Circulation Journal
Circ J 2019; 83: 452–460
doi:10.1253/circj.CJ-18-0609

ORIGINAL ARTICLE
Valvular Heart Disease

Infective Endocarditis in Cancer Patients

— Causative Organisms, Predisposing Procedures, and Prognosis Differ From Infective Endocarditis in Non-Cancer Patients —

Kyu Kim, MD; Darae Kim, MD; Sang-Eun Lee, MD; In Jeong Cho, MD;
Chi Young Shim, MD, PhD; Geu-Ru Hong, MD, PhD; Jong-Won Ha, MD, PhD

Background: Infective endocarditis (IE) in cancer patients is increasing, but because little is known about it in these patients, we analyzed patient characteristics and outcomes and compared these factors in IE patients with and without cancer.

Methods and Results: This retrospective cohort study included 170 patients with IE newly diagnosed between January 2011 and December 2015. Among 170 patients, 30 (17.6%) had active cancer. The median age of IE patients with cancer was higher than that of non-cancer patients. Nosocomial IE was more common in cancer patients. Non-dental procedures, such as intravenous catheter insertion and invasive endoscopic or genitourinary procedures, were more frequently performed before IE developed in cancer patients. *Staphylococcus* was the most common pathogen in cancer patients, whereas *Streptococcus* was the most common in non-cancer patients. In-hospital mortality was significantly higher in cancer patients with IE (34.4% vs. 12.4%, P<0.001). IE was an important reason for discontinuing antitumor therapy and withholding additional aggressive treatment in nearly all deceased cancer patients.

Conclusions: IE is common in cancer patients and is associated with poorer outcomes. Patients with IE and cancer have different clinical characteristics. Additional studies regarding antibiotic prophylaxis before non-dental invasive procedures in cancer patients are needed, as cancer patients are not considered to be at higher risk of IE.

Key Words: Antibiotic prophylaxis; Cancer; Endocarditis

Infective endocarditis (IE) is an uncommon but life-threatening disease.[1] Despite advances in diagnosis, antimicrobial therapy, surgical techniques, and management of complications, the 1-year mortality rate of patients with IE is almost 30%.[1,2] Recent studies have shown remarkable changes in the epidemiological and clinical features of IE. In the past, IE mainly occurred in the younger population (30–40 years old), and the most common pathogen was the viridans group *Streptococcus*, which is part of the normal oral flora.[3] However, the incidence of IE has recently increased in patients aged more than 50 years, and the most common bacterial organism is now *Staphylococcus aureus*.[3,4] Transient bacteremia is known to be a precursor to the development of IE.[5] Therefore, oral antibiotic prophylaxis (AP) has been recommended for patients at risk of developing IE who are undergoing a dental procedure. However, recent European Society of Cardiology, American Heart Association/American College of Cardiology, and National Institute for Health and Care Excellence guidelines have recommended restricting the use of AP, to varying degrees.[5–7] In the elderly, degenerative valve disease, diabetes, and cancer have become the major risk factors for IE.[1] A recent study reported that patients with colorectal, lung, or prostate cancer had a substantially higher incidence of IE than did non-cancer patients.[8] Furthermore, a recent study showed an association between invasive procedures and the development of IE.[9] Cancer patients may constitute a special risk group for the development of IE because they are often subjected to invasive procedures.[10] However, little is known regarding the incidence, provoking factors, and outcomes of IE in patients with cancer. Moreover, it is unclear whether the same principles for AP can be applied in cancer patients. The aims of this study were to determine the clinical characteristics and outcomes of IE patients with cancer and to compare them with IE patients without cancer.

Methods

The study protocol was approved by the Institutional

Received May 22, 2018; revised manuscript received September 27, 2018; accepted October 31, 2018; J-STAGE Advance Publication released online December 15, 2018 Time for primary review: 34 days
Cardiology Division, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
Mailing address: Jong-Won Ha, MD, PhD, FESC, Cardiology Division, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea. E-mail: jwha@yuhs.ac
ISSN-1346-9843

Table 1. Clinical Characteristics of Study Patients With Infective Endocarditis

	Total (n=170)	No cancer (n=140)	Cancer (n=30)	P value
Age, median [IQR]	57.0 [44.0, 67.0]	55.0 [39.5, 66.0]	62.5 [51.0, 69.0]	0.01
Sex (male)	118 (69.4%)	99 (70.7%)	19 (63.3%)	0.5
Underlying conditions				
Structural heart disease	73 (42.9%)	62 (44.3%)	11 (36.7%)	0.57
Bicuspid aortic valve	16 (9.4%)	15 (10.7%)	1 (3.3%)	0.36
Other congenital heart disease	22 (12.9%)	17 (12.1%)	5 (16.7%)	0.71
Degenerative valve disease*	35 (20.6%)	30 (21.4%)	5 (16.7%)	0.74
Previous cardiac surgery	5 (2.9%)	4 (2.9%)	1 (3.3%)	>0.999
Previous IE	5 (2.9%)	5 (3.6%)	0 (0%)	0.65
Diabetes mellitus	24 (14.1%)	19 (13.6%)	5 (16.7%)	0.88
End-stage renal disease	6 (3.5%)	5 (3.6%)	1 (3.3%)	>0.999
Liver cirrhosis	7 (4.1%)	4 (2.9%)	3 (10.0%)	0.20
Autoimmune disease	5 (2.9%)	5 (3.6%)	0 (0%)	0.65
Atrial fibrillation	22 (12.9%)	19 (13.6%)	3 (10.0%)	0.20
COPD	7 (4.1%)	6 (4.3%)	1 (3.3%)	>0.999
HIV infection	0 (0%)	0 (0%)	0 (0%)	>0.999
IV drug use	0 (0%)	0 (0%)	0 (0%)	>0.999
Alcohol abuse	8 (4.7%)	8 (5.7%)	0 (0%)	0.39
Charlson score, median [IQR]	2.0 [1, 3]	2.0 [1, 3]	6.0 [4, 8]	<0.001
Except cancer status	2.0 [1, 3]	2.0 [1, 3]	1.5 [1, 3]	0.93
Site of acquisition				0.003
Community-acquired	111 (65.3%)	99 (70.7%)	12 (40.0%)	0.003
Nosocomial	41 (24.1%)	27 (19.3%)	14 (46.7%)	0.003
Healthcare-related	18 (10.6%)	14 (10.0%)	4 (13.3%)	0.83
Affected valve				
Aortic valve (AV) only	39 (22.9%)	31 (22.1%)	8 (26.7%)	0.77
Mitral valve (MV) only	88 (51.8%)	72 (51.4%)	16 (53.3%)	>0.999
Tricuspid valve (TV) only	11 (6.5%)	7 (5.0%)	4 (13.3%)	0.20
Pulmonary valve only	2 (1.2%)	2 (1.4%)	0 (0%)	>0.999
Two-valve IE	28 (16.5%)	26 (18.6%)	2 (6.7%)	0.19
AV+MV	26 (15.3%)	24 (17.1%)	2 (6.7%)	0.24
AV+TV	2 (1.2%)	2 (1.4%)	0 (0%)	>0.999
Three-valve IE	2 (1.2%)	2 (1.4%)	0 (0%)	>0.999

*Defined as moderate-severe degree of any heart valve insufficiency or stenosis. COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; IQR, interquartile range; IV, intravenous; HIV, human immunodeficiency virus.

Review Board of Severance Cardiovascular Hospital, Seoul, Korea, and complied with the Declaration of Helsinki. Individual consent forms were deemed as not required because of the retrospective study design. Consecutive patients with IE diagnosed in a single center between January 1, 2011, and December 31, 2015, were included in the study. A comparative analysis was performed between IE patients with and without cancer. The index date was the date of IE diagnosis at admission. We extracted samples of patients with similar cancer stage, and treatment policy from the non-IE cancer population during the same period. All medical records of all patients included in the study were retrospectively reviewed.

All study patients met the modified Duke criteria for definite or possible IE.[11,12] The site of IE acquisition was defined following the International Collaboration on Endocarditis recommendations.[13] In brief, community-acquired IE was defined as IE diagnosed within the first 48 h of admission in a patient who did not fulfill the criteria for nosocomial or healthcare-associated infection. Nosocomial IE was defined as IE in a patient who had been hospitalized for >48 h before the onset of signs or symptoms consistent with IE. Healthcare-associated IE was defined as IE diagnosed within 48 h of admission or in an outpatient with any of the following criteria:[14] intravenous therapy, wound care, or specialized nursing care at home within the 30 days before the onset of IE; attendance at a hospital or hemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of IE; hospitalization in an acute-care hospital for ≥2 days during the 90 days before the onset of IE; or residence in a nursing home or long-term care facility. The surgical indication for IE was defined as follows: uncontrolled heart failure or cardiogenic shock, uncontrolled infection, vegetation >10 mm with previous embolization or isolated vegetation >15 mm, or presence of neurologic complications.[5,6]

All patients in the cancer group were histologically diagnosed with cancer of any type prior to IE. Cancer was defined as solid tumor with or without distant localization

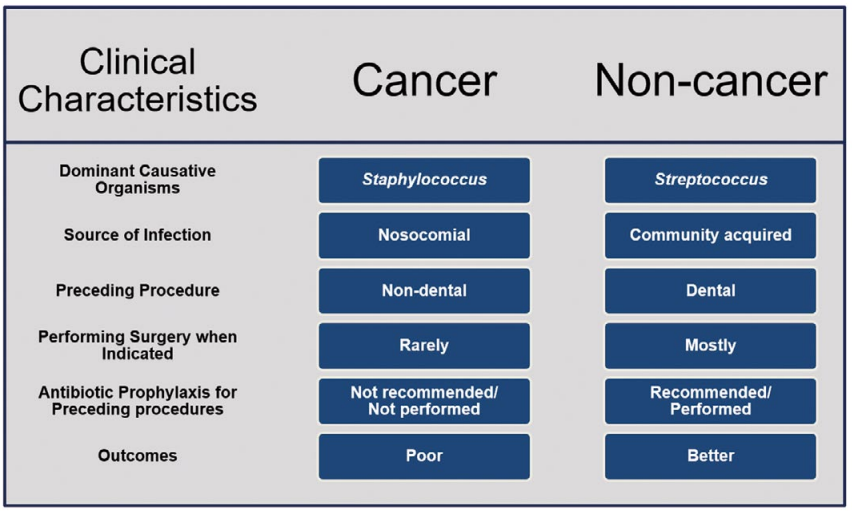

Figure 1. Different characteristics of infective endocarditis in the patients with or without cancer.

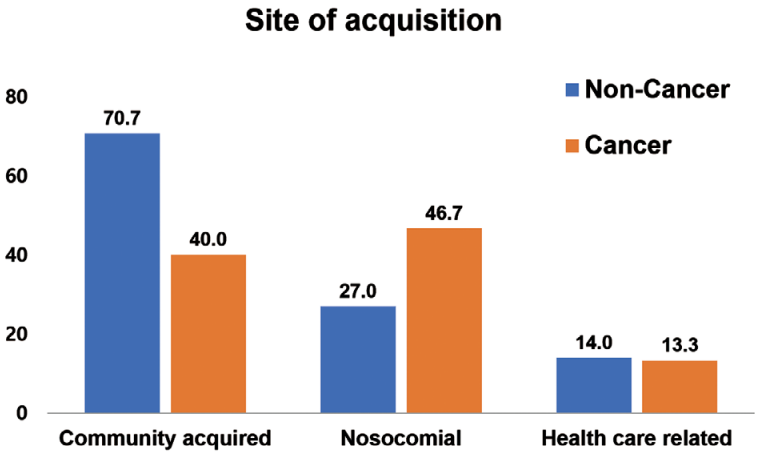

Figure 2. Acquisition site of infective endocarditis in patients with and without cancer.

or hematologic malignancy. Time of cancer diagnosis was defined as histologically confirmed. Duration of cancer was defined as the time from cancer diagnosis to IE development. Cancer stage was divided into 3 groups: localized (cancer found only in the tissue or organ of origin, and no spread to other parts of the body), locally advanced (cancer spread outside the organ of origin, but not to distant parts of the body), and metastatic (cancer spread to other parts of the body). Current cancer status was categorized as no evidence of disease, ongoing antitumor therapy, or no further treatment. Antitumor therapy included chemotherapy, radiation, and surgery.

The Charlson comorbidity index was used as a method of categorizing the comorbidities of the patients.[15] A central nervous system event was defined as an acute neurological deficit of vascular etiology lasting >24 h.[16] Systemic embolization was defined as an embolic event including ischemic stroke. Congestive heart failure was defined and classified according to the American College of Cardiology Foundation/American Heart Association staging system.[17] Predisposing factors consisted of a dental procedure involving a periodontal procedure; a gastrointestinal procedure, including enteroscopy, percutaneous endoscopic gastrostomy, and endoscopic biopsy; and a genitourinary procedure, including prostate biopsy, ureteral stent insertion, and percutaneous nephrostomy catheter insertion. Other invasive procedures such as tissue biopsy, central venous catheterization, chemoport implantation, and percutaneous drainage catheter insertion were also considered predisposing factors. Patients with a prosthetic valve, a permanent pacemaker, or a cardioverter-defibrillator were excluded from the study.

Statistical Analysis

Normally distributed continuous variables are presented as the mean±standard deviation. Non-normally distributed variables are presented as the median and interquartile range. Variables were compared using Student's t-test for parametric data and the Mann-Whitney test for non-parametric data. Categorical variables are presented as

Table 2. Etiology, Diagnosis, and Outcomes of Study Patients With Infective Endocarditis

	Total (n=170)	No cancer (n=140)	Cancer (n=30)	P value
Diagnosis				0.53
Definite IE	140 (82.4%)	117 (83.6%)	23 (76.7%)	
Possible IE	30 (17.6%)	23 (16.4%)	7 (23.3%)	
Etiology				
Staphylococcus species	31 (18.2%)	23 (16.4%)	8 (26.7%)	0.29
MSSA	13 (7.6%)	10 (7.1%)	3 (10.0%)	0.88
MRSA	8 (4.7%)	5 (3.6%)	3 (10.0%)	0.30
MSCoNs	6 (3.5%)	5 (3.6%)	1 (3.3%)	>0.999
MRCoNs	4 (2.4%)	3 (2.1%)	1 (3.3%)	>0.999
Streptococcus species	71 (41.8%)	64 (45.7%)	7 (23.3%)	0.04
Viridans group streptococci	57 (33.5%)	53 (37.9%)	4 (13.3%)	0.02
Other streptococci	14 (8.2%)	11 (7.9%)	3 (10.0%)	0.98
Enterococcus	17 (10.0%)	11 (7.9%)	6 (20.0%)	0.09
HACEK	5 (2.9%)	5 (3.6%)	0 (0%)	0.65
Other gram-positives	1 (0.6%)	1 (0.7%)	0 (0%)	>0.999
Gram-negative	2 (1.2%)	2 (0.7%)	1 (3.3%)	>0.999
Fungi	1 (0.6%)	1 (0.7%)	0 (0%)	>0.999
Negative blood culture	39 (22.9%)	32 (22.9%)	7 (23.3%)	>0.999
Multiple organism	2 (1.2%)	1 (0.7%)	1 (3.3%)	>0.999
Predisposing factors				
Dental procedures	7 (4.1%)	7 (5.0%)	0 (0%)	0.46
GI or GU procedure	8 (4.7%)	4 (2.9%)	4 (13.3%)	0.05
Invasive procedure ≤60 days	27 (15.9%)	17 (12.1%)	10 (33.3%)	0.009
Clinical course				
Stroke	62 (36.5%)	51 (36.4%)	11 (36.7%)	>0.999
Other systemic embolism	29 (17.1%)	25 (17.9%)	4 (13.3%)	0.74
Heart failure	83 (48.8%)	69 (49.3%)	14 (46.7%)	0.95
Atrioventricular block	10 (5.9%)	9 (6.4%)	1 (3.3%)	0.82
Surgery				
Indicated	137 (80.6%)	119 (85.0%)	20 (66.7%)	0.04
Performed	110 (64.7%)	104 (74.3%)	6 (20.0%)	<0.001
Outcomes				
Median hospital days, IQR	36 [25, 49]	32 [25.5, 43]	34.5 [13, 49]	0.65
In-hospital death	33 (19.4%)	17 (12.1%)	16 (53.3%)	<0.001
1-year death	39 (22.9%)	18 (12.9%)	21 (70.0%)	<0.001

GI, gastrointestinal; GU, genitourinary; HACEK, *Haemophilus* species, *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*; IE, infective endocarditis; IQR, interquartile range; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSCoNs, methicillin-sensitive coagulase negative *Staphylococcus*; MRCoNs, methicillin-resistant coagulase negative *Staphylococcus*.

number (percentage), and variables were compared using the chi-square test or Fisher's exact test. Adjusted odds ratios were computed using logistic regression analysis. Stepwise logistic regression analysis was performed including variables with a P-value <0.1 in the univariate analysis. P<0.05 was considered statistically significant.

Results

A total of 170 patients were enrolled in the study, and 30 (17.6%) had active cancer. Baseline characteristics, predisposing factors, and site of acquisition are shown in **Table 1**. The median age was 62.5 years for IE patients with cancer and 55.0 years for IE patients without cancer. The median duration of cancer was 381.0 (interquartile range 37.0–872) days. Among the cancer group, 11 (36.7%), 4 (13.3%), and 15 (50.0%) IE events occurred within 6, within 6–12, and after 12 months of the cancer diagnosis, respectively; 4 (13.3%) cancer patients developed IE after 5 years from the cancer diagnosis. There was no recurrent IE in the cancer group; 73 patients (42.9%) had structural heart disease and diabetes mellitus was the most common comorbidity. There were no patients with human immunodeficiency virus infection, and there were no intravenous drug users in our study population. Only 5 (2.9%) of the patients had a history of a prior IE event and 5 (2.9%) of the patients had had previous cardiac surgery. The median Charlson comorbidity index score was 6.0 in the non-cancer IE group and 2.0 in IE patients with cancer (P<0.001). **Figure 1** schematically demonstrates the different characteristics of IE in the cancer and non-cancer groups.

The sites of acquisition for each group are shown in

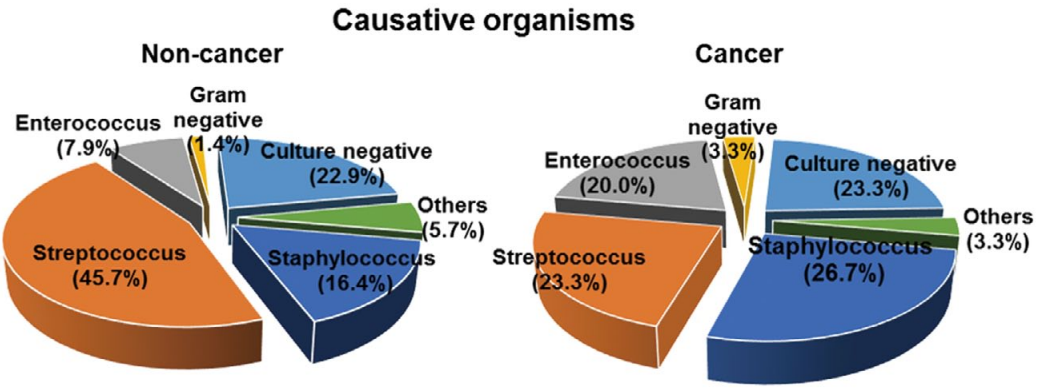

Figure 3. Causative organisms of infective endocarditis in patients with and without cancer.

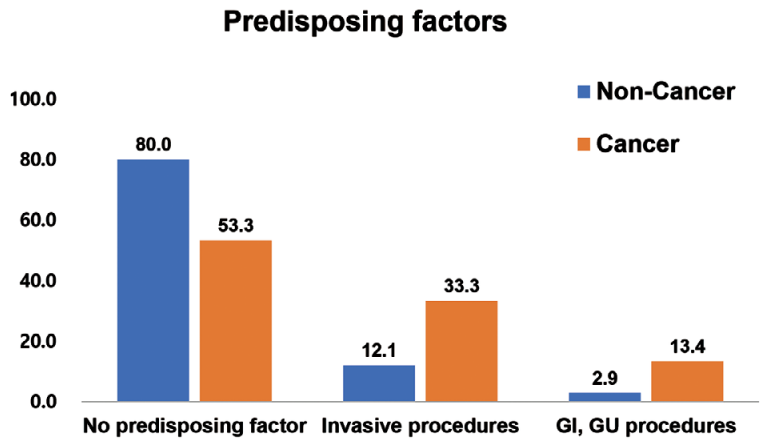

Figure 4. Predisposing factors of infective endocarditis in patients with and without cancer. Invasive procedures included tissue biopsy, central venous catheterization, chemoport implantation, and percutaneous drainage catheter insertion; gastrointestinal (GI) procedures included enteroscopy, percutaneous endoscopic gastrostomy, and endoscopic biopsy; genitourinary (GU) procedures included prostate biopsy, ureteral stent insertion, and percutaneous nephrostomy catheter insertion.

Table 1 and **Figure 2**. In this regard, 99 (70.7%) IE patients without cancer were classified as having community-acquired IE and 12 IE patients with cancer (40%) were classified as having community-acquired IE (P=0.003). Overall, 18 IE patients with cancer (60%) had nosocomial or healthcare-related infections; this difference in the site of acquisition was statistically significant (P=0.003). All patients in this study had native valve IE. The mitral valve was the most common site of infection (67.6% of patients had infection only in the mitral valve). There was no pulmonary valve involvement in IE patients with cancer. When compared with non-IE cancer patients, cancer patients with IE had more history of structural heart disease (36.7% vs. 13.5%, P=0.005). Other baseline characteristics were not significantly different between the groups. All-cause deaths occurred more in the IE-cancer group during the entire follow-up (70% vs. 35%, P=0.005, **Supplementary Table**). Median survival days from cancer diagnosis were not significantly different between the groups.

Etiology and clinical outcomes are shown in **Table 2** and **Figure 3**, respectively. Streptococcal infection was the most common etiology in the non-cancer group (45%). However, *Staphylococcus* was the most common pathogen isolated in cancer patients (26.7%). *Enterococcus* was more commonly isolated in IE patients with cancer (20.0% vs. 7.9%, P=0.09). Approximately 23% of the total study population was classified as having culture-negative IE.

A total of 7 (4.1%) patients had undergone a dental procedure prior to the IE event. Gastrointestinal and genitourinary procedures were more frequently performed before an IE event in cancer patients (13.3% vs. 2.9%, P=0.047). Other invasive procedures, such as tissue biopsy, central venous catheterization, chemoport implantation, and percutaneous drainage catheter insertion, were also more frequently performed in IE patients with cancer than in IE patients without cancer (33.3% vs. 12.1%, P=0.009). Predisposing factors for IE patients are shown in **Figure 4**. *Staphylococcus* was the most common isolate (50.0%) in IE patients with cancer who had undergone an invasive procedure before the onset of IE. *Streptococcus* (50%) and *Enterococcus* (25%) were the most common isolates in those patients undergoing a gastrointestinal or genitourinary procedure. There was no significant difference in clinical complications, including stroke, other systemic embolism, heart failure, and atrioventricular block, between IE patients with cancer and those without cancer. There was no significant difference in the median length of hospital stay between these 2 groups (34.5 vs. 32.0 days, respectively;

Table 3. Baseline Patient Characteristics, and Type, and Stage of Cancer at the Time of IE Diagnosis

	Cancer (n=30)	Survivor (n=14)	In-hospital death (n=16)	P value
Age, median [IQR]	62.5 [51.0, 69.0]	54.0 [49.0, 67.0]	65.0 [58.0, 70.0]	0.13
Sex	19 (63.3%)	9 (64.3%)	10 (62.5%)	>0.999
Charlson comorbidity score, median [IQR]	6.0 [4.0, 8.0]	4.5 [3.0, 6.0]	7.5 [6.5, 8.0]	0.01
Except cancer status	1.5 [1.0, 3.0]	1.0 [1.0, 3.0]	2.0 [1.0, 2.5]	0.22
Type of cancer				0.78*
Stomach	4 (13.3%)	2 (14.3%)	2 (12.5%)	
Colorectal	3 (10.0%)	1 (7.1%)	2 (12.5%)	
Hepatocellular carcinoma	4 (13.3%)	2 (14.3%)	2 (12.5%)	
Head and neck	3 (10.0%)	2 (14.3%)	1 (6.2%)	
Thyroid	1 (3.3%)	1 (7.1%)	0 (0%)	
Lung	2 (6.7%)	1 (7.1%)	1 (6.2%)	
Hematologic	6 (20.0%)	4 (28.6%)	2 (12.5%)	
Breast	1 (3.3%)	0 (0%)	1 (6.2%)	
Ovary	2 (6.7%)	1 (7.1%)	0 (0%)	
Biliary tract	1 (3.3%)	0 (0%)	1 (6.2%)	
Bladder	2 (6.7%)	0 (0%)	2 (12.5%)	
Primary unknown	1 (3.3%)	0 (0%)	1 (6.2%)	
Stage				0.01
Localized	7 (23.4%)	6 (42.9%)	1 (6.2%)	0.05
Locally advanced	4 (13.3%)	3 (21.4%)	1 (6.2%)	0.50
Metastatic	19 (63.3%)	5 (35.7%)	14 (87.5%)	0.01
Status				0.09
No evidence of disease	8 (26.7%)	6 (42.9%)	2 (12.5%)	0.14
Ongoing antitumor therapy	16 (53.3%)	6 (42.9%)	9 (56.2%)	>0.999
No further treatment	6 (20.0%)	1 (7.1%)	5 (31.2%)	0.23

*All P values in specific cancer diagnosis were not significant. IE, infective endocarditis; IQR, interquartile range.

P=0.648). However, in-hospital mortality was significantly higher in IE patients with cancer than in IE patients without cancer (53.3% vs. 12.1%, respectively; P<0.001). IE patients with cancer had a higher 1-year mortality rate than did IE patients without cancer (70.0% vs. 12.9%, respectively; P<0.001). Cancer type and stage at the time of IE diagnosis are shown in **Table 3**. Hematologic malignancy, gastric malignancy, and hepatocellular carcinoma were the most common cancers in our study group; 19 patients (63.3%) had metastatic cancer. With regard to cancer status, 8 (26.3%) patients were in remission, 16 (53.3%) patients were currently receiving antitumor therapy, and 6 (20.0%) patients were receiving palliative care without antitumor therapy. There was no significant difference in the cancer type, current cancer status, and comorbidity index scores (excluding cancer status) between patients who died or survived during hospitalization. However, a significantly higher percentage of patients who died during hospitalization had metastatic cancer compared with those who did not die during hospitalization (87.5% vs. 35.7%, respectively; P=0.01).

Although 20 (66.7%) of 30 patients with IE and cancer were considered to meet the indications for surgery, only 6 (20%) of these patients underwent surgical treatment. The most common type of cancer was hematologic malignancy (33.3%), and no metastatic cancer patient underwent surgery for IE. Meanwhile, in the non-cancer IE group, among the 119 (85%) patients who met the indications for surgery, 104 (74.3%) patients were treated surgically. Patients' baseline characteristics and clinical outcomes according to treatment strategy are shown in **Table 4**. The median age was 54 years in patients who underwent surgery and 65 years in patients not undergoing surgery (P=0.06). The Charlson comorbidity index score (excluding cancer status) was 1.5 in IE patients undergoing surgery and 2.0 in IE patients not treated surgically (P=0.90). Patients with metastatic cancer did not undergo surgery. IE patients with cancer who underwent surgical treatment showed no in-hospital or 1-year deaths; 13 of 14 patients who did not undergo surgery died during hospitalization (P=0.001).

Discussion

There are several key findings in the current study. First, IE was not uncommon in cancer patients (18%) and was associated with a poorer outcome. Second, cancer patients with IE were infected with different causative organisms and frequently had undergone a non-dental procedure before the development of IE. This is clinically important because cancer patients are not considered at a higher risk for IE; therefore, AP is not recommended for cancer patients in the current guidelines. Further prospective studies are needed to clarify the need for AP before non-dental invasive procedures in cancer patients. Third, the occurrence of IE had prognostic relevance in cancer patients. IE was an important reason for the discontinuation of antitumor therapy and the denial of further aggressive treatment in almost all cancer patients who died.

Previous studies have reported increased nosocomial or

Table 4. Baseline Patient Characteristics and Clinical Outcome According to Treatment Policy

	Indicated for surgery (n=20)	Medical treatment only (n=14)	Surgical treatment (n=6)	P value
Age, median [IQR]	62.5 [52.5, 67.0]	65.0 [58.0, 69.0]	54.0 [49.0, 63.0]	0.06
Sex	14 (70.0%)	10 (71.4%)	4 (66.7%)	>0.999
Charlson comorbidity score, median [IQR]	5.5 [3.5, 8.0]	7.0 [5.0, 8.0]	3.5 [3.0, 5.0]	0.01
Except cancer status	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	1.5 [1.0, 3.0]	0.90
Type of cancer				0.61*
Stomach	2 (10.0%)	1 (7.1%)	1 (16.7%)	
Colorectal	2 (10.0%)	2 (14.3%)	0 (0%)	
Hepatocellular carcinoma	3 (15.0%)	2 (14.3%)	1 (16.7%)	
Head and neck	2 (10.0%)	1 (7.1%)	1 (16.7%)	
Thyroid	1 (5.0%)	0 (0%)	1 (16.7%)	
Lung	2 (10.0%)	2 (14.3%)	0 (0%)	
Hematologic	4 (20.0%)	2 (14.3%)	2 (33.3%)	
Breast	0 (0%)	0 (0%)	0 (0%)	
Ovary	0 (0%)	0 (0%)	0 (0%)	
Biliary tract	1 (5.0%)	1 (7.1%)	0 (0%)	
Bladder	2 (10.0%)	2 (14.3%)	0 (0%)	
Primary unknown	1 (5.0%)	1 (7.1%)	0 (0%)	
Stage				0.005
Localized	5 (25.0%)	2 (14.3%)	3 (50.0%)	0.26
Locally advanced	4 (20.0%)	1 (7.1%)	3 (50.0%)	0.11
Metastatic	11 (55.0%)	11 (78.6%)	0 (0%)	0.006
Status				0.11
No evidence of disease	7 (35.0%)	3 (21.4%)	4 (66.7%)	0.15
Ongoing antitumor therapy	9 (45.0%)	7 (50.0%)	2 (33.3%)	>0.999
No further treatment	4 (20.0%)	4 (28.6%)	0 (0%)	0.39
Outcome				
Hospital days, IQR	32 [12.0, 51.5]	22.0 [10.0, 47.0]	34.4 [30.0, 54.0]	0.14
In-hospital death	13 (65.0%)	13 (92.9%)	0 (0%)	0.001
1-year death	13 (65.0%)	13 (92.9%)	0 (0%)	0.07

*All P values in specific cancer diagnosis were not significant. IQR, interquartile range.

healthcare-associated IE in cancer patients.[4,8,10] Demographic features of patients with nosocomial or healthcare-associated IE include older age, concomitant hemodialysis, cancer, diabetes mellitus, and the presence of intracardiac devices rather than intrinsic cardiac risk factors.[1,18] Our single-center retrospective study also showed that the rates of nosocomial and healthcare-associated IE were higher in cancer patients than in non-cancer patients. There was no significant difference in comorbidities, excluding cancer status, between these 2 groups. Cancer patients did have a lower rate of concomitant structural heart disease, although this difference was not statistically significant. In previous studies, the incidence of structural heart disease in IE was reported to be 30–50%,[1,8] but the incidence was lower in the cancer patients in our study. Most patients had unknown status without any cardiac examination before the IE event. In-hospital and 1-year mortality rates were significantly higher in IE patients with cancer compared with IE patients without cancer. Although the overall mortality rate of IE is known to be around 30%,[1,19] the overall mortality rate in our study was lower. However, the mortality rate of IE in patients with cancer was much higher than that seen in IE patients without cancer. In particular, there were no survivors from IE among those with metastatic cancer. Although this finding could be biased, it suggests that prevention of IE in metastatic cancer patients is quite important in real-world practice. Despite these findings, current guidelines do not classify the presence of cancer as an indication for AP.[5–7]

Recent studies have shown that *S. aureus* is the most common cause of IE and that infection with this organism is associated with a higher mortality rate.[4,20,21] Overall, *Streptococcus* was the most common pathogen in our study, but *Staphylococcus* was the most common causative organism in IE patients with cancer. In addition, *Streptococcus* and *Enterococcus* were also more commonly isolated in IE patients with cancer than in IE patients without cancer. Enterococcal IE was more common after gastrointestinal or genitourinary procedures, whereas *Staphylococcus* was the most common pathogen after a preceding invasive procedure such as tissue biopsy, central venous catheterization, chemoport implantation, and percutaneous drainage catheter insertion. When considering the causative organism, it is likely that a preceding procedure may be the causative factor of IE. These findings further underscore the potential benefits of AP prior to procedures in cancer patients. In this study, about 23% of cancer patients had culture-negative IE, a rate higher than reported in a previous study.[1] Cancer is the most common cause of non-bacterial thrombotic endocarditis.[22] However, in this study, all the

patients had a high fever and elevated inflammatory marker levels, suggesting that non-bacterial thrombotic endocarditis is less likely in cancer patients with negative blood cultures. In addition, a similar percentage of patients in the non-cancer group were found to have a negative culture. Furthermore, in some patients, antibiotics were used because of fever without a preceding blood culture before referral. Among the cancer patients, those with a fever received empiric antibiotics before appropriate testing, because of their immune deficiency status, which may also be the reason for the larger number of patients with culture-negative IE.

Surgery was less frequently performed in cancer patients, so the subsequent mortality rate was significantly higher. Only one-fifth of the IE patients with cancer underwent surgery, and the in-hospital mortality rate was 53.3%. By contrast, 74.3% of IE patients without cancer underwent surgery, and the in-hospital mortality rate was 12.1%. Compared with previous studies, the IE mortality rate was higher in IE patients with cancer.[1] Although this increased mortality may be related to the prognosis of the underlying cancer, IE may be fatal in cancer patients, as suggested by the higher in-hospital mortality rate in these patients. Moreover, 11 (78.6%) of 14 cancer patients who did not undergo IE surgery had metastatic cancer and no patients with metastatic cancer underwent surgery; further, almost all patients died during their hospital stay. The reasons for not performing surgery were not available in our data. However, it is highly possible that patients decided not to undergo surgery because of poor prognosis and short life expectancy. In contrast, none of the IE patients with cancer who underwent surgery died during hospitalization. Although we cannot conclude that surgical treatment is associated with a good prognosis in IE patients with cancer, the patients who did not undergo surgery often had to discontinue antitumor therapy because of the endocarditis, and this may have further contributed to the deaths of these patients. Furthermore, IE might be fatal in terms of poor quality of life.

In our study, we found that IE in patients with cancer had different characteristics and etiologies compared with IE in patients without cancer. Moreover, IE in cancer patients was associated with a worse prognosis than that of IE patients without cancer. Our findings emphasize the importance of prevention, because active treatment of IE in patients with cancer is difficult, and antitumor therapy for the patient's underlying cancer is frequently abandoned. In IE patients with cancer, the prevalence of prior gastrointestinal, genitourinary, or other invasive procedures was higher than that seen in IE patients without cancer, and when considering causative organisms, one should keep in mind the high likelihood of IE secondary to an invasive procedure. Therefore, AP prior to invasive procedures should be considered in cancer patients. Further prospective studies are needed to confirm this suggestion.

Study Limitations

First, this was a retrospective and non-randomized study and has the inherent limitations. Second, the study population was small, and thus interpretation of the results may be limited. Because of the nature of the disease, it was difficult to obtain a large study population. Third, the cohort of our study was selected from among patients with IE, and not those with cancer. Thus, we were not able to provide incidence data of IE and IE risk factors in cancer populations. However, we found the specific characteristics of IE in cancer patients through comparison with patients having IE without cancer in terms of preceding invasive procedure, different causative microbes, and survival. Larger randomized multicenter trials focusing on cancer populations may help clarify these issues in the future.

Conclusions

IE is not uncommon in cancer patients and is associated with poorer outcomes. IE was an important reason for the discontinuation of antitumor therapy and the withholding of additional treatment in cancer patients. Patients with IE and cancer have different clinical characteristics, including site of acquisition, pathogen, and the frequency of non-dental procedures before the development of IE. Additional studies regarding AP before non-dental invasive procedures in cancer patients are needed.

References

1. Cahill TJ, Prendergast BD. Infective endocarditis. *Lancet* 2016; **387:** 882–893.
2. Chambers J, Sandoe J, Ray S, Prendergast B, Taggart D, Westaby S, et al. The infective endocarditis team: Recommendations from an international working group. *Heart* 2014; **100:** 524–527.
3. Mylonakis E, Calderwood SB. Infective endocarditis in adults. *N Engl J Med* 2001; **345:** 1318–1330.
4. Delahaye F, M'Hammedi A, Guerpillon B, de Gevigney G, Boibieux A, Dauwalder O, et al. Systematic search for present and potential portals of entry for infective endocarditis. *J Am Coll Cardiol* 2016; **67:** 151–158.
5. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, et al. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009; **30:** 2369–2413.
6. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; **116:** 1736–1754.
7. Richey R, Wray D, Stokes T, Guideline Development G. Prophylaxis against infective endocarditis: Summary of NICE guidance. *BMJ* 2008; **336:** 770–771.
8. Garcia-Albeniz X, Hsu J, Lipsitch M, Logan RW, Hernandez-Diaz S, Hernan MA. Infective endocarditis and cancer in the elderly. *Eur J Epidemiol* 2016; **31:** 41–49.
9. Janszky I, Gemes K, Ahnve S, Asgeirsson H, Moller J. Invasive procedures associated with the development of infective endocarditis. *J Am Coll Cardiol* 2018; **71:** 2744–2752.
10. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: Analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004; **39:** 309–317.
11. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. *Am J Med* 1994; **96:** 200–209.
12. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000; **30:** 633–638.
13. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, et al. Infective endocarditis in adults: Diagnosis, antimicrobial therapy, and management of complications: A scientific statement for healthcare professionals from the American Heart Association. *Circulation* 2015; **132:** 1435–1486.

14. Cockerill FR 3rd, Wilson JW, Vetter EA, Goodman KM, Torgerson CA, Harmsen WS, et al. Optimal testing parameters for blood cultures. *Clin Infect Dis* 2004; **38:** 1724–1730.
15. Charlson ME, Charlson RE, Peterson JC, Marinopoulos SS, Briggs WM, Hollenberg JP. The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008; **61:** 1234–1240.
16. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: A guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Circulation* 2007; **115:** e478–e534.
17. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **62:** e147–e239.
18. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, et al. Challenges in infective endocarditis. *J Am Coll Cardiol* 2017; **69:** 325–344.
19. Pericart L, Fauchier L, Bourguignon T, Bernard L, Angoulvant D, Delahaye F, et al. Long-term outcome and valve surgery for infective endocarditis in the systematic analysis of a community study. *Ann Thorac Surg* 2016; **102:** 496–504.
20. Fernandez-Hidalgo N, Almirante B, Tornos P, Pigrau C, Sambola A, Igual A, et al. Contemporary epidemiology and prognosis of health care-associated infective endocarditis. *Clin Infect Dis* 2008; **47:** 1287–1297.
21. Selton-Suty C, Celard M, Le Moing V, Doco-Lecompte T, Chirouze C, Iung B, et al. Preeminence of Staphylococcus aureus in infective endocarditis: A 1-year population-based survey. *Clin Infect Dis* 2012; **54:** 1230–1239.
22. Steiner I. Nonbacterial thrombotic endocarditis: A study of 171 case reports. *Cesk Patol* 1993; **29:** 58–60 (in Czech).

Supplementary Files

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-18-0609