Long-Term Central Venous Catheter Use and Risk of Infection in Older Adults With Cancer

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ABSTRACT

Purpose

Long-term central venous catheters (CVCs) are often used in patients with cancer to facilitate venous access to administer intravenous fluids and chemotherapy. CVCs can also be a source of bloodstream infections, although this risk is not well understood. We examined the impact of long-term CVC use on infection risk, independent of other risk factors such as chemotherapy, in a population-based cohort of patients with cancer.

Patients and Methods

We conducted a retrospective analysis using SEER-Medicare data for patients age > 65 years diagnosed from 2005 to 2007 with invasive colorectal, head and neck, lung, or pancreatic cancer, non-Hodgkin lymphoma, or invasive or noninvasive breast cancer. Cox proportional hazards regression was used to examine the relationship between CVC use and infections, with CVC exposure as a time-dependent predictor. We used multivariable analysis and propensity score methods to control for patient characteristics.

Results

CVC exposure was associated with a significantly elevated infection risk, adjusting for demographic and disease characteristics. For patients with pancreatic cancer, risk of infections during the exposure period was three-fold greater (adjusted hazard ratio [AHR], 2.93; 95% CI, 2.58 to 3.33); for those with breast cancer, it was six-fold greater (AHR, 6.19; 95% CI, 5.42 to 7.07). Findings were similar when we accounted for propensity to receive a CVC and limited the cohort to individuals at high risk of infections.

Conclusion

Long-term CVC use was associated with an increased risk of infections for older adults with cancer. Careful assessment of the need for long-term CVCs and targeted strategies for reducing infections are critical to improving cancer care quality.

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INTRODUCTION

For vulnerable patients with cancer, acquiring a bloodstream infection can delay treatment, lead to complications, or hasten death.¹⁻³ Well-recognized causes of infections include neutropenia resulting from cancer treatment or disease. Long-term central venous catheters (CVCs), which are placed to facilitate venous access to administer intravenous fluids and treatments, can also be a source of bloodstream infections as well as other complications.⁴ Despite the consequences, our understanding of the extent to which long-term CVCs increase patients' risk of infections independent of other risk factors is limited.

Recently, the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee highlighted the importance of infections related to CVC use and the need for additional re-

search targeting patients with cancer.⁵ Most research and infection prevention efforts related to CVC use have focused on the use of temporary catheters in the inpatient setting or on infections acquired in the hospital setting.^{4,6,7} However, patients with cancer with long-term CVCs often receive care across inpatient and outpatient settings and can have catheters implanted for several months or years. Institution-based studies have provided insight into the harms associated with use of long-term CVCs and risk factors for infections, but many of these studies are limited by small sample size or lack comprehensive data across care settings.^{3,4,8-10} Additional study of the harms associated with use of long-term CVCs in patients with cancer could help refine standards for their use, measure progress toward infection prevention, and quantify the expected impact of quality improvement interventions.

The objective of this study was to determine whether use of long-term CVCs is associated with an increased risk of infections for older adult patients with cancer. We also assessed whether observed relationships would hold for patient groups likely to be at high risk for infections, including older patients, those with more advanced disease, and those with multiple comorbidities. We hypothesized that the presence of a long-term CVC would increase infection risk compared with not having one and that this relationship would also be seen in high-risk patient subgroups.

PATIENTS AND METHODS

We performed a retrospective analysis using population-based SEER-Medicare data (2005 to 2009). We assessed the use of long-term CVCs as a potential risk factor for infections, independent of other risk factors such as chemotherapy.

Data Source

The SEER-Medicare database contains data from two linked population-based sources of information: the SEER cancer registries and Medicare enrollment and claims files. SEER, a consortium of population-based cancer registries sponsored by the National Cancer Institute, currently includes 17 registries covering approximately 26% of the US population.¹¹ SEER registries collect information on site and extent of disease, first course of cancer-directed therapy, and sociodemographic characteristics, with active follow-up for date and cause of death. For adults age ≥ 65 years who are diagnosed with cancer and reside in SEER regions, SEER records have been linked to Medicare claims. Compared with the US elderly population, the SEER-Medicare population has similar age and sex distributions, a slightly higher proportion of individuals living in urban and affluent areas, and a smaller proportion of nonwhite individuals.¹¹

Study Cohort

The study cohort included patients age ≥ 66 years diagnosed with invasive colorectal ($n = 36,272$), head and neck ($n = 8,459$), lung ($n = 56,770$), or pancreatic cancer ($n = 10,536$); non-Hodgkin lymphoma ($n = 14,432$); or invasive or noninvasive breast cancer ($n = 42,271$). We included patient cases diagnosed from 2005 (first year of more detailed Current Procedural Terminology [CPT] codes for long-term CVC use^{12,13}) through 2007. We observed patients for up to 2 years after diagnosis.

We excluded patients whose cancer diagnosis was made only at the time of death, beneficiaries enrolled in a Medicare managed care plan, and patients with incomplete Medicare coverage from the year before cancer diagnosis to ≤ 2 years after diagnosis. Patients were also excluded if they had received hemodialysis or received total parenteral nutrition (TPN) without also receiving chemotherapy.

Covariates and End Points

Demographic information from SEER and Medicare records included age at diagnosis, sex, race (classified as white, black, or other), marital status, urban-rural location, geographic region, and median income in the census tract of residence. We used a modified version of the Charlson comorbidity index as a summary measure of comorbidity burden.^{14,15} Inpatient and outpatient claims from 1 year before diagnosis were used to identify comorbid conditions. Disease and treatment characteristics included SEER historic stage and chemotherapy, radiation therapy, and cancer-directed surgery within 2 years of cancer diagnosis.¹⁶⁻¹⁸ We also searched claims for diagnosis of neutropenia and TPN administration during this period (Data Supplement provides relevant diagnosis and procedure codes).

For this study, we defined long-term CVCs as inclusive of the following device types, regardless of their duration of use: tunneled catheters (eg, Hickman), implanted catheters (eg, ports or pumps), and peripherally inserted central catheters (PICCs). CPT codes were used to identify insertion procedures from Medicare claims within 2 years of a patient's cancer diagnosis: 36558, 36561, 36563, 36566, 36571, and 36569. The current coding system

does not distinguish between tunneled and nontunneled PICCs, so analyses included both types. Insertions were considered unique by procedure date. For patients with codes for multiple catheter types on a single date, the default type assigned was implanted catheter, followed by tunneled catheter. To determine whether a patient had a long-term CVC removal, we used CPT codes 36589 and 36590. Removal of PICCs is not associated with a specific billing code, and we included only insertion information for this group.

The primary outcome was infection potentially related to catheter use. The validity of documentation for infections related to long-term CVC use in patients with cancer has not been extensively tested. Documentation of these infections may involve diagnosis codes that are also used to identify infections related to other sources. For this reason, we included International Classification of Diseases (ninth revision) Clinical Modification codes for infections likely to be relevant to CVC use based on clinical input (Data Supplement). To help confirm the validity of our code selection, we compared patient billing and medical record data for a sample of 270 patients with long-term CVC use at Memorial Sloan Kettering Cancer Center (MSKCC). Using the selected codes, we were able to identify approximately 72% of confirmed central line-associated bloodstream infections (CLABSIs). Of the infections we identified using billing codes, half were confirmed CLABSIs, and 31% were suspected CLABSIs (Data Supplement). For this study, a confirmed infection source was not required. We designed our analysis to assess whether long-term CVC use was related to infection risk more generally.

Statistical Analysis

We used [Cox proportional hazards regression](#) to assess whether use of a long-term CVC was associated with risk of infection. We adjusted for patient, disease, and treatment characteristics (age, sex, race, metropolitan region, geographic region, median income of census tract of residence, stage, comorbidity index, chemotherapy use, radiation therapy use, surgery, and TPN use). Time to event was measured from cancer diagnosis to index infection. Patients were censored at death or end of the 2-year follow-up period. CVC exposure was treated as a time-dependent covariate that switched on at the date of the index CVC insertion and switched off at the date of the last documented CVC removal. This method allowed a patient's information to contribute to the CVC group on days when the patient had a CVC and to the non-CVC group on days when the patient did not. Proportional hazards assumptions over time were assessed with residual plots and were not violated.

We included treatment characteristics (chemotherapy, surgery, radiation therapy, TPN) as time-dependent covariates, and separate analyses were performed by cancer site given differences in disease characteristics and treatment approaches. Because long-term CVC use was not assigned at random, and we observed significant differences in patient, disease, and treatment characteristics between patients with and without long-term CVC use, we used propensity scores to account for potential selection bias.¹⁹ For each cancer site cohort, the predicted probability of having a long-term CVC inserted at any time during follow-up was estimated for each patient using a logistic model that included all covariates potentially predictive of insertion. Multivariable models were then stratified by quintile of the propensity score distribution.

We conducted sensitivity analyses to assess the robustness of our findings regarding specific assumptions. We repeated the analysis including a broader list of infection codes (Data Supplement). We also repeated the analysis reclassifying PICCs as non-long-term CVCs, given the lack of CVC removal information.

To assess the consistency of our main effects, we conducted several subgroup analyses. We limited the sample to patients age ≥ 80 years, patients with ≥ 1 comorbidity, and patients with advanced-stage disease. We also conducted a subgroup analysis for patients with long-term CVCs to assess infection risk by different device types: tunneled catheter, implanted catheter, and PICC. For this model, we used time from CVC insertion to the infection event. For patients with long-term CVCs, we also estimated the proportion of infections documented between a hospital admission and discharge or followed by an admission within 7 days.

All analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC). We considered a two-sided P value $< .05$ to be statistically

significant. The National Cancer Institute approved the use of the SEER-Medicare database for this study, which was deemed exempt by the MSKCC Institutional Review Board.

RESULTS

By 2 years after cancer diagnosis, 13% to 30% of patients had a documented long-term CVC insertion, with the proportion varying by cancer site. A majority of long-term CVCs were implanted ports (66% to 82% by cancer site). Patients with and without long-term CVCs differed in age, stage of disease, and other characteristics (Table 1).

The proportion of patients who acquired an infection was higher among those who had a long-term CVC during the 2-year follow-up period compared with those who did not, for each cancer type (Table 2). Adjusting for demographic, disease, and treatment characteristics, the risk of infection increased significantly while the patient was exposed to a long-term CVC. The risk of infection increased three-fold for patients with pancreatic cancer (adjusted hazard ratio [AHR], 2.93; 95% CI, 2.58 to 3.33) and more than six-fold for patients with breast cancer (AHR, 6.19; 95% CI, 5.42 to 7.07; Table 2; Data Supplement provides full model). Several patient and disease characteristics were associated with infection risk, including stage of disease and comorbidity index (positive association) and treatment (negative association; Data Supplement). An analysis using propensity scores that accounted for patients' baseline risk of having a CVC inserted confirmed our results, although the magnitude of the effect was slightly attenuated (AHR, 2.34 to 5.41 by cancer site).

Expanding the definition of the primary end point by including additional infection codes did not substantially change the likelihood of infection in the group with long-term CVC use in our study (AHR, 2.65 to 7.84 by cancer site), nor did reclassifying PICCs as non-long-term CVCs (AHR, 2.72 to 4.72 by cancer site). Results held when we limited the cohort to high-risk subgroups only: patients age $\geq$ 80 years, those with $\geq$ one comorbid condition, and those with advanced-stage disease (Table 3).

Among patients with long-term CVCs, by 1 month after insertion, 3% to 8% had an infection; by 3 months, 6% to 16% had an infection (Data Supplement provides Kaplan-Meier curves by cancer site). Most infections were documented between a patient's hospital admission and discharge or were followed by an admission within 7 days (75% to 89% by cancer site). In unadjusted analyses, patients with tunneled catheters and PICCs had higher proportions of documented infections than patients with implanted catheters for all cancer sites (range of infection rates by site: implanted catheters, 13% to 27%; tunneled catheters, 23% to 41%; PICCs, 22% to 43%). These findings remained significant in the adjusted model for patients with breast cancer, lung cancer, or NHL but not for patients with head and neck or pancreatic cancer. For patients with colorectal cancer, the difference in infection risk remained significant between tunneled and implanted catheters but not between PICCs and implanted catheters.

DISCUSSION

Our analysis in a large population-based cohort supports the hypothesis that long-term CVC use increases the likelihood of bloodstream

infections in older adults with cancer. This effect seems present independent of chemotherapy use.

Prior estimates of infection rates related to long-term CVCs for patients with cancer have varied widely based on setting, sample characteristics, device type, and infection definition.^{3,9,10,20} In one analysis that pooled infection estimates from institution-based studies of patients with and without cancer, the mean infection rate per 100 devices was 3.6 for implanted ports, 22.5 for tunneled CVCs, and 3.11 for PICCs (per 1,000 device days, 0.1, 1.6, and 1.6, respectively).⁴ We observed $\geq$ three-fold increase in infection risk for patients with cancer with long-term CVC exposure, controlling for patient, disease, and treatment characteristics and exposure time.

Given the nonrandom assignment of CVC use in our cohort, confounding by indication could theoretically have influenced our results. However, the consistency of our results with those of prior studies and inclusion of key characteristics support our finding that long-term CVC use is associated with increased infection risk for patients with cancer age $\geq$ 66 years. We also observed consistent and statistically significant effects when we accounted for the propensity to receive a CVC, excluded PICCs from the long-term CVC definition, limited the cohort to high-risk subgroups, and broadened the diagnosis codes used in our definition of infection. Although we observed a negative association between treatments and infection risk, this finding is most likely explained by the selection of healthier patients for treatment, who are consequently less prone to adverse events such as infections. Across cancer sites, we observed lower infection rates for patients with implanted catheters compared with patients with tunneled catheters or PICCs, consistent with prior studies.⁴ In the adjusted model, these relationships were mixed, suggesting that other patient or treatment characteristics may be related to the use of different CVC types and therefore differences in infection risk.

Although prior studies have demonstrated limited value of claims for identifying hospital-acquired infections related to temporary catheters, use of claims as a data source for studying complications of long-term CVCs is supported.^{21,22} Distinguishing between infections that occurred before or during hospitalization is not relevant for long-term CVCs, because they are often used across settings of care. Also, long-term CVC insertions and removals are associated with specific billing codes in Medicare claims, which allows for a defined infection exposure period. These codes have not been extensively validated, but they were changed in 2004 in response to concerns about the specificity of the coding options.^{12,13} The percent breakdown of long-term CVC types observed in this cohort based on these codes also supports their use for accurate reporting.

Because the infection codes used in this study have not been extensively validated, it would be appropriate to be circumspect when evaluating the magnitude of the observed increase in risk associated with use of long-term CVCs in our analysis. That our local validation study at MSKCC found that the infection codes used in this study generally represented infections or suspected infections associated with CVC use tempers concerns about overestimation to some extent. We also designed our analysis to account for imprecise coding, consistently picking up infections unrelated to CVC use in patients with and without long-term CVCs.

Certain methodologic decisions and data limitations may have affected our estimates. First, we may have overaccounted for CVC exposure time in some patients and underaccounted for it in others. CVC removal information may be incomplete, patients' CVC use may

Table 1. Characteristics of Medicare Beneficiaries Age $\geq$ 66 Years With Cancer (diagnosed 2005 to 2007) With and Without Long-Term CVC Use

Characteristic*	Breast Cancer (%)		Colorectal Cancer (%)		Head and Neck Cancer (%)		Lung Cancer (%)		NHL (%)		Pancreatic Cancer (%)	
	CVC (n = 5,420)	No CVC (n = 36,851)	CVC (n = 9,692)	No CVC (n = 26,580)	CVC (n = 1,339)	No CVC (n = 7,120)	CVC (n = 11,812)	No CVC (n = 44,958)	CVC (n = 4,292)	No CVC (n = 10,140)	CVC (n = 2,744)	No CVC (n = 7,792)
Total	13	87	27	73	16	84	21	79	30	70	26	74
Age, years												
66-69	34	18	22	11	29	20	25	16	18	14	22	11
70-74	31	23	28	17	30	23	31	23	26	19	27	17
75-79	21	23	25	21	20	22	26	25	26	22	28	22
80-84	10	20	16	24	14	18	14	21	20	23	17	24
$\geq$ 85	4	16	9	26	7	16	4	15	10	22	6	25
Male sex	NA†		49	46	68	67	48	52	47	50	46	45
White race (referent, other)	83	88	85	85	83	88	86	87	90	90	83	84
Romano-Charlson comorbidity index‡												
0	62	65	59	55	67	71	72	71	56	58	49	45
1	24	23	25	25	18	16	15	14	24	24	30	29
$\geq$ 2	14	13	17	20	15	13	13	14	19	18	21	26
Disease stage§												
In situ	3	18	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Localized	34	58	21	50	11	26	14	22	22	31	9	11
Regional	48	17	48	29	42	28	27	22	16	13	37	21
Distant	13	5	28	15	16	8	56	50	56	47	48	52
Unknown	1	2	3	7	31	38	3	7	5	9	6	16
Neutropenia diagnosis	52	7	32	8	37	10	45	16	65	31	28	11
Surgery (primary cancer)¶	90	91	87	75	39	45	18	21	NA	NA	30	13
Chemotherapy¶	84	11	74	13	76	23	78	28	83	48	75	24
Radiation therapy¶	56	48	25	9	85	61	58	35	22	21	33	10
TPN	1	< 1	8	1	7	1	3	< 1	5	1	10	1

NOTE. Percentages do not total 100% because of rounding. For treatment variables (surgery, chemotherapy, radiation therapy, TPN) and neutropenia, percentages presented refer to having documented code for procedure or diagnosis. CVC use refers to any long-term CVC use (tunneled catheter, implanted port, PICC) during 2-year follow-up period; differences in CVC use between variables presented are all significant at $P < .05$ based on unadjusted χ^2 test, except for radiation therapy for NHL.

Abbreviations: AJCC, American Joint Committee on Cancer; CVC, central venous catheter; NA, not applicable; NHL, non-Hodgkin lymphoma; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition.

*Additional cohort characteristics included in study: marital status, median income in census tract of residence, geographic region, metropolitan location.

†Men were excluded.

‡Romano-Charlson index was calculated for patients based on claims from year before cancer diagnosis.

§Historic staging, except for NHL, where AJCC staging was used.

¶Neutropenia was not included in final adjusted model, given its collinearity with chemotherapy.

||Variable proportions are reported as defined in adjusted time-to-event model: occurrence before infection event.

Table 2. Infection Risk by Long-Term CVC Use

Type of Cancer	Long-Term CVC Use*			No Long-Term CVC Use*			Unadjusted Model		Adjusted Model		Adjusted Model With Propensity Scores†	
	Total No.	Infection No.	%	Total No.	Infection No.	%	HR‡§	95% CI	HR‡§	95% CI	HR‡§	95% CI
Breast	5,420	860	16	36,851	1,278	3	6.49	5.89 to 7.14	6.19	5.42 to 7.07	5.41	4.72 to 6.21
Colorectal	9,692	1,566	16	26,580	2,278	9	2.71	2.50 to 2.93	3.49	3.18 to 3.81	2.66	2.41 to 2.94
Head and neck	1,339	391	29	7,120	627	9	4.97	4.31 to 5.73	4.47	3.76 to 5.31	4.06	3.41 to 4.83
Lung	11,812	2,614	22	44,958	4,252	9	2.77	2.62 to 2.93	3.23	3.03 to 3.45	2.76	2.58 to 2.95
NHL	4,292	1,315	31	10,140	1,235	12	3.54	3.24 to 3.85	4.75	4.32 to 5.23	3.83	3.48 to 4.22
Pancreatic	2,744	758	28	7,792	979	13	1.98	1.76 to 2.22	2.93	2.58 to 3.33	2.34	2.06 to 2.67

Abbreviations: CVC, central venous catheter; HR, hazard ratio; NHL, non-Hodgkin lymphoma.

*Long-term CVC use refers to any long-term CVC insertion claim during 2-year follow-up period. Some infections occurred before or after long-term CVC exposure period.

†Propensity score model adjusted for all characteristics; propensity scores in quintiles. Accounted for propensity of patient receiving long-term CVC.

‡Infection risk for patients with long-term CVC use compared with patients without long-term CVC use. Exposure was taken into account through time-dependent covariate for long-term CVC use.

§ $P < .001$.

||Adjusted for age, sex, race, marital status, median income in census tract of residence, geographic region, metropolitan location, disease stage, Romano-Charlson comorbidity index, surgery, chemotherapy, radiation therapy, and total parenteral nutrition.

have extended beyond our study period, and intermittent periods without CVC use could not be reliably identified. Second, the SEER-Medicare data set is limited to information collected from Medicare claims and SEER cancer registries. We did not have information on functional status, rationale behind the selection of treatment administration mode, or specific treatment regimens. Nevertheless, we were able to include several important characteristics likely associated with increased infection risk. For example, long-term CVCs are often used for chemotherapy administration in patients with cancer, and chemotherapy-induced neutropenia may be a risk factor for infection. We were able to account for chemotherapy exposure in the analysis using a time-dependent covariate. Lastly, the SEER-Medicare data set primarily includes patients age ≥ 65 years residing in SEER geographic regions, which may limit generalizability. However, the Medicare program covers $>$ half of all patients with cancer in the United States, and older patients may be particularly susceptible to infections and result-

ing complications.^{23,24} Also, the SEER regions represent $> 25\%$ of the population and include a representative and diverse group.¹¹ Despite these limitations, a major strength of this study was the use of a population-based approach to assess infection risk associated with use of long-term CVCs.

Our findings suggest that as recommended by the ASCO Clinical Practice Guidelines Committee, a focus on long-term CVCs as a potential source of infections in patients with cancer is warranted.⁵ There are two primary means by which infections might be prevented. One approach is to reduce unnecessary long-term CVC use. When discretionary, comprehensive information on potential harms can inform decision making regarding treatment administration methods. The second is to implement interventions for infection prevention specific to this patient population that can minimize the potential for harm when long-term CVC use is medically necessary.⁴

For a population-based cohort of older adult patients with cancer, we observed that exposure to long-term CVCs was associated with an increase in a patient's risk of infection, independent of other risk factors such as chemotherapy. Reducing infections associated with long-term CVCs by avoiding unnecessary use or by making their use safer could have a meaningful impact on important patient outcomes.

Table 3. Subgroup Analyses of Infection Risk by Long-Term CVC Use

Type of Cancer	Patients Age ≥ 80 Years		Patients With $\geq$ One Comorbid Condition		Patients With Advanced-Stage Disease	
	HR*†	95% CI	HR*†	95% CI	HR*†	95% CI
Breast	6.60	5.16 to 8.46	5.75	4.79 to 6.90	4.57	3.45 to 6.06
Colorectal	2.81	2.42 to 3.26	3.06	2.69 to 3.47	2.74	2.31 to 3.26
Head and neck	3.36	2.90 to 3.88	3.31	2.95 to 3.71	2.80	2.57 to 3.06
Lung	5.28	4.24 to 6.57	4.97	4.27 to 5.79	3.65	2.82 to 4.72
NHL	4.70	4.01 to 5.51	4.50	3.93 to 5.16	4.39	3.87 to 4.99
Pancreatic	3.17	2.46 to 4.08	2.88	2.43 to 3.40	2.62	2.16 to 3.16

Abbreviations: CVC, central venous catheter; HR, hazard ratio; NHL, non-Hodgkin lymphoma.

*Infection risk for patients with long-term CVC use compared with patients without long-term CVC use based on Cox proportional hazards regression. Exposure was taken into account through time-dependent covariate for long-term CVC use. Adjusted for age, sex, race, marital status, median income in census tract of residence, geographic region, metropolitan location, disease stage, Romano-Charlson comorbidity index, surgery, chemotherapy, radiation therapy, and total parenteral nutrition.

† $P < .001$.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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GLOSSARY TERMS

Cox proportional hazards regression model: a statistical model for regression analysis of censored survival data, examining the relationship of censored survival distribution to one or more covariates. This model produces a baseline survival curve, covariate coefficient estimates with their standard errors, risk ratios, 95% CIs, and significance levels.

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