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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Meta-analysis of the effects of beta blocker on survival time in cancer patients

Chel Hun Choi · Taejong Song · Tae Hyun Kim · Jun Kuk Choi · Jin-Young Park · Aera Yoon · Yoo-Young Lee · Tae-Joong Kim · Duk-Soo Bae · Jeong-Won Lee · Byoung-Gie Kim

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Abstract
Purpose This study was to elucidate the potential benefit of beta blockers on cancer survival.
Methods We comprehensively searched PubMed, Embase, and the Cochrane Library from their inception to April 2013. Two authors independently screened and reviewed the eligibility of each study and coded the participants, treatment, and outcome characteristics. The primary outcomes were overall survival (OS) and disease-free survival (DFS).
Results Twelve studies published between 1993 and 2013 were included in the final analysis. Four papers reported results from 10 independent groups, resulting in a total of 18 comparisons based on data obtained from 20,898 subjects. Effect sizes (hazard ratios, HR) were heterogeneous, and random-effects models were used in the analyses. The meta-analysis demonstrated that beta blocker use is associated with improved OS (HR 0.79; 95 % CI 0.67–0.93; $p = 0.004$) and DFS (HR 0.69; 95 % CI 0.53–0.91; $p = 0.009$). Although statistically not significant, the effect size was greater in patients with low-stage cancer or cancer treated primarily with surgery than in patients with high-stage cancer or cancer treated primarily without surgery (HR 0.60 vs. 0.78, and 0.60 vs. 0.80, respectively). Although only two study codes were analyzed, the studies using nonselective beta blockers showed that there was no overall effect on OS (HR 0.52, 95 % CI 0.09–3.04).
Conclusion This meta-analysis provides evidence that beta blocker use can be associated with the prolonged survival of cancer patients, especially patients with early-stage cancer treated primarily with surgery.

Keywords Beta blocker · Cancer · Survival

Introduction

Previous studies have shown that stress may be linked with the onset of cancer and cancer progression. Catecholamines are the major transmitters of the stress response (Antoni et al. 2006; Ben-Eliyahu 2003; Justice 1985; McEwen 1998; Reiche et al. 2004), and interestingly, beta adrenergic receptors have been identified on nasopharyngeal (Yang et al. 2006), pancreatic (Weddle et al. 2001), breast (Vandewalle et al. 1990), and ovarian (Thaker et al. 2006) cancer cells. In addition, beta adrenergic stimulation is known to lead to increased angiogenesis, tumor invasion (Thaker et al. 2006), resistance to anoikis (Sood et al. 2010), and integrin-mediated cell adhesion (Rangarajan et al. 2003), and these phenotypes are abrogated by a beta adrenergic antagonist.

Several retrospective cohort studies have examined the impact of beta blockers on long-term cancer outcomes. In triple-negative breast cancer patients, the use of beta

Chel Hun Choi, Taejong Song, Jeong-Won Lee, and Byoung-Gie Kim have contributed equally to this paper.

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C. H. Choi · T. H. Kim · J. K. Choi · J.-Y. Park · A. Yoon · Y.-Y. Lee · T.-J. Kim · D.-S. Bae · J.-W. Lee · B.-G. Kim (✉)
Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-Dong, Kangnam-Ku, Seoul 135-710, Korea
e-mail: chelhunchoi@gmail.com; huna0@naver.com

T. Song
Department of Obstetrics and Gynecology, CHA Gangnam Medical Center, CHA University, Seoul, Korea

blockers before surgery was associated with improved recurrence-free survival (Melhem-Bertrandt et al. 2011); moreover, in malignant melanoma patients, beta blocker treatment significantly predicted a reduced mortality (Lemeshow et al. 2011).

Although the benefit of beta blockers is clear in some malignancies, the clinical value of the drug in cancers overall remains unclear. To our knowledge, there are no clinical trials that directly test the impact of beta blockers on survival from cancer. Two clinical trials are currently investigating the role of beta blockers in cancer recurrence and progression in patients with breast (NCT00502684) and colorectal (NCT 00888797) cancer undergoing surgery with curative intent. Despite the ongoing trials, we do not know which patients are the best candidates for this intervention.

The present meta-analysis was performed to assess whether adding beta blockers to the treatment regimen of patients with various types of cancer had an impact on survival. In addition, the study will compare how the study population, such as patients with early-/late-stage cancer or patients treated with/without surgery, influence the effect size.

Materials and methods

The review was planned and conducted in accordance with the PRISMA guidelines for meta-analysis and the recommendations of the Cochrane Collaboration (Furlan et al. 2009). This was a meta-analysis of published summary data and therefore did not require ethics approval.

Search strategy

We performed electronic searches in PubMed/MEDLINE (1960–2013), Embase (1980–2013), and the Cochrane Library. The literature search was constructed using key words such as "neoplasm" or "cancer" for disease; "beta blocker" for intervention; and "progression," "recurrence," "survival," or "mortality" for outcome. The complete search strategy for PubMed was as follows: ("neoplasm" OR "tumor" OR "cancer" OR "carcinoma" OR "adenocarcinoma") AND ("beta blocker" OR "atenolol" OR "propranolol" OR "metoprolol" OR "arotinolol" OR "betaxolol" OR "bevantolol" OR "bisoprolol" OR "carteolol" OR "carvedilol" OR "celiprolol") AND ("progression" OR "recurrence" OR "metastasis" OR "survival" OR "mortality"), and the search strategy was adapted for each database as necessary. Reference lists and conference proceedings were also searched to identify additional potential studies. The last systematic search was dated May 14, 2013.

Study selection

A study that met the following conditions was eligible for inclusion in the study: (1) participants must have a cancer diagnosis; (2) beta blockers must be used in the treatment group; (3) studies must be a comparative study; (4) outcome variable must be the survival time; and (5) it must be possible to calculate a hazard ratio (HR) for survival with an associated variance between the treatment and control group. If this was not directly reported in the primary report, it must be possible to obtain it by other means.

A study was excluded from this meta-analysis under the following conditions: (1) if two or more studies were reported by the same institution and/or authors and showed an overlap between the results; (2) if multi-center studies contained data which were already included in a single-center study; and (3) if a HR with 95 % confidence interval (CI) for survival was not directly reported, or it was impossible to calculate that from the paper.

Coding variables

The following variables were used for coding the study: publication year, number of subjects in the control and intervention groups, mean age, type of cancer, metastatic/nonmetastatic cancer dominant, and whether surgery was done or not. The name of the first author and the year of publication of the article were used for identification purposes. When there were subgroups in the article, they were coded independently for the subgroup analysis. Two reviewers (CHC and TS) independently extracted the data from all included studies. A third reviewer (BGK) was consulted to resolve disagreements.

Type of effect size

The primary outcome analyzed was overall survival (OS). Another point of interest was disease-free survival (DFS). For each study, a log hazard ratio (lnHR) with its standard error was calculated. In some of the primary reports, these parameters were reported directly. In other studies, we had to estimate them from other reported data using the methods provided (Parmar et al. 1998).

Predefined subgroup analysis was conducted to assess the role of beta blocker in different cancers, different stages, and different primary treatment modalities (surgery or not). Most cancer types can be staged using one of the following classification systems: the overall stage groupings (I–IV) and the TNM staging. In the present study, we divided studies into either "early stage dominant" or "late stage dominant" with more or <50 % of cases having stage I/II or T1/T2, respectively. For the treatment history, surgery was the important variable in the assessment of beta

blocker efficacy, and studies were divided into either "surgery done" or "surgery not done."

Statistical analysis

Because we compared the effect on a wide range of different cancers, we decided to use random-effects modeling overall. The analyses were done using RevMan version 5.2 (Cochrane Collaboration, Oxford, UK). The lnHR and its variance were pooled using an inverse variance-weighted average, and the results were presented as HR and 95 % CI. Statistical heterogeneity in the results of the trials was assessed by the chi-square test (DerSimonian and Laird 1986) and was expressed as the I^2 index, as described by Higgins et al. (Higgins et al. 2003). A funnel plot was produced to assess the possibility of publication bias. A sensitivity analysis was performed to test the stability of our conclusions, and it was prespecified. The treatment effect was examined based on the time to publication and sample size.

Results

Literature search

The flow chart of the systematic search is summarized in Fig. 1. A total of 181 citations were identified from the MEDLINE and Embase database. After review by all of the authors, a total of 12 papers fulfilled the inclusion criteria and were eligible for this study (Barron et al. 2011; De Giorgi et al. 2011; Diaz et al. 2012; Ganz et al. 2011; Grytli et al. 2013; Grytli et al. 2014; Heitz et al. 2013; Hole et al. 1993; Lemeshow et al. 2011; Melhem-Bertrandt et al. 2011; Powe et al. 2010; Wang et al. 2013). In one of the studies excluded, beta blocker was compared with other antihypertensive drugs, and so, we judged the groups in this study to not qualify as proper treatment and control groups (Shah et al. 2011). Four papers reported results from 10 independent groups with different types of cancer (Barron et al. 2011; Grytli et al. 2013; Higgins and Thompson 2002). This resulted in a total of 18 comparisons based on the data obtained from 20,898 subjects.

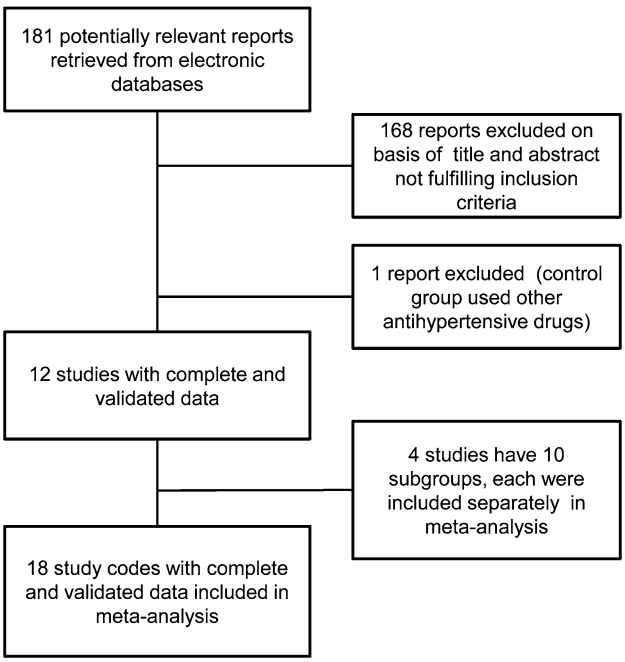

Fig. 1 Study flow diagram

Reporting of information

A detailed description of all included studies is presented in Table 1. Of the 12 trials, four were done on breast cancer, two on ovarian cancer, two on melanoma, two on prostate cancer, one on NSCLC, and one on mixed cancers. Of the 18 study codes, nine were classified as "low-stage dominant," and seven as "high-stage dominant," according to the definitions. Similarly, ten were classified as "surgery done," and six "surgery not done." The beta blockers used were diverse and mixed in many studies. Of them, beta 1 selective blocker was used mainly in 11 study codes, and only 2 study codes analyzed nonselective beta blocker separately.

A funnel plot showed the existence of possible publication bias as there was a relative lack of studies in the lower right portion (Fig. 2). Because of the low number of studies, this plot was not very informative, but it is regarded as good practice to routinely publish such plots in meta-analyses.

Survival

The meta-analysis for the total sample of studies shows a significant treatment effect. Beta blocker usage was associated with a significant improvement in OS (HR 0.79; 95 % CI 0.67–0.93; $p = 0.004$) (Fig. 3). The sample was marginally heterogeneous ($\chi^2 = 41.97$, $df = 17$, $p = 0.0007$, $I^2 = 59$ %).

A subgroup analysis demonstrated that OS was significantly improved even when the meta-analysis was restricted to low-stage dominant cancer (HR 0.60; 95 % CI 0.40–0.90; $p = 0.01$) or high-stage dominant (HR 0.78; 95 % CI 0.66–0.91; $p = 0.002$) (Fig. 4) cancer. Although statistically not significant, the effect sizes were greater in low-stage dominant subjects. Similarly, beta blocker showed a more pronounced positive impact on OS for patients treated with surgery (HR 0.60; 95 % CI 0.42–0.86;

Table 1 Overview of the studies

Study	Country	Design	No. of patients		Cancer type	Stage	Surgery	Beta blocker	Exposure definition	Follow-up (months)
			Exposure	Control						
Barron (2011)	Ireland/USA	Matched case-control	70	140	Breast	I/II (78.5 %); III/IV (15.4 %)	Yes	Nonselective	Year before cancer diagnosis	42
Barron (2011)	Ireland/USA	Matched case-control	525	1,050	Breast	I/II (67.4 %); III/IV (24.5 %)	Yes	Beta 1 selective	Year before cancer diagnosis	42
De Giorgi et al. (2011)	Italy	Hospital-based retrospective cohort	30	91	Thick Melanoma	NA	Yes	NA	For 1 year or more	30
Diaz et al. (2012)	USA	Hospital-based retrospective cohort	23	225	Ovarian	III/IV (100 %)	Yes	Beta 1 selective (75 %); nonselective (13 %)	At least 2 records more than 6 months apart	NA
Ganz et al. (2011)	USA	Obsevational data from LACE cohort	204	1,372	Breast	I/II (96.9 %); III/IV (3.1 %)	Yes	Beta 1 selective (82 %); nonselective (14 %)	During the year before or year after diagnosis	NA
Grytli et al. 2014	Norway	Cancer Registry of Norway	1,115	2,446	Prostate	High-risk or metastatic	No	Beta 1 selective (78 %)	At least one prescription before diagnosis and repeated prescription at least once after diagnosis	39
Grytli et al. 2013	Norway	Data from Oslo II study	35	228	Prostate	T1/T2 (38 %); T3/T4 (62 %)	No	Beta 1 selective (80.2 %); nonselective (19.8 %)	Self reported use	122
Grytli et al. 2013	Norway	Data from Oslo II study	25	202	Prostate	T1/T2 (86 %); T3/T4 (14 %)	Yes	Beta 1 selective (80.2 %); nonselective (19.8 %)	Self reported use	122
Heitz et al. (2013)	Germany/Canada	Hospital-based retrospective cohort	38	343	Ovary	Recurrent	No	Beta 1 selective (84.2 %); nonselective (15.8 %)	Ever-user	17
Hole et al. (1993)	Scotland	Hospital-based retrospective cohort	2,676	NA	Mixed	Mixed	Mixed	Atenolol	NA	NA
Hole et al. (1993)	Scotland	Hospital-based retrospective cohort	1,164	NA	Mixed	Mixed	Mixed	Other (nonselective)	NA	NA
Lemeshow et al. (2011)	Denmark	Population based cohort study	216	2,638	Melanoma	I/II (100 %)	Yes	NA	>90d prior to diagnosis	59
Lemeshow et al. (2011)	Denmark	Population based cohort study	21	278	Melanoma	III/IV (100 %)	No	NA	>90d prior to diagnosis	59
Lemeshow et al. (2011)	Denmark	Population based cohort study	247	2,638	Melanoma	I/II (100 %)	Yes	NA	90d prior to diagnosis	59
Lemeshow et al. (2011)	Denmark	Population based cohort study	28	278	Melanoma	III/IV (100 %)	No	NA	90d prior to diagnosis	59

Table 1 continued

Study	Country	Design	No. of patients		Cancer type	Stage	Surgery	Beta blocker	Exposure definition	Follow-up (months)
			Exposure	Control						
Melhem-Bertrandt et al. (2011)	USA	Hospital-based retrospective cohort	102	1,311	Breast (NAC)	I/II (58.5 %); III/IV (41.5 %)	Yes	Beta 1 selective (89 %)	Taking at the start of neoadjuvant chemotherapy	55
Powe et al. (2010)	UK	Hospital-based retrospective cohort	43	374	Breast (operable)	I/II (91.3 %); III (8.7 %)	Yes	Beta 1 selective (74.4 %); nonselective (25.6 %)	Prior to cancer diagnosis	120
Wang et al. (2013)	USA	Hospital-based retrospective cohort	155	567	NSCLC	III/IV (95 %)	No	Beta 1 selective (86 %); nonselective (14 %)	NA	44

$p = 0.005$) than patients not treated with surgery (HR 0.80; 95 % CI 0.69–0.93; $p = 0.003$) (Fig. 5).

Analysis according to cancer type showed significant effects in breast cancer (HR 0.58; 95 % CI 0.35–0.99; $p = 0.04$), ovarian cancer (HR 0.66; 95 % CI 0.48–0.92; $p = 0.01$), and NSCLC (HR 0.78; 95 % CI 0.63–0.97; $p = 0.03$), but not in prostate cancer (HR 0.61; 95 % CI 0.23–1.60; $p = 0.31$) and melanoma (HR 0.76; 95 % CI 0.43–1.33; $p = 0.34$) (Supplemental Fig. 1). Of interest, although only 2 study codes were analyzed, the studies using nonselective beta blocker were found not to have an overall effect on OS (HR 0.52, 95 % CI 0.09–3.04) (Supplemental Fig. 2).

Trials after the year 2000 only and trials with larger samples only (more than 300 patients) were examined separately for the sensitivity analysis, and no significant difference was found in this subset analysis (Table 2).

Data on DFS could be extracted from seven papers, accounting for 4,878 patients. The patients receiving beta blocker had a significantly longer DFS than those not receiving beta blocker, with a benefit percentage of 31 % (95 % CI 9–47 %, $p = 0.009$) (Fig. 6).

Discussion

To the best of our knowledge, this study is the first attempt at quantifying the effects of beta blockers on cancer survival. A total of twelve papers were investigated, and most of these papers had recently been published. When all the outcomes from each study were pooled together, there was a significant benefit with the addition of beta blocker not only for OS but also for DFS. Although there was a marginal heterogeneity between the studies included, the results of this meta-analysis are important because the data were gathered from more than 20,000 various cancer patients who were followed up for a sufficient duration of time. Another main finding from the present analysis is that beta blocker had more dramatic association effects in patients who had low-stage cancer and/or who had received surgical treatment for their cancer than in patients with high stage and/or in whom surgery was not the primary treatment. This result can be particularly important in designing trials investigating the role of beta blocker in cancer survival.

The results of this meta-analysis are supported by in vitro and in vivo animal studies using a variety of human tumor lines. They indicated that activation of tumor beta adrenergic receptors can (1) enhance the production of several metastasis-promoting factors, including VEGF, matrix metalloproteinase 2 (MMP-2), and MMP-9, interleukin 6 (IL-6), and IL-8, and (2) facilitate tumor angiogenesis, survival, migration, proliferation, and resistance to

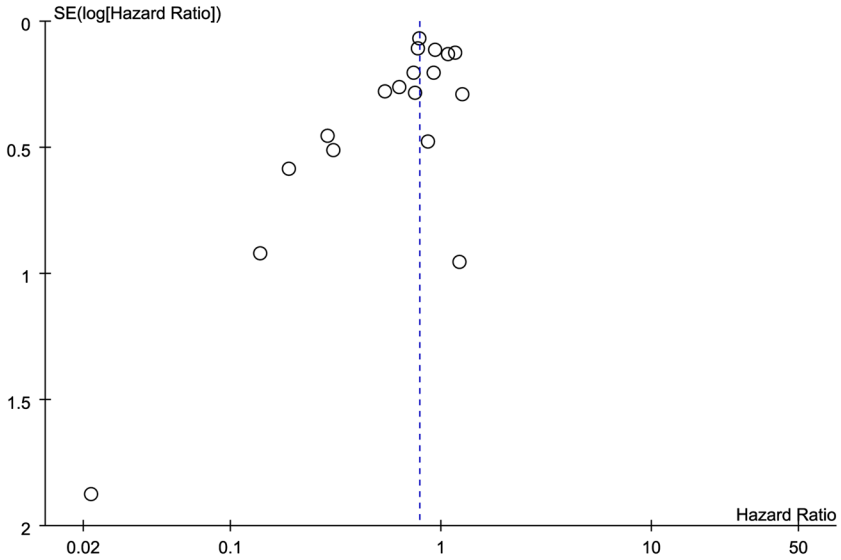

Fig. 2 Funnel plot of comparison: beta blocker versus control group for all studies. Outcome: OS for all patients. There may be some factors accounting for the small amount of asymmetry, such as the exclusion of small trials with negative results that were not published, differences in trial quality or true study heterogeneity

anoikis—effects that are all blocked by beta blockers (Bernabe et al. 2011; Masur et al. 2001; Sood et al. 2006, 2010; Thaker et al. 2006; Yang et al. 2006, 2009).

Interestingly, there was a trend for low-stage subjects to benefit more dramatically from using a beta blocker than high-stage subjects. This suggests that the treatment is effective in controlling the initial stages of the metastatic process, rather than treating established metastatic foci. Some epidemiologic studies have shown that beta blocker was associated with reduction in cancer rates (Barron et al. 2011; Powe et al. 2010), which is evidence for the role of beta blocker in blocking cancer initiation and progression. In addition, beta adrenergic stimulation is known to lead to resistance to anoikis, which is a hallmark of malignant transformation that allows detached cells to survive (Sood et al. 2010).

Similar to stage of cancer, patients treated with surgery showed a more pronounced impact with beta blocker, although this finding was not statistically significant. Because early-stage patients tend to undergo surgery, we do not know whether a surgical factor or a stage factor was associated with the effect size of beta blocker. Surgery has been suspected to facilitate the progression of preexisting micrometastasis and the initiation of new metastases via several mechanisms such as increased shedding of tumor cells (Yamaguchi et al. 2000), increased levels of growth

Study or Subgroup	log[Hazard Ratio]	SE	Beta blocker Total	Control Total	Weight	Hazard Ratio IV, Random, 95% CI
De Giorgi 2011	-3.8167	1.87448802	30	91	0.2%	0.02 [0.00, 0.87]
Grytli 2013-1	-1.9661	0.92020098	35	228	0.8%	0.14 [0.02, 0.85]
Barron 2011-1	-1.6607	0.58668652	70	140	1.7%	0.19 [0.06, 0.60]
Powe 2010	-1.2344	0.45865269	43	374	2.6%	0.29 [0.12, 0.72]
Lemeshow 2011-3	-1.1712	0.51462452	247	2638	2.2%	0.31 [0.11, 0.85]
Diaz 2012	-0.6162	0.28210636	23	225	5.3%	0.54 [0.31, 0.94]
Melhem-Bertrandt 2011	-0.4463	0.26221722	102	1311	5.7%	0.64 [0.38, 1.07]
Heitz 2013	-0.3011	0.20686995	38	343	7.3%	0.74 [0.49, 1.11]
Ganz 2011	-0.2744	0.28551826	204	1372	5.2%	0.76 [0.43, 1.33]
Wang 2013	-0.2485	0.11122559	155	567	10.8%	0.78 [0.63, 0.97]
Grytli 2014	-0.2357	0.0721488	1115	2446	12.1%	0.79 [0.69, 0.91]
Lemeshow 2011-4	-0.1393	0.48023656	28	278	2.4%	0.87 [0.34, 2.23]
Lemeshow 2011-1	-0.0726	0.20869537	216	2638	7.2%	0.93 [0.62, 1.40]
Hole 1993-1	-0.0619	0.11601523	2676	0	10.6%	0.94 [0.75, 1.18]
Barron 2011-2	0.077	0.13240367	525	1050	10.0%	1.08 [0.83, 1.40]
Hole 1993-2	0.157	0.126766	1164	0	10.2%	1.17 [0.91, 1.50]
Grytli 2013-2	0.1989	0.95435732	25	202	0.7%	1.22 [0.19, 7.92]
Lemeshow 2011-2	0.2311	0.29127034	21	278	5.0%	1.26 [0.71, 2.23]
Total (95% CI)			**6717**	**14181**	**100.0%**	**0.79 [0.67, 0.93]**

Heterogeneity: Tau² = 0.05; Chi² = 41.97, df = 17 (P = 0.0007); I² = 59%
Test for overall effect: Z = 2.86 (P = 0.004)

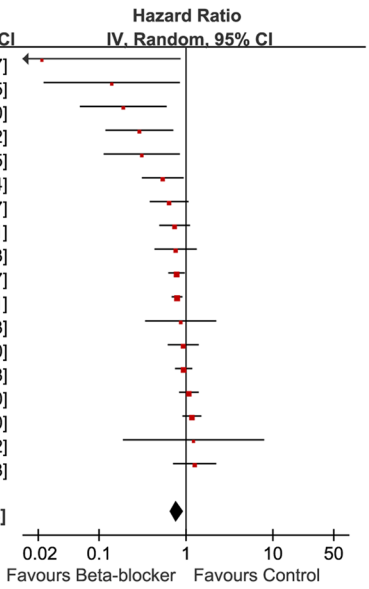

Fig. 3 Meta-analysis of OS: beta blocker versus control

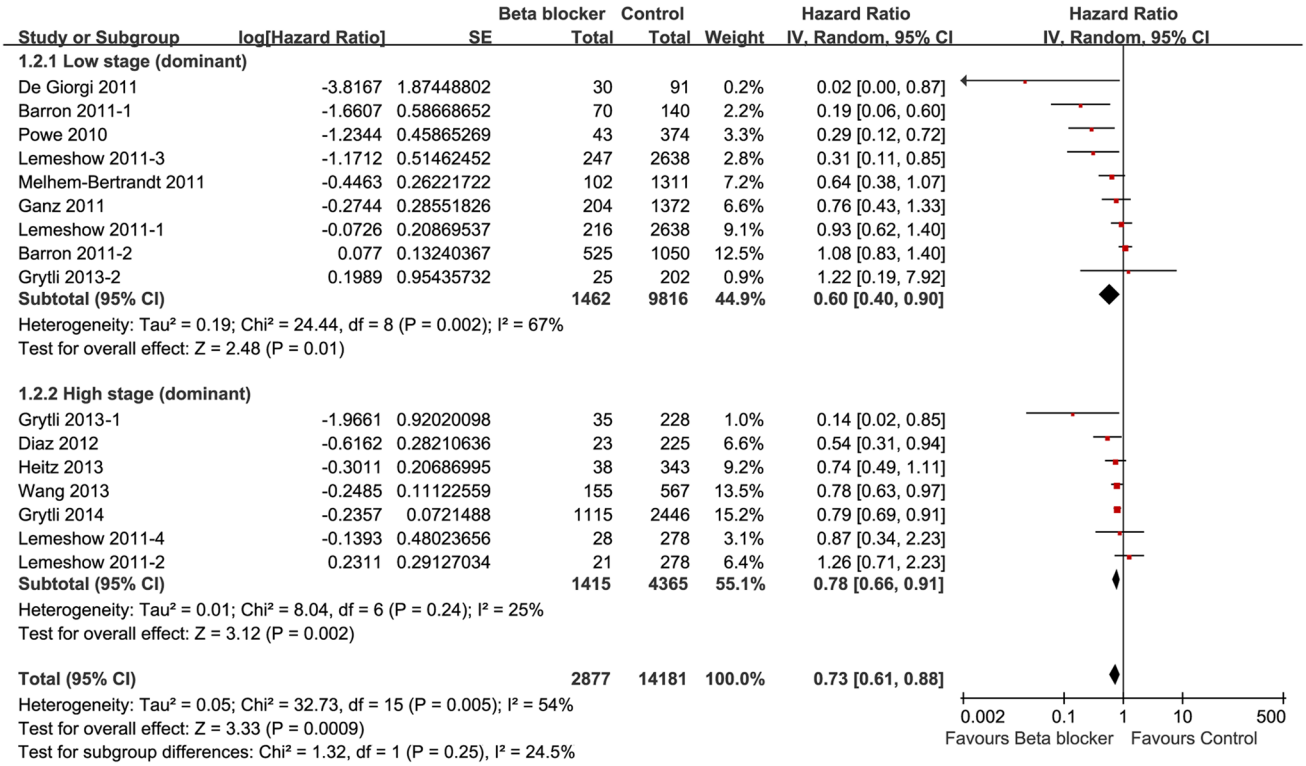

Fig. 4 Meta-analysis of OS according to stage

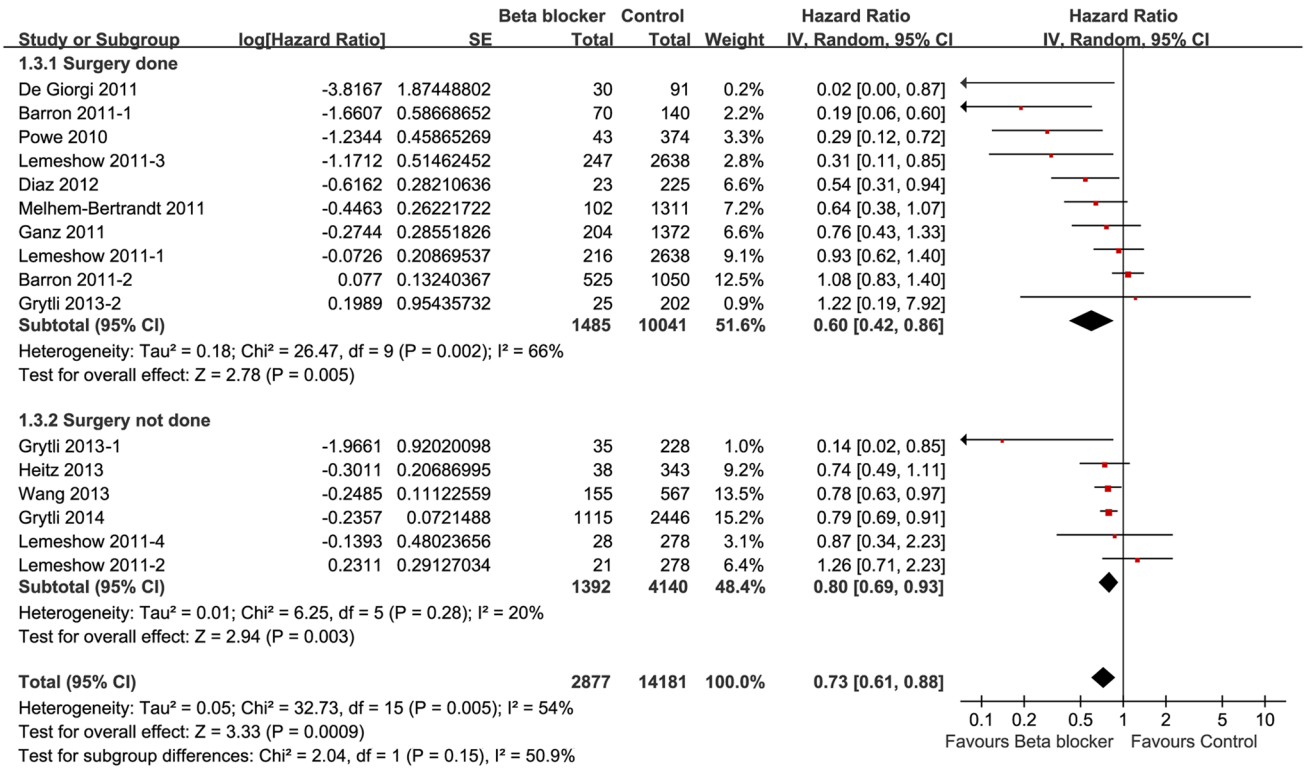

Fig. 5 Meta-analysis of OS according to primary treatment (with or without surgery)

Table 2 Sensitivity analyses

	No. of comparisons	HR (95 % CI)	*p*
Overall survival			
All trials (fixed)	18	0.84 (0.78–0.92)	<0.0001
All trials (random)	18	0.79 (0.67–0.93)	0.004
Exclusion of trials before 2000	16	0.73 (0.61–0.88)	0.0009
Exclusion of small trials (<300 patients)	12	0.84 (0.73–0.97)	0.02

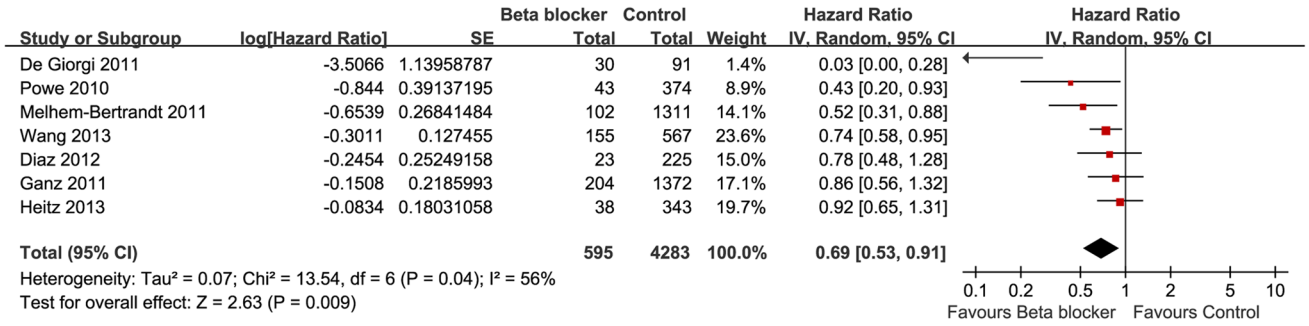

Fig. 6 Meta-analysis of DFS: beta blocker versus control

factors (Abramovitch et al. 1999), and decreased antiangiogenic factors (e.g., endostatin) (O'Reilly et al. 1997). And one of the mechanisms is through the increase of catecholamines which are known to act directly on malignant cells, activating several processes that are critical for tumor metastatic activity, including tumor cell proliferation (Bernabe et al. 2011; Mathew et al. 2011), extracellular matrix invasion capacity (Mathew et al. 2011), resistance to apoptosis (Kerros et al. 2010; Roche-Nagle et al. 2004; Sood et al. 2010), and secretion of proangiogenic factors (Thaker et al. 2006; Wei et al. 2004; Yang et al. 2009). Lee et al. have shown that, in mice with ovarian cancer, propranolol mitigated the effects of surgical stress on tumor growth and angiogenesis (Lee et al. 2009). According to the preclinical data and the results of this study, the perioperative period would theoretically present an opportunity to eradicate cancer or successfully arrest its progression.

There are some limitations in this study. First, although retrospective cohort studies have many methodological shortcomings, they are included in this study because there are no randomized controlled trials yet investigating this subject. Second, for the evaluation of surgical factors, extensive surgeries such as colon, hepatobiliary, or stomach cancer can give more information than breast cancer or melanoma, but studies examining those cancers were not researched in this analysis. Third, there is a variation in effect sizes (heterogeneity), and it may be due to systematic differences among the studies. The studies used various beta blockers with different types of subjects in different settings. Another limitation is the possible existence of some unpublished studies, which could lead to potential publication bias in this study, with the favoring of published positive studies. Lastly, we could not analyze the type of beta blocker that produced these effects because most studies combined beta blockers in their analyses.

In summary, though there are some limitations in this study, beta blocker usage was associated with prolonged survival of cancer patients in this meta-analysis, especially in patients with early-stage cancer that had been treated primarily with surgery. Therefore, beta blocker can be considered a standard approach for adjuvant therapy in various types of cancer. In addition, this approach is also advantageous in that it uses commonly administered medications that are relatively safe and inexpensive. Further trials must be explored with larger patient cohorts.

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Conflict of interest None.

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