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Original Article

Analysis of the correlation among hypertension, the intake of β-blockers, and overall survival outcome in patients undergoing chemoradiotherapy with inoperable stage III non-small cell lung cancer

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Abstract: It is known that hypertension could increase the plasma levels of VEGF and that β-blockers propranolol could counteract the effect. Our aim was to explore the possibility of improving survival outcomes for patients with and patients without hypertension. In addition, we also compared the efficacy of the usage of β-blockers in inoperable non-small cell lung cancer (NSCLC) patients. We retrospectively reviewed 1753 NSCLC patients who underwent concurrence/sequential chemoradiotherapy in our hospital from 1994 to 2005. A total of 606 inoperable patients with stage III were enrolled in this study. Fifty-five patients survived until the follow-up date of May 2011. From the 606 patients, 123 of them had hypertension. We identified 11 of them who took β-blockers orally. Kaplan-Meier methods and Cox proportional hazard model were utilized to analyze the overall survival (OS) outcome among patients with hypertension and patients without hypertension. After that, we compared the patients who took β-blockers with patients who did not take β-blockers in the whole stage III cohort using the same approaches. The Kaplan-Meier analysis revealed that there were no significant survival outcomes between hypertension and non-hypertention groups (P>0.05). No significant difference was found between using β-blockers and not using them in the hypertention group (P>0.05). We also found no statistical significance between using β-blockers and not using them in the whole cohort of 606 NSCLC patients (P>0.05). The results from both univariate or multivariate analysis using the Cox proportional hazards regression model indicated that there was no statistical difference between hypertension and non-hypertension group. There was also no difference between using β-blockers and not using them in the whole stage III cohort (P>0.05). For the patients with hypertension, the usage of β-blockers did not influence the overall survival in stage III inoperable NSCLC. Further randomized clinical trials will be warranted to validate this finding.

Keywords: NSCLC, hypertension, β-blockers, VEGF, OS, propranolol

Introduction

The efficacy of the β-blockers propranolol against infantile capillary hemangiomas was reported in June 2008 [1]. To date, propranolol has become the first line medication for infantile hemangiomas(IH) [2]; however, the mechanisms are still unclear. Several hypotheses were mentioned, including cellular apoptosis, the effect of vasoconstriction and hypoxia, downregulation of basic fibroblast growth factor, and vascular endothelial growth factor (VEGF) [3].

VEGF was also one of the most important factors in tumor proliferation by stimulating the growth of new blood tumor vessels [4]. Accordingly, the efficacy of anti-angiogenic medication has been proved to be effective in non-small cell lung cancer (NSCLC) [5, 6]. Several retrospective studies have shown that the possible clinical effect of β-blockers medicines in

patients undergoing treatment for multiple types of cancers [7-10]. However, several retrospective studies showed the inconsistent survival outcome of patients' intake of propranolol in NSCLC [11-13]. Choi et al. conducted a meta-analysis and mentioned there was a trend for low-stage subjects to benefit more dramatically from using β-blockers than high-stage subjects [14]. Since most of the early stage patients underwent surgery rather than chemoradiotherapy, the mix of different stages of the enrolled patients could be the reason for those studies' major bias.

In addition, some epidemiological evidence showed that blood pressure had been associated with cancer risk [15-17]. People with essential hypertension (EH) were found to have higher levels of VEGF in the plasma [18]. Furthermore, several studies indicated that hypertension could stimulate the expression of VEGF in the plasma due to the damage of the microvascular environment [19, 20].

Since VEGF has been highly associated with the prognostic of cancer patients [21-23], these findings have led to several hypotheses: Did patients with hypertension have worse survival outcome or not? If not, did the survival outcome improve by using the β-blockers? Hence, we conducted a large-scale retrospective study of inoperable NSCLC patients with stage III who underwent radical concurrent/sequence chemoradiation therapy. The objective of this study was to estimate the efficacy of β-blockers in prolonging the OS of this cohort patient.

Materials and methods

Study population

We retrospectively reviewed the 1753 inoperable NSCLC patients who underwent concurrent/sequential radiotherapy and chemotherapy in the medical database of Hunan Cancer Hospital from 1994 to 2005. A total of 606 eligible patients were enrolled in this study. We verified usage of medications and survival/death status by contacting the patients or their relatives by telephone, mail, and e-mail.

The inclusion criteria were as follows: (I) diagnosed and pathologically confirmed NSCLC, (II) receipt of radiotherapy and chemotherapy without surgery, (III) stage III under the criteria of American Joint Committee of Cancer (AJCC) 7th edition [24]. Exclusion criteria included the following: (I) history or findings of significant valvular heart disease (i.e., more than a mild valvular insufficiency or stenosis), hyperthyroidism or hypothyroidism and dilated or hypertrophic cardiomyopathy, (II) atrial fibrillation, (III) pregnancy or lactation, and/or (IV) a major systemic illness such as systemic lupus erythematosus. The retrospective study was approved by the Ethics Committee of the Hunan Cancer Hospital, Changsha, China.

Measurement and definition

The patient database contained detailed patient demographic data, the patients' status (smoking index, gender, age, and alcohol), TNM stage, pathological type, and mortality data. The disease was re-staged by the 7th edition of the AJCC TNM staging system [24], and the pathological tumor types were determined according to the WHO's NSCLC classification.

Clinical endpoint

The data set was completed from information obtained from relatives or the survivors as of May 2011. Our main points of interest were deaths from NSCLC; deaths of non-NSCLC cases were not examined for the study.

Statistics analysis

Differences in the distribution of baseline clinicopathologic characteristics between different groups were compared using the chi-square test or student's t-test. We used chi-square test for categorical variables and student's sample t-test for continuous variables, respectively. Descriptive statistics are presented as percentages or mean values with standard deviations (SD). Kaplan-Meier analysis was performed for clinical outcomes, and the statistical significance was determined by the log-rank test. Cox proportional hazards regression models adjusted for potential confounders were used to study the relationship between relative risk of death events and β-blockers medication at baseline. First, univariate Cox regression analyses were carried out to examine the association between each potential confounder and clinical outcomes. Potential confounders for outcomes included TNM stage, alcohol volume, smoking index, age, gender, and blood pressure. Second,

Table 1. Baseline characteristics between hypertension and non-hypertension among 606 patients

Variables	Hypertension	Non-Hypertension	*p*
	N/Mean ± SD	N/Mean ± SD	
Age	54.74 ± 9.283	57.18 ± 8.957	0.009
Gender			0.341
Male	106	431	
Female	17	52	
Alcohol			0.213
Yes	59	262	
No	64	221	
β-blockers			0.000
Yes	11	0	
No	112	483	
T Stage			0.112
T_{0-2}	62	205	
T_{3-4}	61	278	
N Stage			0.062
N_{0-1}	17	103	
N_{2-3}	106	380	
Chemotherapy			0.844
Yes	112	437	
No	11	46	
Pathology			0.660
Adeno	74	301	
Non-Adeno	49	182	

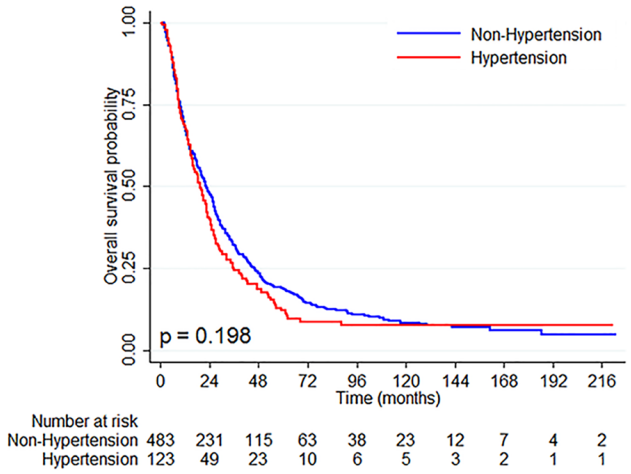

Figure 1. In all 606 patients, this figure shows the comparison of overall survival between the patients with or without hypertension via Kaplan-Meier analysis.

we fitted separate univariate Cox regression models to evaluate the influence of each covariate in the strength of association between β-blockers medication and clinical outcomes. Estimates derived from Cox regressions were presented as hazard ratios and 95% confidence intervals (CI). Statistical analyses were performed using SPSS version 23.0 (SPSS Inc, Chicago, Illinois, USA) and Stata 14.0 (Stata Corp. LP, College Station, TX, USA). All *p*-values were two-sided, and *p*-values of <0.05 were considered statistically significant.

Results

A total of 606 eligible patients with stage III were included in the first study. Among them, 123 patients had hypertension (2, 17, and 104 patients with grade 3, 2, 1, respectively) and 483 patients did not have hypertension. Eleven of them who took β-blockers orally were identified during the treatment.

The analysis of overall survival outcome among patients with hypertension or non-hypertension

The mean ages of patients with hypertension and non-hypertension were 57.18 ± 8.957 and 54.74 ± 9.283 years (P<0.05), respectively. It is understandable that the usage of β-blockers was significant between this two hypertension and non-hypertension groups due to the purpose of the medication. The other variables including gender, smoking index, T/N stage, and pathology were well balanced (P>0.05) (**Table 1**).

The Kaplan-Meier estimator shows the median overall survival were 19.48 ± 2.270 and 22.37 ± 1.466 months between hypertension and non-hypertension patients, respectively. However, there was no significant statistical difference in this cohort of patients (P=0.198) (**Figure 1**).

The analysis of overall survival outcome between patients who took β-blockers and those who did not

Among the 606 patients, 11 patients orally took the β-blockers during the treatment. The mean ages were 61.41 ± 5.127 and 55.12 ± 9.286 in patients who took β-blockers and patients who did not, respectively (P= 0.018). The other variables, including gender,

Table 2. Baseline characteristics between β-blockers and non-β-blockers among 606 patients

Variables	β-blockers	Non-β-blockers	*p*
	N/Mean ± SD	N/Mean ± SD	
Age	61.41 ± 5.127	55.12 ± 9.286	0.025
Gender			0.638
Male	10	527	
Female	1	68	
Smoking Index	580.00 ± 509.51	576.46 ± 469.92	0.981
Alcohol			0.363
Yes	4	317	
No	7	278	
Hypertension			0.000
Yes	11	112	
No	0	483	
T Stage			0.579
T_{0-2}	5	262	
T_{3-4}	6	333	
N Stage			0.702
N_{0-1}	1	119	
N_{2-3}	10	476	
Chemotherapy			0.277
Yes	9	540	
No	2	55	
Pathology			0.348
Adeno	5	370	
Non-Adeno	6	225	

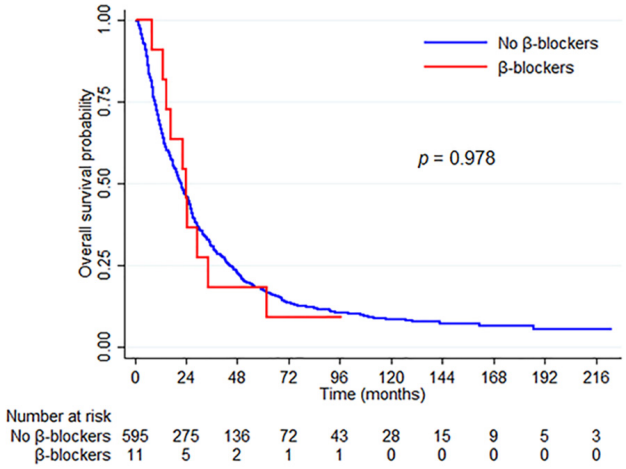

Figure 2. In all 606 patients, this figure shows the comparison of overall survival between the patients who orally took the beta-blocker medicine or not.

smoking index, T/N stage, and pathology were well balanced (P>0.05) (**Table 2**).

The Kaplan-Meier analysis showed the median overall survival times were 23.918 ± 4.359 and 18.530 ± 2.086 months between patients who took β-blockers and those who did not, respectively. However, no significant statistical difference was found in this cohort of patients (P=0.978) (**Figure 2**).

The analysis of overall survival outcome of patients' intake β-blockers in the cohort of hypertension patients

Table 3 illustrated patients who took β-blockers and those who did not in the hypertension group (123 patients). The Kaplan-Meier analysis showed the median overall survival times were 23.918 ± 4.359 and 21.684 ± 1.360 months between β-blockers intake and non-intake patients, respectively. However, there was no significant statistical difference in this cohort of patients (P=0.617) (**Figure 3**).

The multivariable analysis by the Cox proportional hazard model among 606 patients

We utilized univariate analysis to investigate the potential confounders associated with survival outcomes. There were no significant differences (**Table 4**). There were also no differences in multivariable analysis (**Table 5**).

The multivariable analysis via Cox proportional hazard model among 123 hypertension patients

We utilized univariable Cox proportional hazard model to analysis the potential confounders associated with survival outcomes. No significant differences were found in univariate and multivariate analysis, respectively (**Tables 6**, **7**).

Discussion

To our knowledge, this is the first study of a large-scale retrospective follow-up investigation of survival outcomes in non-operable NSCLC patients with stage III regarding hypertension and the usage of β-blockers.

Several studies have claimed that essential hypertension increase the serum VEGF levels [18]. Moreover, hypertension could cause the high level of plasma vascular endothelial growth factor (VEGF) due to the microvascular

Table 3. Baseline characteristics between β-blockers and non-β-blockers among 123 hypertension patients

Variables	β-blockers	Non-β-blockers	*p*
	N/Mean ± SD	N/Mean ± SD	
Age	61.41 ± 5.127	56.73 ± 9.158	0.018
Gender			0.532
Male	10	96	
Female	1	16	
Smoking Index	580.00 ± 509.51	589.51 ± 491.75	0.951
Alcohol			0.534
Yes	4	55	
No	7	57	
Hypertension			0.000
Yes	11	112	
No	0	483	
T Stage			0.731
T_{0-2}	5	57	
T_{3-4}	6	55	
N Stage			0.634
N_{0-1}	1	16	
N_{2-3}	10	96	
Chemotherapy			0.256
Yes	9	103	
No	2	9	
Pathology			0.343
Adeno	5	69	
Non-Adeno	6	43	

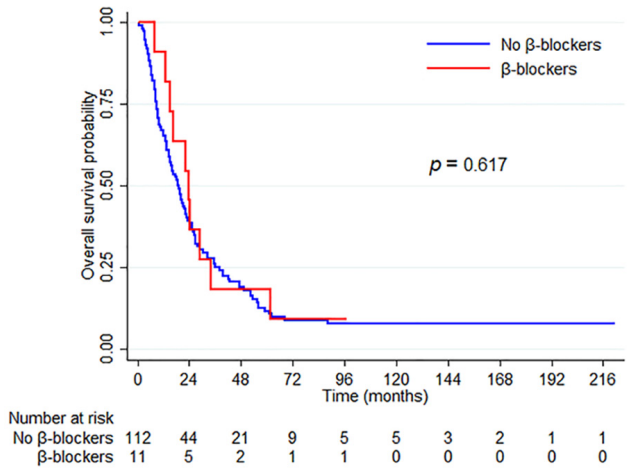

Figure 3. In the cohort of hypertension patients, this figure shows the comparison of overall survival between the patients who orally took the beta-blocker or not.

damage [19, 20]. VEGF is the most important regulator of pathological or physiological angiogenesis [25]. Furthermore, several studies have demonstrated that the overexpression of VEGF was associated with tumor progression and poor prognosis in many tumor types [26-28].

Although the potential link between hypertension and high level of VEGF might exist, Lee et al. conducted a prospective study on the relationship of hypertension, smoking, and mortality of lung cancer in healthy people from 1992 to 1994. Despite not considering the possible bias due to the effect of different stages, pathology and treatment comparing to this study, no statistical significance were found between hypertension and mortality of lung cancer, which was consistent with ours to some degree [29]. However, Dyer et al. and Xie et al. had an adverse conclusion [30, 31].

To date, propranolol, as an anti-hypertension medication, has been shown to be highly effective and has become the first-line treatment for infantile hemangiomas [2]. However, the mechanisms are still unclear. Recent in vitro experiments demonstrate the following possible mechanisms: (a) β-blockers significantly decrease expression levels of hypoxia inducible factor (HIF-1α) in urine, serum, and hemangioma tissues. However, the over-expression of HIF-1α suppresses the effect of β-blockers on VEGF [32, 33]. (b) β-blockers decrease VEGF levels by the down-regulation of the PI3K/Akt/eNOS/VEGF pathway [34]. This information validates that β-blockers could down-regulate the expression of VEGF in vivo.

Furthermore, Wong et al. found that the abnormal activities of tumor cell proliferation related cytokines, including the expression of VEGF and cyclooxygenase-2 (COX-2), the activity of Matrix metalloproteinase-9 (MMP-9) and the release of prostaglandin E(2) (PGE (2)) could be eliminated by the β(1)- and β(2)-selective antagonist in vitro [35]. Barron et al. reviewed large amount of preclinical, epidemical and clinical data relevant to the association between β-blockers and breast cancer progression, multiple possible aspects, which might be affected by β-Adrenergic receptor expression were listed, including tumor growth, metastasis, cell death, angiogenesis,

Table 4. Univariable analysis of prognostic factors with OS among 606 patients

Variables	OS	*p*
	HR (95% CI)	
Age (years)	1.000 (0.997-1.016)	0.173
Gender		
Male	1.00	--
Female	1.009 (0.777-1.310)	0.946
Smoking Index	1.00 (1.000-1.000)	0.931
Alcohol		
Yes	1.00	--
No	0.990 (0.837-1.172)	0.911
β-blockers		
Yes	1.00	--
No	1.009 (0.539-1.886)	0.978
T stage		
T_{0-2}	1.00	--
T_{3-4}	1.068 (0.903-1.264)	0.441
N stage		
N_{0-1}	1.00	--
N_{2-3}	0.836 (0.676-1.034)	0.099
Pathology		
Adeno	1.00	--
Non-adeno	1.074 (0.904-1.274)	0.417
Chemotherapy		
Yes	1.00	--
No	0.906 (0.684-1.200)	0.737

Table 5. Multi-variables analysis of prognostic factors with OS among 606 patients

Variables	OS	*p*
	HR (95% CI)	
Age (years)	1.000 (0.997-1.016)	0.173
Gender		
Male	1.00	--
Female	1.024 (0.771-1.361)	0.870
Smoking Index	1.00 (1.000-1.000)	0.667
Alcohol		
Yes	1.00	--
No	0.987 (0.831-1.171)	0.878
β-blockers		
Yes	1.00	--
No	1.212 (0.630-2.333)	0.564
T stage		
T_{0-2}	1.00	--
T_{3-4}	1.000 (0.827-1.208)	1.000
N stage		
N_{0-1}	1.00	--
N_{2-3}	0.838 (0.659-1.065)	0.148
Pathology		
Adeno	1.00	--
Non-adeno	1.063 (0.891-1.268)	0.499
Chemotherapy		
Yes	1.00	--
No	0.881 (0.663-1.170)	0.382

migration, invasion, immune response [36]. The β(1,2) unselective blocker medication, such as propranolol, might have the potential anti-cancer effects.

The limitations of our study were that we did not demonstrate the better overall survival outcome by intake of a β blocker, and it was consistent with the conclusion by Aydiner et al. [13] and Cata et al. [12]. However, Wang et al. indicated propranolol improved the distant-metastasis-free survival, disease-free survival, and OS in NSCLC patients [11].

Given the possible unbalanced plasma level of VEGF baseline between hypertension and non-hypertension patients, we conducted the analysis in only hypertension patients. However, no significant differences were found between beta-blocker users or non-beta blocker users in OS.

Finally, due to the limitations of handwritten medical records, further information on other complications or drug combinations about the NSCLC patients is unavailable. All the patients have no results of plasma level VEGF or the other cytokines. At the time of data collection, the technology of radiation therapy at Hunan Cancer Hospital was 2D conformable radiotherapy, not 3D. These factors may have confounded the observed results and merit further exploration.

In conclusion, the use of beta-blockers was not associated with the overall survival outcomes in stage III inoperable NSCLC patients. However, given the limitations of our study and the potential effect of anti-β-Adrenergic receptors, it is beneficial to perform a randomized clinical trial study with relevant cytokines levels.

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Table 6. Univariable analysis of prognostic factors of OS among 123 hypertension patients

Variables	OS	*p*
	HR (95% CI)	
Age (years)	1.000 (0.978-1.023)	0.988
Gender		
Male	1.00	--
Female	1.004 (0.591-1.705)	0.988
Smoking Index	1.00 (1.000-1.001)	0.514
Alcohol		
Yes	1.00	--
No	0.975 (0.673-1.412)	0.892
β-blockers		
Yes	1.00	--
No	1.180 (0.616-2.260)	0.618
T stage		
T_{0-2}	1.00	--
T_{3-4}	1.224 (0.844-1.775)	0.287
N stage		
N_{0-1}	1.00	--
N_{2-3}	0.587 (0.329-1.048)	0.072
Pathology		
Adeno	1.00	--
Non-adeno	0.800 (0.547-1.170)	0.251
Chemotherapy		
Yes	1.00	--
No	1.005 (0.524-1.928)	0.987

Table 7. Multi-variables analysis of prognostic factors with OS among 123 hypertension patients

Variables	OS	*p*
	HR (95% CI)	
Age (years)	0.992 (0.966-1.018)	0.530
Gender		
Male	1.00	--
Female	0.909 (0.484-1.707)	0.766
Smoking Index	1.00 (1.000-1.001)	0.695
Alcohol		
Yes	1.00	--
No	0.978 (0.667-1.434)	0.910
β-blockers		
Yes	1.00	--
No	1.230 (0.624-2.426)	0.549
T stage		
T_{0-2}	1.00	--
T_{3-4}	1.065 (0.702-1.615)	0.767
N stage		
N_{0-1}	1.00	--
N_{2-3}	0.565 (0.287-1.113)	0.099
Pathology		
Adeno	1.00	--
Non-adeno	0.790 (0.532-1.173)	0.243
Chemotherapy		
Yes	1.00	--
No	0.936 (0.477-1.838)	0.848

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Disclosure of conflict of interest

None.

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References

[1] Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB and Taieb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008; 358: 2649-2651.

[2] Fuchsmann C, Quintal MC, Giguere C, Ayari-Khalfallah S, Guibaud L, Powell J, McCone C and Froehlich P. Propranolol as first-line treatment of head and neck hemangiomas. Arch Otolaryngol Head Neck Surg 2011; 137: 471-478.

[3] Leaute-Labreze C and Taieb A. [Efficacy of beta-blockers in infantile capillary haemangiomas: the physiopathological significance and therapeutic consequences]. Ann Dermatol Venereol 2008; 135: 860-862.

[4] Ajani J and Allgood V. Molecular mechanisms in cancer: what should clinicians know? Semin Oncol 2005; 32: 2-4.

[5] Cui J, Cai X, Zhu M, Liu T and Zhao N. The efficacy of bevacizumab compared with other targeted drugs for patients with advanced NSCLC: a meta-analysis from 30 randomized controlled clinical trials. PLoS One 2013; 8: e62038.

[6] Botrel TE, Clark O, Clark L, Paladini L, Faleiros E and Pegoretti B. Efficacy of bevacizumab (Bev) plus chemotherapy (CT) compared to CT

alone in previously untreated locally advanced or metastatic non-small cell lung cancer (NSCLC): systematic review and meta-analysis. Lung Cancer 2011; 74: 89-97.
[7] Powe DG, Voss MJ, Zanker KS, Habashy HO, Green AR, Ellis IO and Entschladen F. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget 2010; 1: 628-638.
[8] Barron TI, Connolly RM, Sharp L, Bennett K and Visvanathan K. Beta blockers and breast cancer mortality: a population- based study. J Clin Oncol 2011; 29: 2635-2644.
[9] Lemeshow S, Sorensen HT, Phillips G, Yang EV, Antonsen S, Riis AH, Lesinski GB, Jackson R and Glaser R. beta-Blockers and survival among Danish patients with malignant melanoma: a population-based cohort study. Cancer Epidemiol Biomarkers Prev 2011; 20: 2273-2279.
[10] Melhem-Bertrandt A, Chavez-Macgregor M, Lei X, Brown EN, Lee RT, Meric-Bernstam F, Sood AK, Conzen SD, Hortobagyi GN and Gonzalez-Angulo AM. Beta-blocker use is associated with improved relapse-free survival in patients with triple-negative breast cancer. J Clin Oncol 2011; 29: 2645-2652.
[11] Wang HM, Liao ZX, Komaki R, Welsh JW, O'Reilly MS, Chang JY, Zhuang Y, Levy LB, Lu C and Gomez DR. Improved survival outcomes with the incidental use of beta-blockers among patients with non-small-cell lung cancer treated with definitive radiation therapy. Ann Oncol 2013; 24: 1312-1319.
[12] Cata JP, Villarreal J, Keerty D, Thakar DR, Liu DD, Sood AK and Gottumukkala V. Perioperative beta-blocker use and survival in lung cancer patients. J Clin Anesth 2014; 26: 106-117.
[13] Aydiner A, Ciftci R, Karabulut S and Kilic L. Does beta-blocker therapy improve the survival of patients with metastatic non-small cell lung cancer? Asian Pac J Cancer Prev 2013; 14: 6109-6114.
[14] Choi CH, Song T, Kim TH, Choi JK, Park JY, Yoon A, Lee YY, Kim TJ, Bae DS, Lee JW and Kim BG. Meta-analysis of the effects of beta blocker on survival time in cancer patients. J Cancer Res Clin Oncol 2014; 140: 1179-1188.
[15] Radisauskas R, Kuzmickiene I, Milinaviciene E and Everatt R. Hypertension, serum lipids and cancer risk: A review of epidemiological evidence. Medicina (Kaunas) 2016; 52: 89-98.
[16] Schairer C, Gadalla SM, Pfeiffer RM, Moore SC and Engels EA. Diabetes, abnormal glucose, dyslipidemia, hypertension and risk of inflammatory and other breast cancer. Cancer Epidemiol Biomarkers Prev 2017; [Epub ahead of print].
[17] Liang Z, Xie B, Li J, Wang X, Wang S, Meng S, Ji A, Zhu Y, Xu X, Zheng X and Xie L. Hypertension and risk of prostate cancer: a systematic review and meta-analysis. Sci Rep 2016; 6: 31358.
[18] Belgore FM, Blann AD, Li-Saw-Hee FL, Beevers DG and Lip GY. Plasma levels of vascular endothelial growth factor and its soluble receptor (SFlt-1) in essential hypertension. Am J Cardiol 2001; 87: 805-807, a809.
[19] Tsai WC, Li YH, Huang YY, Lin CC, Chao TH and Chen JH. Plasma vascular endothelial growth factor as a marker for early vascular damage in hypertension. Clin Sci (Lond) 2005; 109: 39-43.
[20] Ayerden Ebinc F, Haksun E, Ulver DB, Koc E, Erten Y, Reis Altok K, Bali M, Turgay A and Sindel S. The relationship between vascular endothelial growth factor (VEGF) and microalbuminuria in patients with essential hypertension. Intern Med 2008; 47: 1511-1516.
[21] Zhang JX, Cai MB, Wang XP, Duan LP, Shao Q, Tong ZT, Liao DZ, Li YY, Huang MY, Zeng YX and Shao JY. Elevated DLL4 expression is correlated with VEGF and predicts poor prognosis of nasopharyngeal carcinoma. Med Oncol 2013; 30: 390.
[22] Kim TJ, Lee YS, Kang JH, Kim YS and Kang CS. Prognostic significance of expression of VEGF and Cox-2 in nasopharyngeal carcinoma and its association with expression of C-erbB2 and EGFR. J Surg Oncol 2011; 103: 46-52.
[23] Pan J, Tang T, Xu L, Lu JJ, Lin S, Qiu S, Chen G and IW KT. Prognostic significance of expression of cyclooxygenase-2, vascular endothelial growth factor, and epidermal growth factor receptor in nasopharyngeal carcinoma. Head Neck 2013; 35: 1238-1247.
[24] Edge SB and Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-1474.
[25] Ferrara N. Role of vascular endothelial growth factor in the regulation of angiogenesis. Kidney Int 1999; 56: 794-814.
[26] Loncaster JA, Cooper RA, Logue JP, Davidson SE, Hunter RD and West CM. Vascular endothelial growth factor (VEGF) expression is a prognostic factor for radiotherapy outcome in advanced carcinoma of the cervix. Br J Cancer 2000; 83: 620-625.
[27] Lee YH, Tokunaga T, Oshika Y, Suto R, Yanagisawa K, Tomisawa M, Fukuda H, Nakano H, Abe S, Tateishi A, Kijima H, Yamazaki H, Tamaoki N, Ueyama Y and Nakamura M. Cell-retained isoforms of vascular endothelial growth factor (VEGF) are correlated with poor prognosis in osteosarcoma. Eur J Cancer 1999; 35: 1089-1093.
[28] Duque JL, Loughlin KR, Adam RM, Kantoff PW, Zurakowski D and Freeman MR. Plasma levels of vascular endothelial growth factor are in-

creased in patients with metastatic prostate cancer. Urology 1999; 54: 523-527.
[29] Lee SY, Kim MT, Jee SH and Im JS. Does hypertension increase mortality risk from lung cancer? A prospective cohort study on smoking, hypertension and lung cancer risk among Korean men. J Hypertens 2002; 20: 617-622.
[30] Dyer AR, Stamler J, Berkson DM, Lindberg HA and Stevens E. High blood-pressure: a risk factor for cancer mortality? Lancet 1975; 1: 1051-1056.
[31] Xie L, Wu K, Xu N, Chen D, Chen J and Lu S. Hypertension is associated with a high risk of cancer. J Hum Hypertens 1999; 13: 295-301.
[32] Zhang L, Mai HM, Zheng J, Zheng JW, Wang YA, Qin ZP and Li KL. Propranolol inhibits angiogenesis via down-regulating the expression of vascular endothelial growth factor in hemangioma derived stem cell. Int J Clin Exp Pathol 2014; 7: 48-55.
[33] Li P, Guo Z, Gao Y and Pan W. Propranolol represses infantile hemangioma cell growth through the beta2-adrenergic receptor in a HIF-1alpha-dependent manner. Oncol Rep 2015; 33: 3099-3107.
[34] Pan WK, Li P, Guo ZT, Huang Q and Gao Y. Propranolol induces regression of hemangioma cells via the down-regulation of the PI3K/Akt/eNOS/VEGF pathway. Pediatr Blood Cancer 2015; 62: 1414-1420.
[35] Wong HP, Ho JW, Koo MW, Yu L, Wu WK, Lam EK, Tai EK, Ko JK, Shin VY, Chu KM and Cho CH. Effects of adrenaline in human colon adenocarcinoma HT-29 cells. Life Sci 2011; 88: 1108-1112.
[36] Barron TI, Sharp L and Visvanathan K. Beta-adrenergic blocking drugs in breast cancer: a perspective review. Ther Adv Med Oncol 2012; 4: 113-125.