), followed by a low BMI <18.5 (HR = 2.09, P/S = 81). The remaining nine poor independent prognostic factors are: increased serum LDH (HR = 1.74, P/S = 48), adrenal metastasis (HR = 1.52, P/S = 52), performance status ECOG 1 (HR 1.45, P/S = 35), low serum albumin (HR = 1.45, P/S = 32), male gender (HR = 1.39, P/S = 37), bone metastasis (HR 1.39, P/S = 29), large cell or NOS histology (HR = 1.29, P/S = 30), mediastinal nodal involvement (HR = 1.23, P/S = 42), and treatment without bevacizumab (HR = 1.18, P/S = 25).

Prognostic Factors and Nomogram Predicting Six-Month Progression Free Survival

Using a similar method, we fit clinical data of ECOG 4599 into Cox models to identify independent poor prognostic factors (Table 3) and build a nomogram (Fig. 1B) to predict 6M-PFS. From 26 clinical variables, we identified 15 poor factors in univariate analysis. In

multivariate analysis, only seven stood out as independent poor factors for 6M-PFS, including: skin metastasis (HR = 3.13, P/S = 103), treatment without bevacizumab (HR = 1.52, P/S = 37), bone metastasis (HR = 1.41, P/S = 27), liver metastasis (HR = 1.40, P/S = 33), low serum albumin (HR = 1.39, P/S = 29), performance status ECOG 1 (HR = 1.21, P/S = 19), and mediastinal nodal involvement (HR = 1.14, P/S = 21).

Validation of the Nomograms

The 1Y-OS and 6-M PFS nomograms were constructed from the test set of 50% randomly sampled data and validated by the validation set of the remaining 50% data. To validate the models, patients in the validation set were divided into quartile groups based on their prognostic scores: low risk, low-intermediate risk, high-intermediate risk and high risk. As shown in Figure 2, the predicted survival (x-axis) for each quartile group was compared with the observed/actual survival (y-axis). The dotted line in the figure illustrates the ideal scenario in which the predicted survival perfectly matches the observed survival. We found that the predicted survival was within the 95% confidence intervals of the observed survival (arrows) and both 1Y-OS and 6M-PFS lines follow the “ideal line”. The finding demonstrates a good agreement between predicted and observed survivals.

Case Examples on How to Use the Prognostic Nomograms

Using our nomograms, one could predict the probability of a NSCLC patient surviving one year or longer and achieving a six-month or longer disease-free progression interval with first-line paclitaxel and carboplatin with or without bevacizumab. For example, patient 1, a woman with large cell lung cancer, ECOG performance status 1, BMI <18.5, bone metastasis, serum albumin below the lower limit of normal, and receiving PC as first-line treatment, has a total prognostic score of 232 for overall survival and 112 for progression free survival (Figures 3A–B). On the nomograms, those scores correspond to an estimate 1Y-OS chance of 13% and 6M-PFS chance of 26%. However, if this patient were treated with the triplet therapy of PCB, her total prognostic score would be 207 for overall survival and 75 for PFS. Thus, her predicted 1Y-OS and 6M-PFS would be 20% and 40%, respectively.

In another example, patient 2 is a woman with a lung adenocarcinoma with a malignant effusion who has none of the poor baseline factors (Figure 3C–D). Should she be treated with PCB, her total prognostic score would be 0 for both overall survival and PFS, and as such, her estimated 1Y-OS and 6M-PFS chance would be 81% and 65%. However, if she were treated with PC alone, her prognostic score would be 25 for overall survival and 37 for PFS, corresponding to a 1Y-OS and 6M-PFS chance of 76% and 53%, respectively.

In both patients in the above examples, adding bevacizumab to paclitaxel and carboplatin prolongs both 1Y-OS and 6M-PFS. However, the relative gain with bevacizumab appears more profound in the first patient who has a much worse prognosis than the second patient who has none of baseline poor prognostic factors. Indeed, the addition of bevacizumab in patient 1 results in a 50% improvement in 1Y-OS (from 13% to 20%), whereas in patient 2, bevacizumab only leads to a 7% improvement in survival (from 76% to 81%).

DISCUSSION

During the last few decades, progresses in biology, diagnostics and therapy have resulted in a slow but steady improvement in the treatment of advanced NSCLC. Overall median survival of patients with metastatic disease improved from 5–6 months in 1980s to 12 months at present with the incorporation of targeted drugs such as bevacizumab into conventional chemotherapy. However, survival among patients varies significantly, based

upon tumor biology and clinical factors, such as poor performance status and significant weight loss. Other factors including gender, metastasis, or laboratory abnormality such as leukocytosis and increased LDH were suggested in some but not all studies. Table 4 shows the findings of five large retrospective analyses based on selected randomized studies from cooperative groups conducted within the last three decades.[1,5–7]

In our prior analysis which is based on ECOG 5592 and ECOG 1594, we found six poor prognostic factors predicting survival of NSCLC patients treated with platinum-based doublets involving paclitaxel, docetaxel, or gemcitabine, including: skin metastasis, lower performance status 1 or 2, loss of appetite, liver metastasis, ≥ four metastatic sites, and no prior surgery.[1] There are several differences between our prior and current analysis. This analysis is based on the trial ECOG 4599 which accrued bevacizumab eligible population only (non-squamous histology, no significant hemoptysis). Furthermore, we included both clinical and laboratory variables. More importantly, the treatment regimen involved paclitaxel and carboplatin with or without bevacizumab.

In this analysis, 11 poor survival factors were identified. Similar to our previous report, we found that skin metastasis carries the worst survival prognosis with a highest HR (4.49) and prognostic score (130) in the 1Y-OS model. Skin metastasis also predicted the worst 6M-PFS. Although skin metastasis from primary lung cancer is an uncommon event, reported in only 4–12% of patients in prior ECOG studies involving all NSCLC histology subtypes, and in 1.4% in ECOG 4599, its presence likely suggests an aggressive biological behavior of the disease causing widespread metastasis. Other investigators also found the negative impact of skin or subcutaneous spread on survival in NSCLC.[5,7]

Significant weight loss of more than 5–10% total body weight within 6-month period and loss of appetite have been considered among the most important negative prognostic factors in NSCLC. However, not all patients are able to quantify their weight loss. Therefore, in this study, we decided to evaluate BMI at baseline, prior to the start of chemotherapy, which can be calculated easily based on patient's weight and height, as a potential prognostic factor. The results demonstrated that underweight patients with BMI <18.5 had a poorer survival compared to those with normal or overweight (BMI ≥18.5), corresponding to the second highest HR (2.09). Interestingly, the relation between excess body weight and cancer mortality has been documented in many cancer types, although the underlying mechanism is not clear yet. In a report involving more than 900,000 American adults accrued in the prospective Cancer Prevention Study II, high BMI was in general associated with increased cancer related death rates in both obese men and women cohorts with BMI ≥35.0.[8] That observation was seen across several solid and hematologic cancers, with the only exception being lung cancer. Indeed, contrary to other cancers, BMI was inversely correlated to lung cancer mortality. The relative risk of lung death in cohorts with BMI ≥35.0 in that study was approximately 0.67. Low serum albumin level is also a poor prognostic overall survival in our model, with a HR of 1.45. It is possible that low BMI, low serum albumin, and weight loss/loss of appetite all are biologic indicators of an aggressive cancer leading to a quick decline in nutritional and overall general health status.

Accumulating data have suggested that there is a gender difference between women and men with lung cancer.[9] Some studies have suggested that women are more susceptible to carcinogenic effects of cigarette smoking.[10,11] On the other hand, female patients with NSCLC are more likely to be never-smokers,[12] have adenocarcinoma,[9] harbor mutations in the EGF receptor,[13] and live longer than their male counterparts with chemotherapy[9]. In this analysis, although there was no difference in PFS, men had a lower chance of surviving at one year, with a HR of 1.39. The difference in outcome suggests gender is an important

factor in designing clinical trials, and that gender should be a stratification factor in randomized trials.

In our analysis, patients with large cell carcinoma or NOS histology had a poorer survival compared to those with adenocarcinoma or adenocarcinoma with lepidic pattern suptype, with a HR of 1.29. It was unclear if the histology of NOS cases was undefined due to poor histological differentiation or lacking of tissue samples from fine needle aspiration. Patients with poorly differentiated, high-grade cancer may have more aggressive course and poorer prognosis.

Our study demonstrated that increase in LDH was significantly associated with shorter one-year survival with a HR of 1.74. LDH is an enzyme which catalyzes the forward and backward conversion of pyruvate to lactate, an important step in the process of cellular glycolysis and energy production. Cancer cells primarily metabolize glucose into lactate through the anaerobic glycolysis (Warburg effect), while most normal cells rely on the more efficient oxidative phosphorylation in mitochondria to produce ATP. The isozyme M-LDH (LDH-5) is increased in several human tumors compared to normal tissues,[14] and elevated serum LDH is associated with chemotherapy and radiation resistance,[15] as well as poor prognosis in a variety of cancers including NSCLC.[6,15,16] The overexpression of LDH-5 in NSCLC tumor samples was linked to the expression of several angiogenic markers (VEGF, bFGF, bFGFR), the hypoxia-inducible factor HIF 1∝, and survival in patients with resected disease.[15,17] Findings from our study as well as others suggest that serum LDH and albumin are two simple blood tests which can be used to evaluate prognosis in NSCLC patients. However, it should be noted that LDH is not specific, as it can also be elevated in patients with underlying medical diseases such as cardiac, lung and liver disorders. Prospective studies are needed to validate the prognostic value of tumor LDH-5 expression for clinical use.

Finally, the addition of bevacizumab to chemotherapy is a positive prognostic factor for improved PFS and one-year survival rate. In regard to PFS, bevacizumab is the second most important factor, second only to skin metastasis. Compared to triplet therapy PCB, treatment with paclitaxel and carboplatin alone correlated with a HR of 1.52 for PFS. However, the benefit of bevacizumab on one-year survival appeared relatively modest in comparison to other factors. Indeed, among the 11 poor factors predicting one–year survival, bevacizumab impacts the least with a HR of 1.18 in patients receiving chemotherapy alone. Although survival advantages of bevacizumab in NSCLC have been proven, the drug is associated with certain morbid and fatal adverse effects such as bleeding, GI perforation or fistula. Because of the modest gain by adding bevacizumab to chemotherapy in patients without poor prognostic factors (such as patient 2 in the above example), patients with good factors and borderline risks to bevacizumab (for example, hemoptysis <1/2 teaspoon, labile hypertension) may elect a non-bevacizumab containing regimen, either with standard chemotherapy or enrolling into clinical trials.

Multiple potential biomarkers for bevacizumab and other antiangiogenic agents such as VEGF, basic fibroblast growth factor (b-FGF), intercellular adhesion molecule (ICAM), E-selectin, thrombospondin-2, microvessel density have been investigated in clinical trials in lung cancer as well as other cancers.[18–21] However, to date, no biomarkers for anti-angiogenic therapy have yet been validated for clinical use. Thus, these nomograms may be helpful in identifying NSCLC patients most likely to benefit from the addition of bevacizumab to chemotherapy. By doing so, one may maximize the therapeutic gain, while minimizing potential morbidity and mortality and reduce the cost to the health care system.

In conclusion, our analysis identified several clinical factors predicting survival in non-squamous NSCLC patients treated with first-line paclitaxel and carboplatin with or without bevacizumab. Our nomograms offer a tool to estimate the possibility of survival. Those prognostic factors and models may help investigators in designing clinical trials and assist clinicians in selecting the most appropriate therapy for their patients.

Acknowledgments

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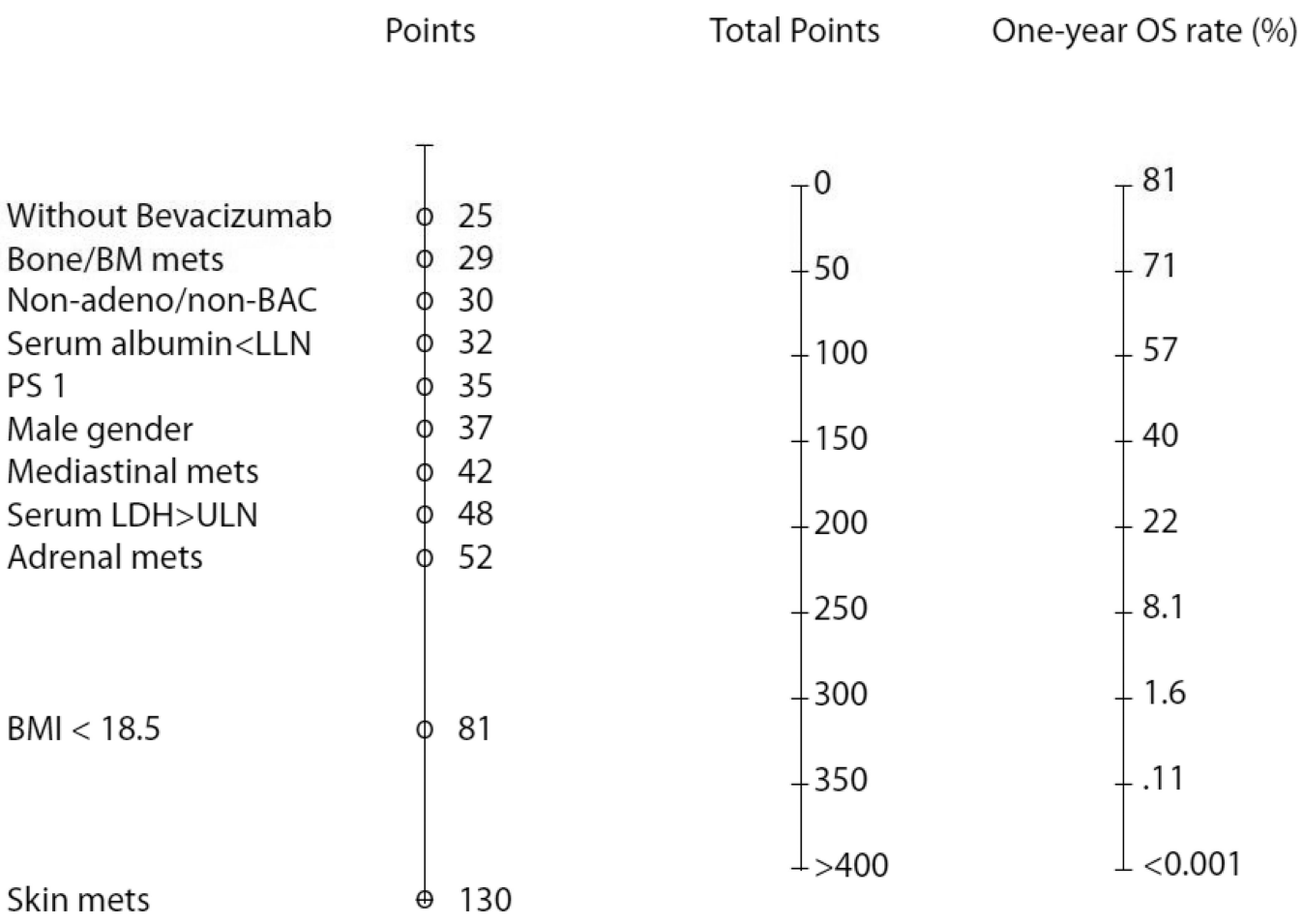
1A



1B

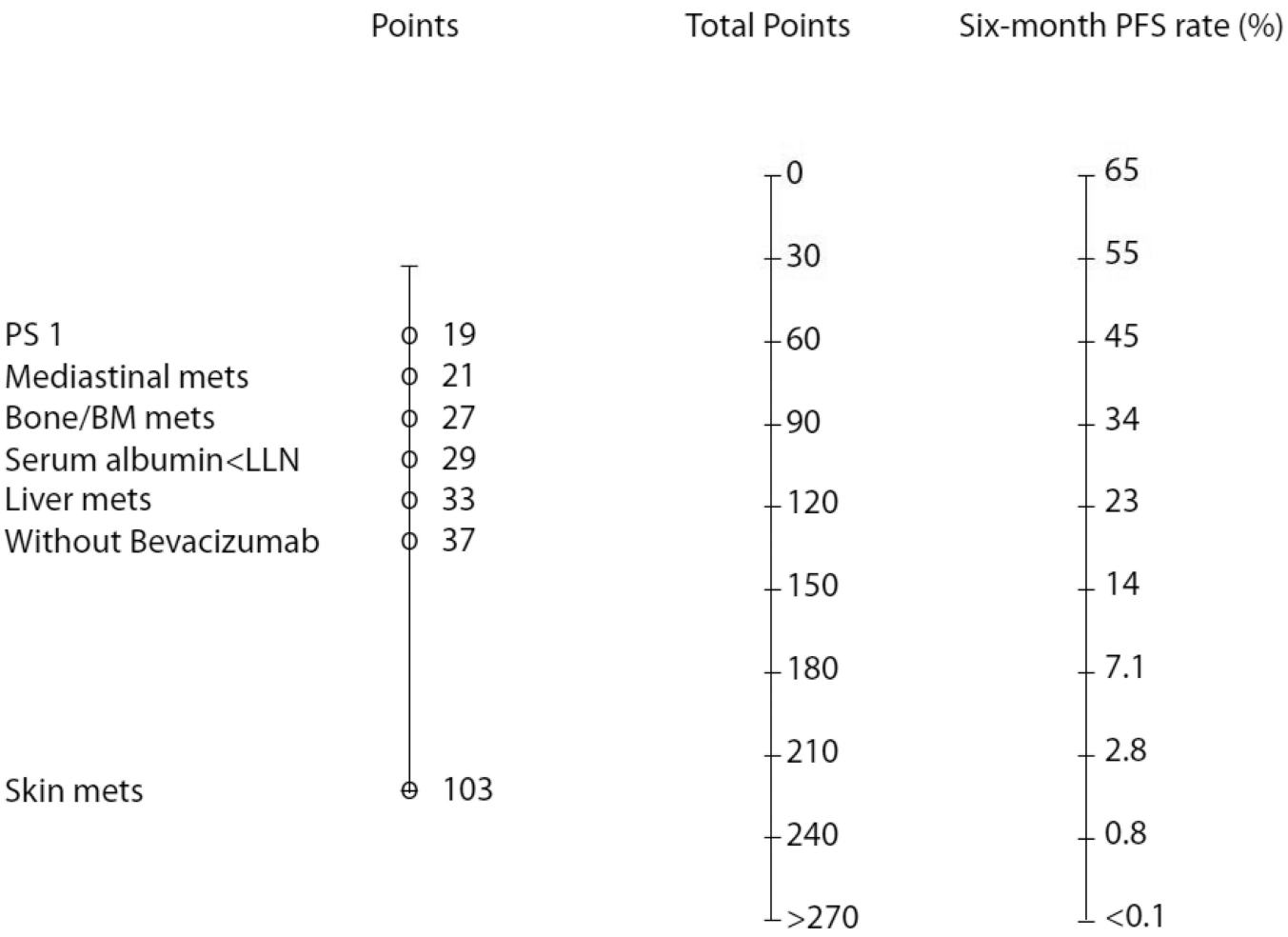
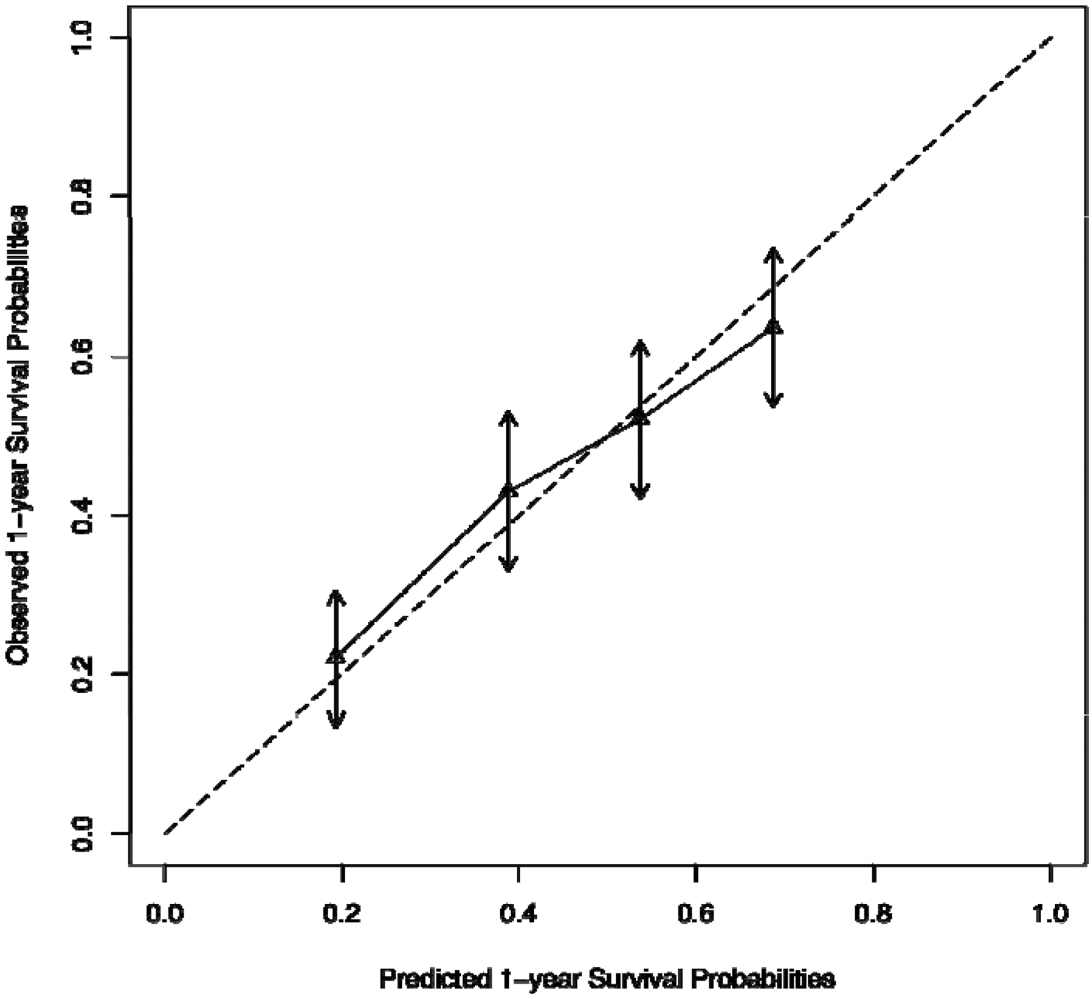


Figure 1.
Prognostic Nomograms Predicting: (A) One-Year Survival; (B) Six-Month Progression Free Survival.

2A



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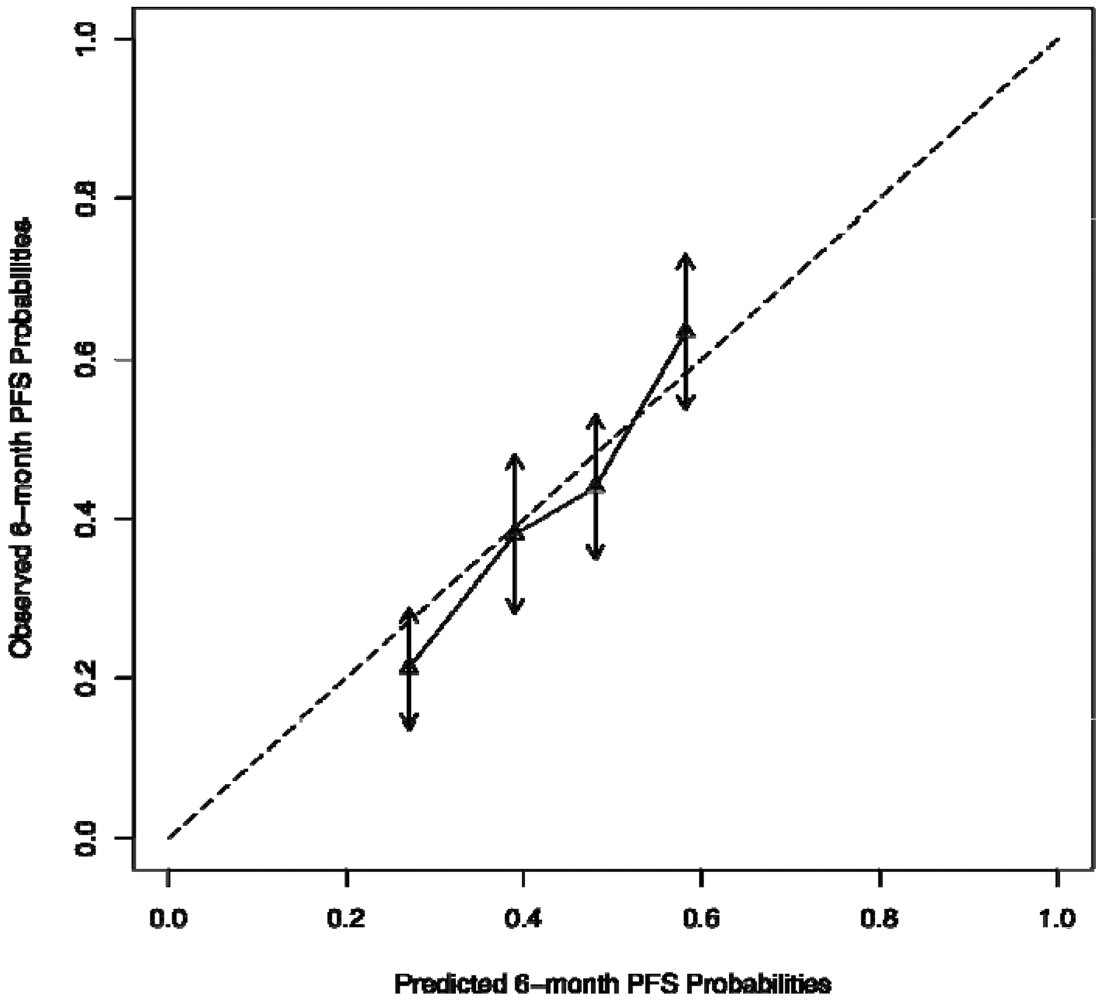
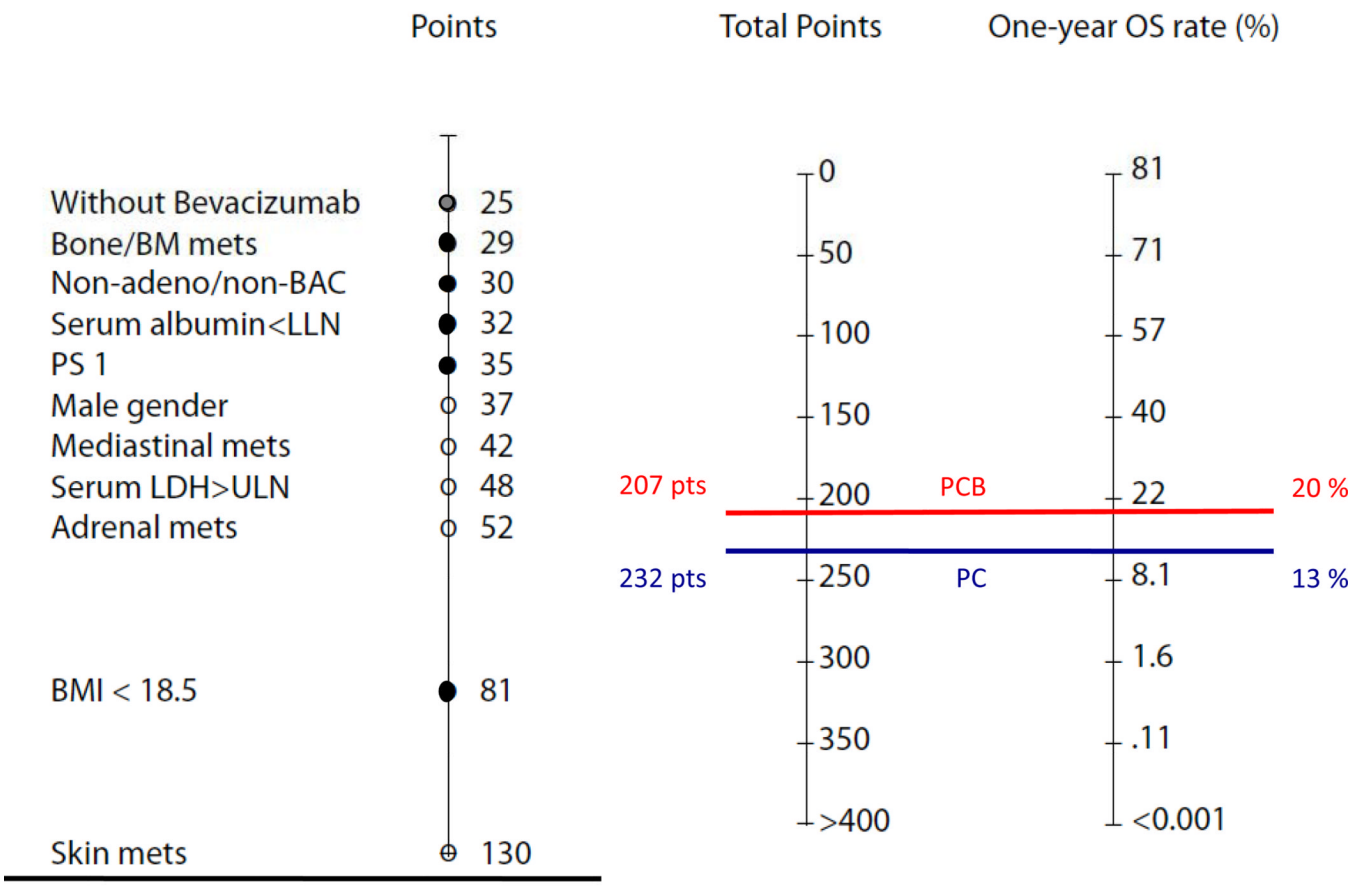


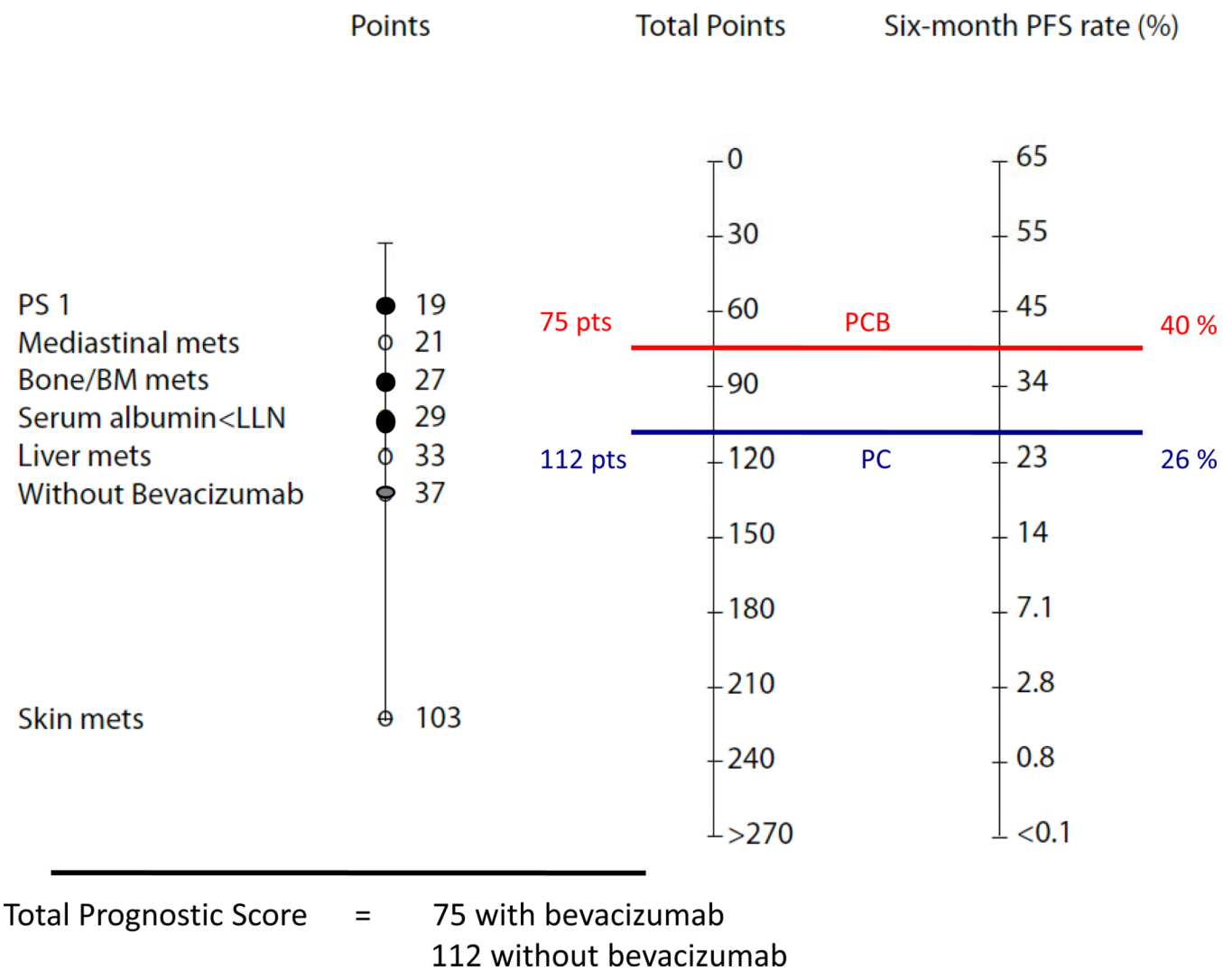
Figure 2.
Comparison of Predicted Survival with Observed Survival of Quartile Groups of Patients in the Validation Set: (A) One-Year Survival; (B) Six-Month Progression Free Survival. The dotted line is the "ideal" line if there is a perfect match between predicted and observed survival. The vertical arrows represent 95% confidence intervals of observed survival.

3A



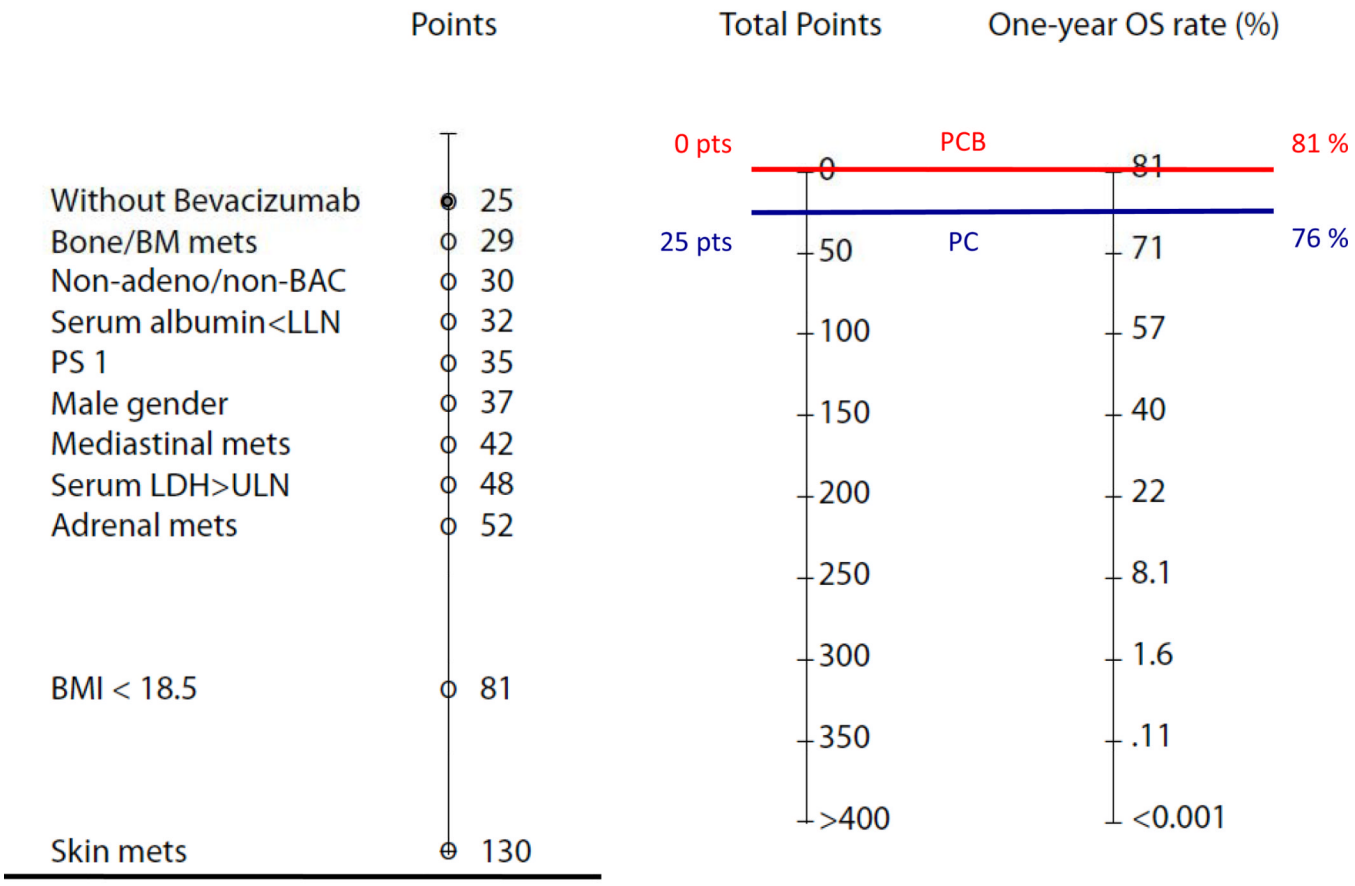
Total Prognostic Score = 207 with bevacizumab
232 without bevacizumab

3B



Total Prognostic Score = 75 with bevacizumab
112 without bevacizumab

3C



Total Prognostic Score = 0 with bevacizumab
25 without bevacizumab

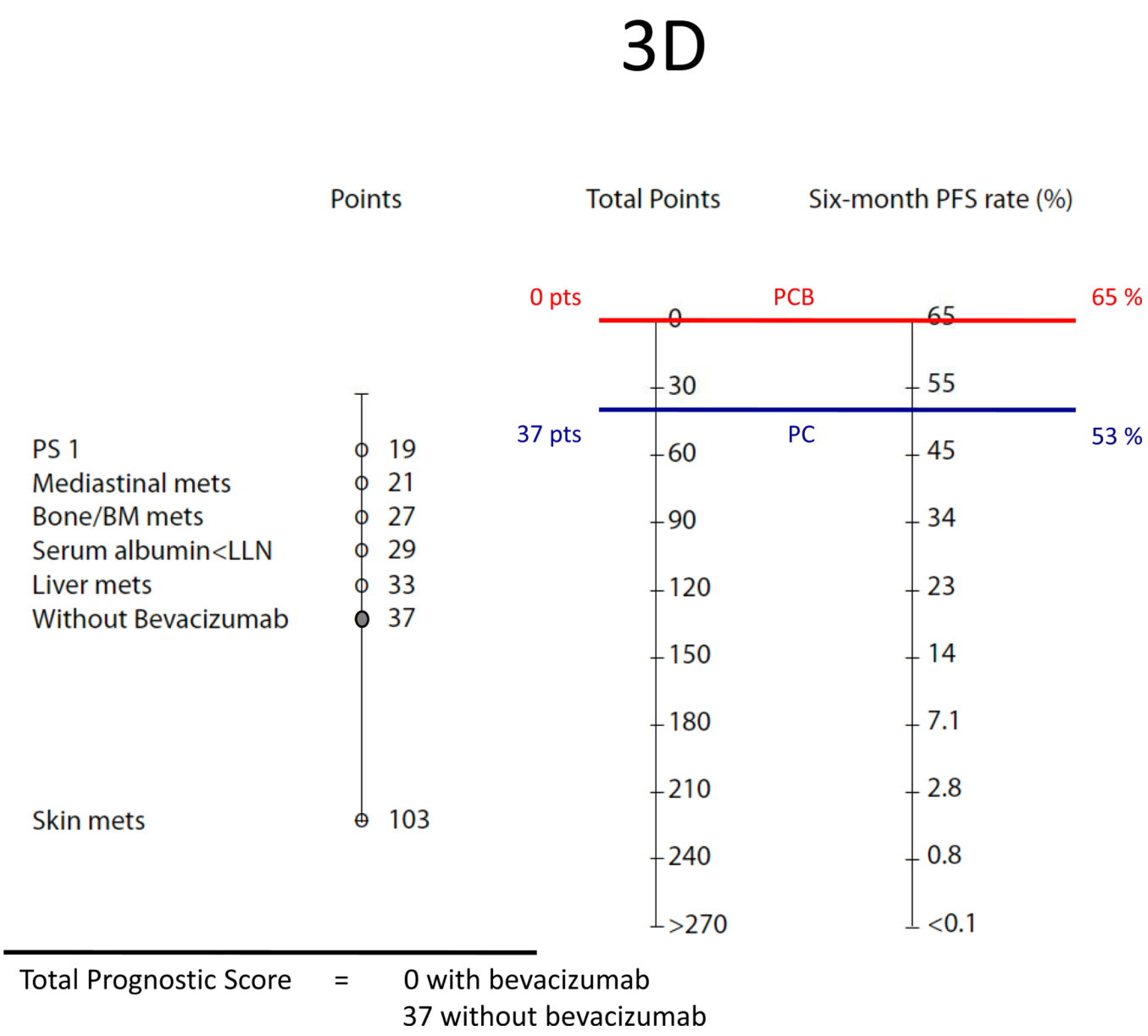


Figure 3.

Examples of the Nomograms:

(A) Predicted one-year survival of patient 1 who is a woman with large cell lung cancer (PS 30), ECOG performance status 1 (PS 35), BMI <18.5 (PS 81), bone metastasis (PS 29) and low serum albumin (PS 32). Treated with PC alone (PS 25), her total prognostic score is 232 points (30+35+81+29+32+25). If bevacizumab is added to the doublet, her total prognostic score is 207 points (30+35+81+29+32);

(B) Predicted six-month PFS of patient 1. Treated with PC alone, her prognostic score is 112 points (19+27+29+37). If bevacizumab is added to the doublet, her prognostic score is 75 points (19+27+29);

(C) Predicted one-year survival of patient 2 who is a woman with an adenocarcinoma of the lung with malignant effusion, otherwise having none of poor baseline factors. Treated with PC alone, her total prognostic score is 25 points. If bevacizumab is added to the doublet, her total prognostic score is 0;

(D) Predicted six-month PFS of patient 2. Treated with PC alone, her prognostic score is 37 points. If bevacizumab is added to the doublet, her prognostic score is 0.

Table 1

Patient Characteristics.

Patient Characteristics		Patients (Total n= 850)	
		n	%
Bevacizumab Treatment	Yes	417	49
	No	433	51
Age	<70	648	76
	≥ 70	202	24
Gender	Female	387	46
	Male	463	54
Race	White	730	86
	Other	120	14
Stage	IIIB	105	12
	IV/Recurrent	745	88
Performance Status	0	343	40
	1	507	60
Histology *	AC	586	69
	ACLP	23	3
	LCC	46	5
	NOS	160	19
	Other	32	4
Hilar Nodes	Present	335	39
Mediastinal Nodes	Present	439	52
Supraclavicular/Scalene Nodes	Present	72	8
Pleural Effusion	Present	322	38
Malignant Effusion	Present	169	20
Pleural Metastasis	Present	223	26
Ipsilateral Lung Metastasis	Present	381	45
Contralateral Lung Metastasis	Present	280	33
Liver Metastasis	Present	163	19
Bone/Bone Marrow Metastasis	Present	267	31
Adrenal Metastasis	Present	125	15
Skin Metastasis	Present	12	1.4
Distant Metastasis > 3 sites **	Present	165	19
Prior Radiation Therapy	Yes	70	8
	No	780	92
Body Mass Index (BMI)	< 18.5	30	4
	18.5–24.9	349	41
	25–29.9	304	36
	≥ 30	167	20

Patient Characteristics		Patients (Total n= 850)	
		n	%
Body Surface Area (BSA)	≥ 2	269	32
	< 2	581	68
Low Serum Albumin (< LLN)	Present	240	28
High Serum LDH (> ULN)	Present	273	32
Proteinuria	Negative	673	80
	Trace	136	16
	1+ or Higher	34	4

*AC, adenocarcinoma; ACLP, adenocarcinoma with lepidic pattern (bronchio-alveolar carcinoma); LCC, large cell carcinoma; NOS, not otherwise specified.

**Ipsilateral or contralateral lung, pleura, liver, adrenal, brain, bone, BM, skin.

Table 2

Independent Poor Prognostic Factors of Overall Survival

Patient Characteristics	Hazard Ratio	p-value	Prog Score
Skin Metastasis	4.49	<0.0001	130
Low BMI < 18.5	2.09	0.0003	81
High Serum LDH (> ULN)	1.74	<0.0001	48
Adrenal Metastasis	1.52	0.0002	52
PS 1 (vs. PS 0)	1.45	<0.0001	35
Low Serum Albumin (< LLN)	1.45	<0.0001	32
Gender - Male	1.39	0.0002	37
Bone Metastasis	1.39	0.0002	29
Histology - LCC/NOS (vs. AC/ACLP)	1.29	0.006	30
Mediastinal Nodes	1.23	0.02	42
No Bevacizumab (PC Alone)	1.18	0.05	25

Table 3

Independent Poor Prognostic Factors of Progression Free Survival

Patient Characteristics	Hazard Ratio	p-value	Prog Score
Skin Metastasis	3.13	0.0001	103
No Bevacizumab (PC Alone)	1.52	<0.0001	37
Bone Metastasis	1.41	<0.0001	27
Liver Metastasis	1.40	0.0002	33
Low Serum Albumin (< LLN)	1.39	<0.0001	29
PS 1 (vs. PS 0)	1.21	0.01	19
Mediastinal Nodes	1.14	0.07	21

Table 4

Survival Prognostic Factors and Prediction Models for Non-Small Cell Lung Cancer from Five Retrospective Analyses

	ECOG Finkelstein, 1986[5]	**SWOG Albain, 1991[6]**	**ELCWP Paesmans, 1995[7]**	**ECOG Hoang, 2005[1]**	**ECOG Hoang, 2011**
Database	2 phase III (EST 2575 & 1581)	5 phase III 9 phase II	3 phase III 4 phase II	2 phase III (ECOG 1592 & 1594)	1 phase III (ECOG 4599)
Patient number	893	2531	1052	1436	850
Disease stage	Metastatic	Locally advanced or metastatic	Unresectable I-IV	Wet IIIB, IV, or recurrent	Wet IIIB, IV, or recurrent
Histology	Any NSCLC histology	Any NSCLC histology	Any NSCLC histology	Any NSCLC histology	Non-squamous NSCLC
Line of treatment	First-line	First-line or previously treated	First-line or previously treated	First-line	First-line
Chemotherapy regimens	Various older platin and non-platin based regimens	Various older platin and non-platin based regimens; mono versus combined	Various platin-based, second-generation regimens; mono versus combined	Platin-based, third-generation doublets	Paclitaxel, carboplatin with or without bevacizumab
Survival Median, months 1-year, % 2-year, %	< 6 19 4	5.1 16 -	7 - 7.4	8.2 33 11	10.3/12.3 * 44/51 * 15/23 *
No. of factors analyzed	36	15 (not all patients)	23	27	26
Independent negative survival prognostic factors identified from multivariate analyses	1. Lower PS (1–2) 2. Bone metastasis 3. Male gender 4. Weight loss 5. Subcutaneous metastasis 6. Large cell carcinoma 7. Shoulder/arm pain 8. Liver metastasis	<u>All patients:</u> 1. Lower PS (≥2) 2. Non-platin drugs 3. Male gender 4. Age < 70 <u>PS 0–1 patients:</u> 1. Hb < 11 2. Abnormal LDH 3. Abnormal calcium 4. ≥2 metastatic lesions 5. Non-platin drugs	1. Stage IV (vs. earlier stages) 2. Lower PS (≤70) 3. Increased WBC 4. Skin metastasis 5. Increased calcium 6. Abnormal ANC 7. Age > 60 8. Male gender	1. Skin metastasis 2. Lower PS (1–2) 3. Loss of appetite 4. Liver metastasis 5. ≥4 metastatic sites 6. No prior lung surgery	1. Skin metastasis 2. Low BMI <18.5 3. Increased LDH 4. Adrenal metastasis 5. Lower PS (1) 6. Low serum albumin 7. Male gender 8. Bone metastasis 9. LCC/NOS histology 10. Mediastinal nodal metastasis 11. No bevacizumab (PC alone)
Survival prediction model or prognostic subgroups	Discriminant function requiring calculation to predict if an individual will survive > 1 year or not	Three prognostic subgroups based on recursive partitioning and amalgamation	Four prognostic subgroups with different 1- and 2-year survival, based on recursive partitioning and amalgamation	Nomogram with a scoring system to predict 1-and 2-year survival probability of individual patients	Nomogram with a scoring system to predict probability of 1-year survival and 6-month PFS of individual patients

* without bevacizumab/with bevacizumab

Abbreviations: ECOG, Eastern Cooperative oncology Group; SWOG, Southwest Oncology Group; ELCWP, European Lung Cancer Working Party; PS, performance status; Hb, hemoglobin; LDH, lactic dehydrogenase; WBC, white blood count; ANC, absolute neutrophil count; BMI, body mass index; LCC, large cell carcinoma; NOS, not otherwise specified.