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Transcatheter aortic valve replacement in patients with a history of cancer: Periprocedural and long-term outcomes

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TRANSCATHETER AORTIC VALVE REPLACEMENT IN PATIENTS WITH A HISTORY OF CANCER: PERI-PROCEDURAL AND LONG-TERM OUTCOMES

ABSTRACT

Background

A history of cancer is incorporated into the surgical risk assessment of patients undergoing surgical aortic valve replacement through the Society for Thoracic Surgeons (STS) score. However, the prognostic significance of cancer in patients treated with transcatheter aortic valve replacement (TAVR) is unclear. As the cancer survivorship population increases, it is imperative to establish the efficacy and safety of TAVR in patients with severe symptomatic aortic stenosis (AS) and a history of malignancy.

Objectives

The primary goal of this study was to assess the peri-procedural outcomes and long-term mortality in patients with a history of cancer undergoing TAVR.

Methods

A systematic review of PubMed, MEDLINE and EMBASE was conducted to identify studies reporting outcomes in patients with a history of malignancy undergoing TAVR. A meta-analysis was performed using a random effects model with a primary outcome of all-cause mortality and cardiac mortality at longest follow-up. On secondary analyses, procedural safety was assessed.

Results

A total of 13 observational studies with 10,916 patients were identified in the systematic review. Seven studies including 6,323 patients were included in the quantitative analysis. Short-term mortality (Relative Risk [RR] 0.61, 95%CI 0.36-1.01; p=0.06) and long-term all-cause mortality (RR 1.24, 95%CI 0.95-1.63; p=0.11) were not significantly different when comparing patients with and without a history of cancer . No significant difference in the rate of peri-procedural complications including stroke, bleeding, acute kidney injury and pacemaker implantation were noted.

Conclusion

In patients with severe AS undergoing TAVR, a history of cancer was not associated with adverse short or long-term survival. Based on these findings, TAVR should be considered in all patients with severe symptomatic aortic stenosis, irrespective of their history of malignancy.

PROSPERO Registration: CRD42019131895

INTRODUCTION

The incidence of cancer and valvular disease both increase exponentially with age and together constitute leading causes of death in the Western world (1). Aortic stenosis (AS) is a common native valve lesion and represents almost half the cases of valvular heart disease (2). The progression of aortic calcification may be accelerated by cancer therapies and as such AS imposes a high cardiovascular burden in cancer survivors (3). Although increasingly common in clinical practice, the management of these complex cases remains subject to significant physician bias as there is a lack of evidence-based guidelines relevant to cancer patients, who have traditionally been excluded from cardiovascular trials (4).

Current Heart Team risk assessment incorporates a history of cancer as a covariate in the Society for Thoracic Surgeons (STS) score. However, this has not been validated in patients undergoing transcatheter aortic valve replacement (TAVR). TAVR for the treatment of severe AS is being increasingly performed as an alternative to surgical aortic valve replacement (SAVR) even in patients at low surgical risk (5-7). Although SAVR is not contraindicated in patients with AS and a history of malignancy, it is associated with a higher morbidity, including need for blood transfusion, pneumonia, re-intubation, cerebrovascular events, bleeding and sepsis (8,9). As such, patients with symptomatic severe AS and cancer may be more appropriately managed with a percutaneous approach. However, supporting data is limited as the clinical trials comparing TAVR to SAVR were not stratified to allow for randomized comparisons in this sub-population (10).

Recent studies have shown that cancer may predict long-term mortality in patients undergoing TAVR (11,12). However, these results are difficult to generalise to a broader oncology population due to the inclusion of patients with advanced malignancies and poor cancer-specific prognosis. As modern advances in cancer therapy have considerably improved cancer survival (13), the assessment of appropriateness or futility of invasive valvular intervention is becoming increasingly common. It is thus imperative to establish the efficacy and safety of TAVR in this complex patient subset. Accordingly, we conducted a systematic review and meta-analysis to assess the peri-procedural outcomes and long-term mortality in patients with a history of cancer undergoing TAVR.

METHODS

Data Sources

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement was followed (14). A comprehensive literature search was performed through the MEDLINE, EMBASE and PubMed databases from establishment to April 2019 using the following terms: “transcatheter aortic valve replacement”, “percutaneous aortic valve replacement”, “transcatheter aortic valve implantation”, “percutaneous aortic valve implantation”, “TAVR”, “TAVI”, “aortic stenosis”, “cancer”, “neoplasm”, “malignancy”, “active”, “radiation”, “radiotherapy” with no restrictions on language. Reference lists of reviewed articles were screened to identify further relevant studies. When outcome reporting was incomplete, the study authors were contacted for further information. MeSH terms used for the MEDLINE search strategy are presented in Table S1 in the Supplementary Appendix.

Study Selection

Inclusion criteria were as follows: (1) studies performed in patients with severe aortic stenosis and cancer; (2) study design comparing patients with cancer undergoing TAVR to patients without cancer undergoing TAVR; (3) reporting a minimum of 30-day outcomes; and (4) reporting outcomes assessed using the Valve Academic Research Consortium 2 (VARC2) definitions. In the final meta-analysis we included only patients with a history of cancer. We performed a sub-analysis of the co-primary outcomes in studies examining patients with active cancer.

Quality Assessment

Study quality was assessed using the Newcastle-Ottawa Scale for non-randomised studies in meta-analyses(15). Two reviewers (ACM, WC) independently extracted the data. Assessment of quality on this instrument was judged on study group selection, study-group comparability and outcome assessment. Studies meeting ≥5 criteria were considered to be high quality.

Outcome Assessment

The primary outcomes were all-cause mortality and cardiac mortality at longest available follow up. Secondary endpoints were short-term (30 day) all-cause mortality and procedural safety. A sub-analysis was performed to evaluate short and long-term all-cause mortality and periprocedural complication rates in patients with active cancer.

Statistical Analysis

Descriptive statistics are presented as mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. For comparison of outcomes across the cancer and no-cancer groups, summary estimates for relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CI) were calculated using the Der Simonian and Laird random-effects model. Random-effects analysis was pre-specified in preference to a fixed-effects model in this study due to clinical variations in study types and populations assessed. Statistical heterogeneity was quantified using the I^2 statistic. The I^2 statistic provides an estimate of the amount of variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochrane Q statistic. An $I^2 \geq 80\%$ was considered to be significant inter-study heterogeneity (16). As the number of included studies was less than ten, we did not perform tests to assess for publication bias (17). We considered a p-value <0.05 as statistically significant. Statistical analyses were performed using Comprehensive Meta-Analysis Software (Version 3, Biostat, Englewood, NJ, USA).

The PRISMA Checklist can be found in the supplementary appendix (Table S3).

RESULTS

The preliminary literature search yielded 1,616 studies. We eliminated 1,086 studies after initial screening. Details of the literature search and excluded studies are reported in Figure 1. Thirteen studies were included in the qualitative synthesis (11,12,18-28). A total of seven observational studies with 6,323 patients were included in the quantitative analysis (12,23-28). This included 628 (9.9%) patients with a history of cancer. Follow-up ranged from six months to five years. All seven studies included patients with a history of any cancer and three studies examined only patients with a history of cancer treated with chest radiation therapy (24,25,28). On pooled analysis, patients with a history of cancer were younger (78.5, 95% CI 77.4 – 79.7 years vs 80.9, 95% CI 80.0 – 81.7 years; p=0.002). There was no significant difference in gender, STS score, baseline ejection fraction, NYHA class or procedural site of access between groups (p value for all >0.05). Patient characteristics in the included studies are presented in Table 1. A sub-analysis examining patients with active cancer(11,12,22) and patients who with a history of thoracic radiation were performed. Patient characteristics in the included studies of the sub-analysis are presented in Supplementary Table S2.

Methodological Quality of Data

The quality of included studies was assessed using the Newcastle Ottawa Scale for Non-Randomised Studies. In brief, a study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories and a maximum of two stars for Comparability, totalling a maximum score of 9 stars (15). All included studies in the meta-analysis scored greater than 5 stars and as such were deemed to be of high quality (Supplementary Table S3).

Meta-Analysis of the Primary and Secondary Outcomes

The co-primary outcome of long-term all-cause mortality was not significantly different when comparing patients with and without a history of cancer (RR 1.24, 95% CI 0.95-1.63; p=0.11) with moderate heterogeneity (I^2 63%, p=0.013). The co-primary outcome of cardiac mortality was lower in patients with a history of cancer (RR 0.70, 95% CI 0.51-0.96; p=0.03; I^2=0%, p=0.933).

There was a trend towards lower short-term all-cause mortality in patients with a history of cancer (RR 0.61, 95% CI 0.36-1.01; p=0.06) (Figure 2). Of note, there were no significant differences in the rates of peri-procedural complications including stroke (RR 1.07, 95% CI 0.65-1.78; p=0.78), acute kidney injury (RR 1.02, 95% CI 0.80-1.30; p=0.89), bleeding (RR 1.07, 95% CI 0.92-1.25; p=0.36) and pacemaker implantation (RR 0.99, 95% CI 0.81-1.20; p=0.89) (Figure 3).

Sub-Analysis of the Primary and Secondary Outcomes in Patients with Active Cancer

The sub-analysis of patients with active cancer is presented in Figure 4. Long term all-cause mortality was significantly higher in patients with active cancer (OR 1.92, 95% CI 1.44 – 2.56; p<0.001) with low heterogeneity (I^2=0%, p=0.51). Short-term all-cause mortality was similar between the active cancer and no cancer groups (OR 0.81, 95% CI 0.45-1.45; p=0.48,

I^2=0%, p=0.48). Cardiac mortality was not consistently reported and as such was not meta-analysed.

Sub-Analysis of Patients with a Past History of Thoracic Radiation

The sub-analysis of patients with a history of thoracic radiation is presented in the supplementary appendix. Long-term all-cause mortality was comparable between groups (RR 1.29, 95% CI 0.82 – 2.01; p=0.27) (Figure S1).

DISCUSSION

The purpose of this meta-analysis was to determine the prognostic significance of cancer in patients with severe AS undergoing TAVR. From this analysis, three conclusions merit attention. Firstly, TAVR appears to be a safe and efficacious treatment option for patients with severe AS and a history of cancer. Secondly, a past history of cancer was not associated with adverse short or long-term survival and was in-fact associated with lower cardiac mortality. Thirdly, although patients with active cancer have comparable short-term mortality and peri-procedural complication rates, they suffer from higher all-cause long-term mortality.

The incidence of cancer and valvular disease both increase exponentially with age and together constitute leading causes of death in the Western world (1). As the cancer survivorship population increases, it is imperative to establish the efficacy and safety of TAVR in this group as they represent a growing proportion of patients presenting with symptomatic severe AS (27).

Symptomatic severe AS is associated with a high mortality without intervention, irrespective of cancer status (29). This is particularly apparent in studies from the pre-TAVR era which demonstrate a significant survival advantage in oncology patients undergoing SAVR, regardless of cancer stage (30). Current Heart Team risk assessment using the STS score incorporates a history of cancer and chest radiation as covariates due to the greater burden of periprocedural complications in this group (7).

Therapeutic advances in chest radiotherapy have improved survival in patients with thoracic malignancy. As a result, patients are living long enough to unveil latent cardiac toxicity (31). Of note, valvular disease imposes a high cardiovascular burden in cancer survivors and is associated with significant therapeutic challenges (3,32). Consistent with prior evidence, a recent study in patients with a history of chest irradiation undergoing SAVR demonstrated a significantly greater morbidity and mortality than age and sex-matched controls (33). Additionally, peri-operative complications such as stroke, bleeding and a greater requirement for blood transfusions and inotropic support, along with longer intensive care unit and in-hospital stay was seen in the irradiated group. Although the innovation of TAVR has provided a platform to treat these patients at increased surgical risk, there is limited data surrounding peri-procedural outcomes. A recent study by Zhang et al examining TAVR vs SAVR in patients with severe AS and a history of chest radiation has demonstrated favourable results in the TAVR group with lower adjusted 30-day all-cause mortality, less postoperative atrial fibrillation and shorter hospitalization compared with SAVR, despite older age, a higher STS score and more baseline comorbidities (10). Consistent with Zhang et al, in our study the rates of complications reported as more frequent in patients undergoing

SAVR were not significantly elevated in the TAVR population (34). This supports the use of TAVR in patients with a history of cancer, especially those with very severe valvular disease facing a high risk of cardiac mortality.

Given the prognostic significance of severe symptomatic AS and the increased morbidity associated with surgical intervention in cancer patients, it is imperative to establish whether utilisation of a less invasive treatment method may be favourable in this subset. In our analysis, a history of cancer was not associated with adverse short or long-term survival in patients undergoing TAVR. In fact, patients with a history of cancer have a lower cardiac mortality following TAVR. This may reflect a degree of selection bias whereby cancer patients that were ultimately deemed suitable for TAVR by the Heart Team may have represented a lower cardiovascular risk cohort. As we lacked individual patient data, we were unable to assess this in this study. Regardless, the value of intervention for severe AS is evident in this cohort. The Heart Team, in collaboration with the treating oncologists are invaluable in this context to ensure these patients are not being undertreated. However, patient selection for TAVR in the oncology population must involve careful consideration of disease prognosis, both from the perspective of the oncologist and the cardiologist. Landes et al recently described the outcomes of patients with active cancer undergoing TAVR in a large registry study (11). Although effective and safe in the short term, the use of TAVR in current oncology patients was found to carry a worse intermediate prognosis compared with patients without cancer. The juxtaposition of active cancer, to cured cancer as presented in our study, highlights the importance of individualised assessment regarding the appropriateness or futility of invasive valvular intervention.

To our knowledge, this is the largest meta-analysis examining TAVR outcomes in a population of patients with a history of cancer. Although the assessment of study quality was high, the observational nature of the included studies is subject to bias. A further significant limitation was the intermediate duration of median follow-up. Of note, our primary meta-analysis was limited to studies examining patients with a history of malignancy and separated patients with active cancer. The intention was to assess the utility of TAVR in a stable oncology population with an excellent cancer prognosis that may have been previously excluded from intervention (35,36). However, the authors acknowledge that the diversity of this population may reduce the generalisability of our findings. In contrast, the results of recent large scale studies examining patients with active cancer are difficult to relate to a larger oncology population due to the wide variation in cancer stage and prognosis (11). Prospective registries with longer-term follow up, stratified by cancer stage and estimated life expectancy are essential to evaluate whether the benefits of this technique can be generalised to all oncology patients, including those with active cancer.

CONCLUSION

In patients with severe AS undergoing TAVR, a history of cancer was not associated with adverse short or long-term survival. Based on these findings, to avoid the substitution of one malignant condition with another, TAVR should be considered in all patients with symptomatic severe AS and a perceived life expectancy of greater than 12-months, irrespective of their history of malignancy.

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FIGURE LEGEND

FIGURE 1: PRISMA Diagram

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram

FIGURE 2: Mortality

Risk Estimates for Survival for Cancer Patients vs Non-cancer Patients Undergoing TAVR

FIGURE 3: Peri-Procedural Complications

Risk Estimates for Peri-procedural Complications for Cancer Patients vs Non-cancer Patients Undergoing TAVR

FIGURE 4: Mortality in Active Cancer Patients

Risk Estimates for Survival for Active Cancer Patients vs Non-cancer Patients Undergoing TAVR

TABLE 1: Study and Patient Characteristics Included in the Meta-Analysis

		Nuis 2013	Dijos 2015	Bouleti 2017	Bleiziffer 2017	Mangner 2018	Berkovitch 2018	Gajanana 2019
Cancer Patients (n)		197	19	26	NR	251	91	44
Non-cancer Patients (n)		1499	167	26	996	1471	386	1150
Cancer Type		All	All	All	All	All	All	All
Design		Observational	Observational	Observational	Observational	Observational	Observational	Observational
Follow Up		12-months	6-months	30-months	36-months	12-months	28-months	12-months
Age (years)	Cancer	NR	68.3	73.4	NR	80	79.4	76
	No Cancer	NR	82.5	73.3	NR	81	81.8	82
	p Value	NR	<0.001	0.39	NR	0.08	<0.01	0.002
Male (%)	Cancer	NR	36.8	50.0	NR	42.2	52.0	23.0
	No Cancer	NR	56.4	50.0	NR	42.7	52.0	51.0
	p Value	NR	0.1	1.00	NR	0.004	ns	<0.001
STS Sore	Cancer	NR	NR	5.0	NR	6.6	4.6	7
	No Cancer	NR	NR	4.7	NR	6.7	5.7	8
	p Value	NR	NR	0.50	NR	0.84	0.02	0.20
Diabetes (%)	Cancer	NR	5.3	0	NR	41.4	34.0	31.0

	No Cancer	NR	31.3	27.0	NR	43.6	40.0	34.0
	p Value	NR	0.02	0.001	NR	0.51	ns	0.60
CAD (%)	Cancer	NR	47.3	54.0	NR	51.6	47.0	NR
	No Cancer	NR	58.1	46.0	NR	53.1	48.0	NR
	p Value	NR	0.37	1.00	NR	0.90	ns	NR
HTN (%)	Cancer	NR	47.3	46.0	NR	93.2	82.0	86.0
	No Cancer	NR	77.6	85.0	NR	93.6	85.0	93.0
	p Value	NR	0.01	0.24	NR	0.96	ns	0.12
Renal Imp (%)	Cancer	NR	NR	NR	NR	34.3	24.0	18.0
	No Cancer	NR	NR	NR	NR	30.0	22.0	40.0
	p Value	NR	NR	NR	NR	0.30	ns	0.002
Previous CVA (%)	Cancer	NR	0	4	NR	10.4	18.0	9.0
	No Cancer	NR	6.1	8	NR	9.8	14.0	12.0
	p Value	NR	0.6	<0.001	NR	0.90	ns	0.60
Lung Disease (%)	Cancer	NR	47.3	50	NR	20.0	NR	21.0
	No Cancer	NR	36.9	35	NR	16.9	NR	16.0
	p Value	NR	0.37	0.15	NR	0.27	NR	0.40
PVD (%)	Cancer	NR	10.5	12.0	NR	11.2	10.0	27.0

	No Cancer	NR	33.5	4.0	NR	11.7	11.0	29.0
	p Value	NR	0.04	<0.001	NR	0.56	ns	0.70
NYHA III-IV (%)	Cancer	NR	73.6	81.0	NR	79.3	NR	82.1
	No Cancer	NR	86.6	88.0	NR	77.1	NR	79.0
	p Value	NR	0.17	0.001	NR	0.70	NR	0.63

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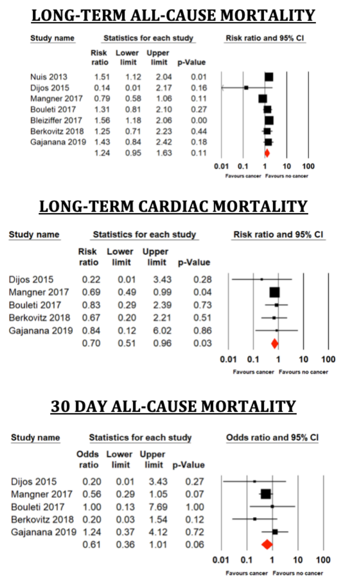
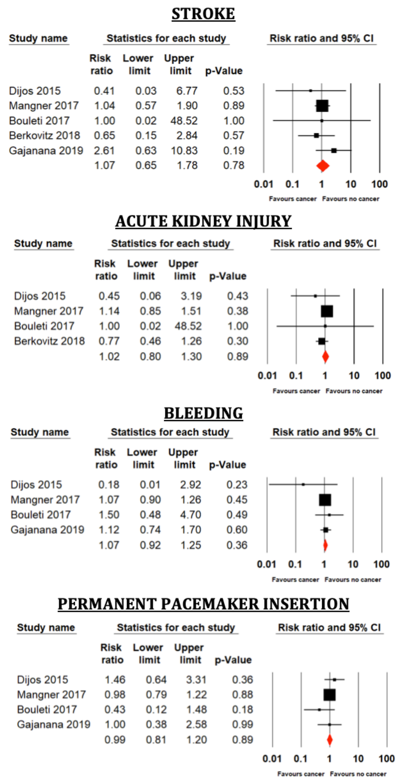
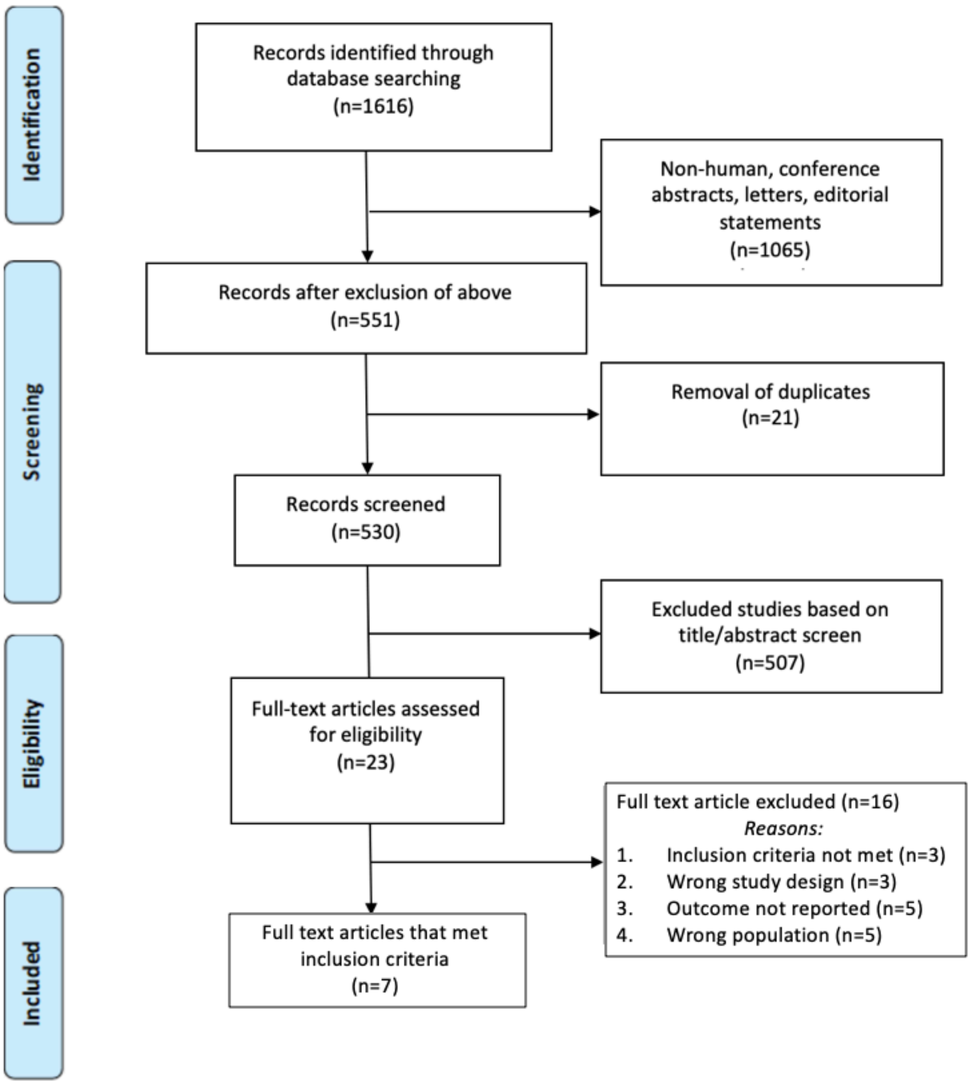
2



CCD_28969_FIGURE 2300.tiff



CCD_28969_FIGURE 3300.tif



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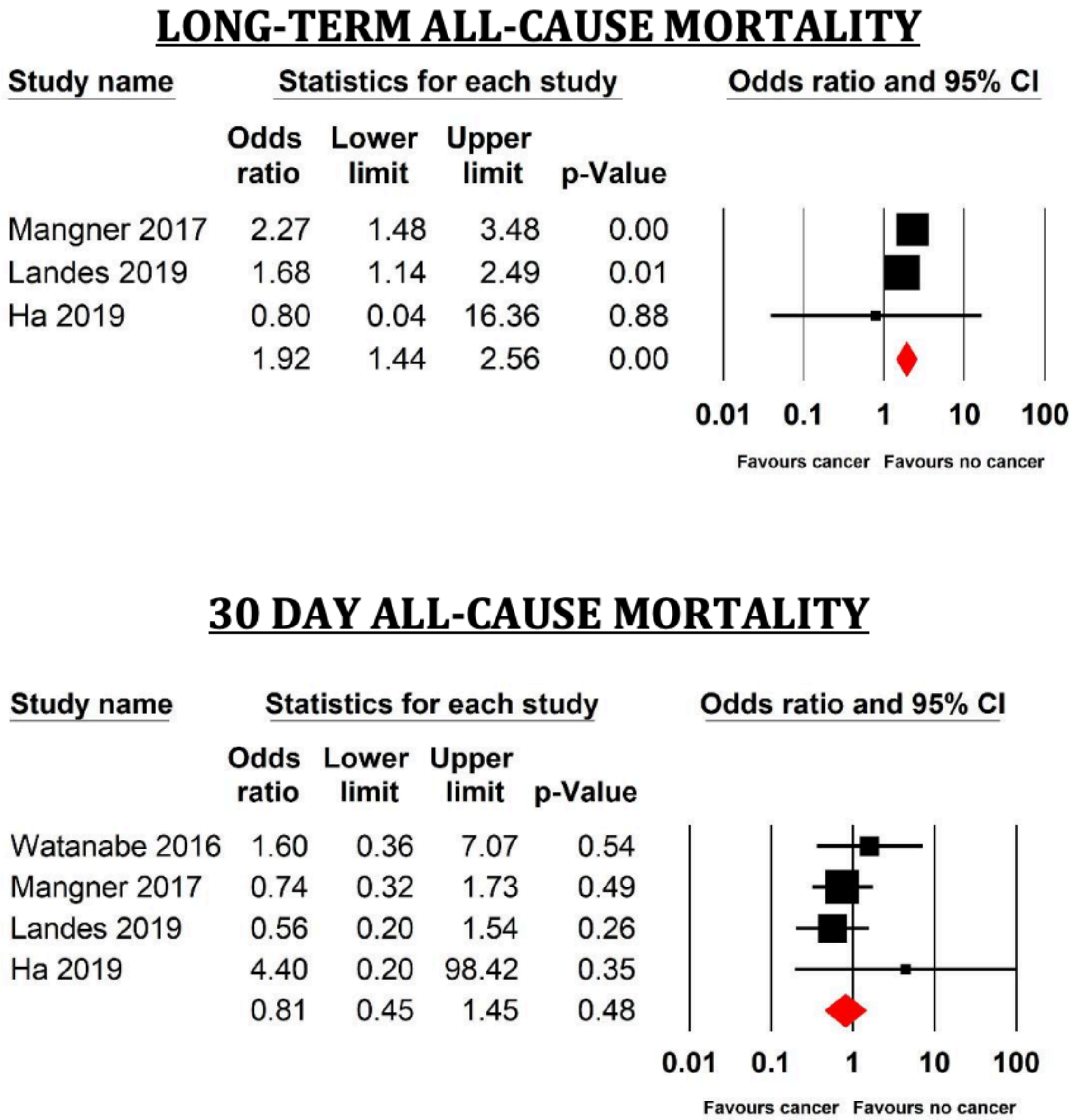

CCD_28969_FIGURE_4_V2.tiff

TABLE 1: Study and Patient Characteristics Included in the Meta-Analysis

		Nuis 2013	Dijos 2015	Bouleti 2017	Bleiziffer 2017	Mangner 2018	Berkovitch 2018	Gajanana 2019
Cancer Patients (n)		197	19	26	NR	251	91	44
Non-cancer Patients (n)		1499	167	26	996	1471	386	1150
Cancer Type		Any	Any	Any	Any	Any	Any	Any
Design		Observational	Observational	Observational	Observational	Observational	Observational	Observational
Follow Up		12-months	6-months	30-months	36-months	12-months	28-months	12-months
Age (years)	Cancer	NR	68.3	73.4	NR	80	79.4	76
	No Cancer	NR	82.5	73.3	NR	81	81.8	82
	p Value	NR	<0.001	0.39	NR	0.08	<0.01	0.002
Male (%)	Cancer	NR	36.8	50.0	NR	42.2	52.0	23.0
	No Cancer	NR	56.4	50.0	NR	42.7	52.0	51.0
	p Value	NR	0.1	1.00	NR	0.004	ns	<0.001
STS Sore	Cancer	NR	NR	5.0	NR	6.6	4.6	7
	No Cancer	NR	NR	4.7	NR	6.7	5.7	8
	p Value	NR	NR	0.50	NR	0.84	0.02	0.20
Prior Radiation (%)	Cancer	NR	100	100	NR	NR	100	100
Diabetes (%)	Cancer	NR	5.3	0	NR	41.4	34.0	31.0
	No Cancer	NR	31.3	27.0	NR	43.6	40.0	34.0
	p Value	NR	0.02	0.001	NR	0.51	ns	0.60
CAD (%)	Cancer	NR	47.3	54.0	NR	51.6	47.0	NR
	No Cancer	NR	58.1	46.0	NR	53.1	48.0	NR

	p Value	NR	0.37	1.00	NR	0.90	ns	NR
HTN (%)	Cancer	NR	47.3	46.0	NR	93.2	82.0	86.0
	No Cancer	NR	77.6	85.0	NR	93.6	85.0	93.0
	p Value	NR	0.01	0.24	NR	0.96	ns	0.12
Renal Imp (%)	Cancer	NR	NR	NR	NR	34.3	24.0	18.0
	No Cancer	NR	NR	NR	NR	30.0	22.0	40.0
	p Value	NR	NR	NR	NR	0.30	ns	0.002
Previous CVA (%)	Cancer	NR	0	4	NR	10.4	18.0	9.0
	No Cancer	NR	6.1	8	NR	9.8	14.0	12.0
	p Value	NR	0.6	<0.001	NR	0.90	ns	0.60
Lung Disease (%)	Cancer	NR	47.3	50	NR	20.0	NR	21.0
	No Cancer	NR	36.9	35	NR	16.9	NR	16.0
	p Value	NR	0.37	0.15	NR	0.27	NR	0.40
PVD (%)	Cancer	NR	10.5	12.0	NR	11.2	10.0	27.0
	No Cancer	NR	33.5	4.0	NR	11.7	11.0	29.0
	p Value	NR	0.04	<0.001	NR	0.56	ns	0.70
NYHA III-IV (%)	Cancer	NR	73.6	81.0	NR	79.3	NR	82.1
	No Cancer	NR	86.6	88.0	NR	77.1	NR	79.0
	p Value	NR	0.17	0.001	NR	0.70	NR	0.63