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ORIGINAL ARTICLE

Retrospective Study

Risk of critical limb ischemia in long-term uterine cancer survivors: A population-based study

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Abstract

BACKGROUND

The risk of critical limb ischemia (CLI) which causes ischemic pain or ischemic loss in the arteries of the lower extremities in long-term uterine cancer (UC) survivors remains unclear, especially in Asian patients, who are younger at the

diagnosis of UC than their Western counterparts.

AIM

To conduct a nationwide population-based study to assess the risk of CLI in UC long-term survivors.

METHODS

UC survivors, defined as those who survived for longer than 5 years after the diagnosis, were identified and matched at a 1:4 ratio with normal controls. Stratified Cox models were used to assess the risk of CLI.

RESULTS

From 2000 to 2005, 1889 UC survivors who received surgery alone or surgery combined with radiotherapy (RT) were classified into younger (onset age < 50 years, n = 894) and older (onset age ≥ 50 years, n = 995) groups. While compared with normal controls, the younger patients with diabetes, hypertension, and receiving hormone replacement therapy (HRT) were more likely to develop CLI. In contrast, the risk of CLI was associated with adjuvant RT, obesity, hypertension, and HRT in the older group. Among the UC survivors, those who were diagnosed at an advanced age (> 65 years, aHR = 2.48, P = 0.011), had hypertension (aHR = 2.18, P = 0.008) or received HRT (aHR = 3.52, P = 0.020) were at a higher risk of CLI.

CONCLUSION

In this nationwide study, we found that the risk factors associated with CLI were similar in both cohorts except for adjuvant RT that was negligible in the younger group, but positive in the older group. Among the survivors, hypertension, advanced age, and HRT were more hazardous than RT. Secondary prevention should include CLI as a late complication in UC survivorship programs.

Key Words: Uterine cancer; Critical limb ischemia; Radiotherapy; Survivorship

Core Tip: The risk of critical limb ischemia (CLI) in long-term uterine cancer (UC) survivors remains unclear, especially in Asian patients. In this nationwide study, a total of 1889 UC survivors were classified into younger and older groups. We found that the risk factors associated with CLI were similar in both cohorts except for adjuvant radiotherapy (RT) that was negligible in the younger group, but positive in the older group. Among these survivors, hypertension, advanced age, and hormone replacement therapy were more hazardous than RT. Secondary prevention should include CLI as a late complication in UC survivorship programs.

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INTRODUCTION

Uterine cancer (UC) is the most common gynecologic malignancy in developed areas[1]. The incidence of UC is increasing at a rate of 1%-2% per year in Western and Asian countries[2,3]. In Western populations, 15% of UC patients are under the age of 50 years[4,5], however, around 40% of UC patients in Taiwan are younger than 50 years of age[3]. The patients with loco-regional disease in the United States, which comprises 89% of all cases of UC, have a great prognosis since the 5-year survival rates for local disease and regional disease are 95.3% and 67.5%, respectively[4,5]. Due to the high survival rate, UC survivorship care should include the management of many health issues, such as late side effects in post-treatment cancer survivors. The long-term survivors are commonly defined as patients who are alive for more than 5 years after diagnosis[6]. The well-being of long-term cancer survivors may be as well as persons with similar age and demographic characters[7]. However, even 5 years or more after diagnosis, patients can continue to face the physical effects related to treatment. Thus, concerns have been raised about the detrimental impact of late complications owing to treatment in their survivorship [7,8].

Surgery is the principal treatment for local-regional UC, and radiotherapy (RT) has become the standard adjuvant treatment of choice for patients with high-risk factors[9]. Major pelvic surgery may result in lympho-vascular complications such as deep vein thrombosis or lymph edema[10,11]. In addition, RT can cause local inflammation, oxidative stress, fibrosis and in-field cardiovascular disease [12]. Several studies have reported that RT increased the risk of ischemic stroke in patients with head and neck cancers[13,14].

Peripheral arterial disease (PAD) is a cardiovascular disease that encompasses all chronic arterial occlusive diseases of the arteries other than coronary arteries and the aorta caused by atherosclerosis. The most prevalent sites of PAD are the lower extremities, which may cause leg or pelvic pain, intermittent claudication, and limited mobilization. Women with PAD have been reported to have an increased prevalence of coexisting coronary artery disease and ischemic stroke, and higher all-cause mortality[15]. The risk of PAD has been reported in cervical cancer patients[16,17], however few studies have investigated the risk of PAD in UC survivors. A study from the US using the SEER Utah Cancer Registry revealed that among the UC patients treated with surgery alone or surgery with adjuvant RT, the risk of PAD was 24% higher in the patients with RT than in those who received surgery alone during the first 5 years of follow-up. However, no long-term effect of adjuvant RT was observed 5 years after the diagnosis[2].

These previous studies took a broad definition of PAD, however, delayed diagnoses are common in the PAD patients especially when the symptoms are mild. In this study, we focused on critical limb ischemia (CLI) which presents a relatively severe clinical syndrome related to PAD and causes ischemic pain or ischemic loss in the arteries of the lower extremities. Furthermore, Asian patients with UC are younger on average, the risk of PAD in younger survivors may be different from that in Western patients. Therefore, a nationwide population-based study was conducted to assess the risk of CLI in UC long-term survivors, defined as patients who survived for more than 5 years after diagnosis. We also assessed whether age, treatment modality, income level, comorbidities, and hormone replacement therapy (HRT) are associated with the risk of CLI.

MATERIALS AND METHODS

Data sources

The data used in this study were sourced from the Registry of Catastrophic Illness (RCI) and Longitudinal Health Insurance Database 2005 (LHID2005), which are two subsets of records from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD is a nationwide database containing longitudinal medical records of beneficiaries enrolled in the National Health Insurance (NHI) program, which provides comprehensive health care coverage for over 98% of the Taiwanese population. The evaluation process for patients in the RCI database is conducted by a panel of specialists who follow a strict process of reviewing medical records, imaging, and pathology reports, therefore, it was used to identify patients with UC or other cancers. The LHID2005 contains original claims data for 1000000 beneficiaries randomly sampled from the entire population in 2005. All information on comorbidities and treatment modalities (for UC cases) from 1995-2012 was available for analysis from inpatient and outpatient records. This retrospective study was approved by the Institutional Review Board (IRB) of Chang Gung Medical Foundation (201600205B0). This study is based in part on data from the NHIRD provided by the NHI Administration, Ministry of Health and Welfare and managed by National Health Research Institutes. This is a secondary use of individuals' healthcare data and all personal information has been removed by de-identification, so that specific persons and their identities cannot be re-identified or be linked to other database. In accordance with the Declaration of Helsinki, this study did not increase the risk of participants, and the IRB approves the waiver of the informed consent form.

Study design

The primary endpoint of this study was the development of CLI during the follow-up period (2005-2012). CLI was identified if the patients were hospitalized with a major or minor diagnosis of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes: 440.0x, (atherosclerosis of the aorta), 440.2x (atherosclerosis of native arteries of the extremities), 440.8x (atherosclerosis of other specified arteries), 440.9x (generalized and unspecified atherosclerosis), 443.9x (peripheral vascular disease, unspecified), 444.0x (arterial embolism and thrombosis of the abdominal aorta), 444.2x (arterial embolism and thrombosis of other specified arteries), 447.8x (other specified disorders of arteries and arterioles), 447.9x (unspecified disorders of arteries and arterioles).

To evaluate the risk of CLI in UC survivors (ICD-9-CM code: 179 or 182), subgroup analysis was performed according to the age at the diagnosis of UC: < 50 years (younger group) and ≥ 50 years (older group). For each group, two study cohorts were compared: a UC survivor group and a matched control group. The survivors were defined as those who survived for longer than 5 years after the diagnosis of UC, and the first day after 5 years of survivorship was defined as the index date. Originally, the UC group comprised 4022 patients who were diagnosed between 2000 and 2005. However, 2133 patients

were excluded due to any one of the following criteria: aged < 20 or > 80 years at diagnosis of UC, survived for less than 5 years, developed second cancers during follow-up or CLI before the index date, incomplete individual information, and received treatment modalities other than surgery alone and surgery with adjuvant RT. Finally, 894 younger and 995 older survivors were eligible for this study. Normal controls were matched using propensity score, calculated as the probability of being a case (UC) according to baseline variables, including age at the index date, sex, urbanization level, and income-related insurance payment. At a ratio of 1:4, four corresponding controls were selected for each UC case based on the closest propensity score. Thus, a total of 7556 controls aged 25-85 years without any history of cancers or CLI before the index date were selected from the LHID2005. The index date of each control was assigned to be the same as that of the corresponding UC survivor. The survival time for all groups was defined as the number of years from the index date to a new diagnosis of CLI, withdrawal from the NHI program (mostly due to death, and a few cases owing to immigration, imprisonment, and others), or December 31st, 2012, whichever occurred first. Comorbidities related to CLI including hypertension, diabetes, atrial fibrillation, hyperlipidemia, chronic kidney disease, morbid obesity and smoking-related diseases, and diagnoses of these comorbidities were confirmed by at least three clinical visits or at least one hospitalization during the 12 mo prior to the index date. We identified HRT (G03C, G03F) according to the Anatomical Therapeutic Chemical Classification system, and retrieved prescription data from NHI files. The dosage of HRT was defined as the average number of days of taking HRT per year from the diagnosis of UC to the date of last follow-up.

Statistical analysis

Baseline characteristics are presented as means with standard deviations or frequencies with percentages. Comparisons between UC survivors and controls were performed using generalized estimating equations[18] which takes into account correlations within each cluster (1 UC case and 4 matched controls). Similarly, stratified Cox proportional hazards models were used to assess the risk of CLI between two groups, and the results are presented as crude hazard ratios (HRs) and adjusted HRs (aHRs) with *P* values. In addition, the cumulative incidence rates of CLI were calculated and compared between groups by applying a competing risk model proposed by Kalbfleisch and Prentice[19] and Gray[20]. Among the UC survivors, risk factors related to CLI were assessed using a Cox proportional hazards models. Data were managed and analyzed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, United States). All statistical tests were two-sided at 0.05 Level of significance.

RESULTS

Characteristics of the study participants

From 2000 to 2005, a total of 1889 eligible UC 5-year survivors were identified from the RCI, and 7556 controls were selected from the LHID2005. The baseline characteristics are listed and two cohorts were comparable with respect to sex, age, and income-related insurance payment (all $P \geq 0.600$) for both age groups (Table 1). In the younger group, the UC survivors had higher rates of comorbidities including hypertension (27.39% *vs* 14.15%, $P < 0.001$), diabetes (18.34% *vs* 5.54%, $P < 0.001$), hyperlipidemia (10.63% *vs* 5.87%, $P < 0.001$), obesity (4.92% *vs* 3.19%, $P = 0.010$) and duration of HRT (percentage of > 1 mo: 15.44% *vs* 6.10%, $P = 0.033$) than the matched controls. However, the controls had a higher rate of smoking-related diseases than the survivors (9.82% *vs* 4.36%, $P < 0.001$). In contrast, compared with the older controls, the UC survivors had similar prevalence rates of all comorbidities, except for lower rates of morbid obesity (1.81% *vs* 3.09%, $P = 0.031$) and smoking-related diseases (7.33% *vs* 18.52%, $P < 0.001$), and a higher rate of diabetes (23.72% *vs* 20.50%, $P = 0.026$).

Risk factors for a CLI event in the younger survivors

The crude incidence rates of CLI were higher in the younger survivors than in the matched controls, but the difference was not significant (198.21 *vs* 117.17 per 100000 person-years, $P = 0.212$, Table 1). In univariate analysis, those who received HRT for longer than 1 mo (HR ≥ 3.67, $P \leq 0.027$) or had any one of the following comorbidities were at a higher risk of developing CLI: diabetes (HR = 4.49, $P = 0.002$), hypertension (HR = 2.89, $P = 0.007$), hyperlipidemia (HR = 3.12, $P = 0.010$) (left panel, Table 2). The adjusted HRs also revealed that the younger patients with diabetes (aHR = 2.93, $P = 0.033$), hypertension (aHR = 2.93, $P = 0.033$), and receiving HRT (aHR ≥ 2.89, $P \leq 0.038$) were more likely to develop PAD (right panel, Table 2). In contrast, both the surgery alone and surgery + RT subgroups had a similar risk to the normal controls (aHR = 0.75 and 0.34, respectively, both $P \leq 0.083$).

Risk factors for a CLI event in the older survivors

In the older group, the crude incidence rates of CLI were not different between two groups (436.25 *vs* 380.54 per 100000 person-years, $P = 0.599$, Table 1). Consistently, univariate analysis also showed that the survivors were at a higher but not significant risk of CLI compared with the controls (HR = 1.17, $P = 0.503$). However, obesity, diabetes, hypertension and receiving HRT for longer than 6 mo increased the

Table 1 Characteristics of uterine cancer survivors and matched normal controls

Characteristic	UC survivors, onset age < 50 years (*n* = 894)	Normal controls (*n* = 3576)	*P* value	UC survivor, onset age 50 years (*n* = 995)	Normal controls (*n* = 3980)	*P* value
Age at index date (yr)	48.00 ± 5.63	47.82 ± 5.74		63.09 ± 6.83	63.23 ± 7.25	
25-40	88 (9.84)	352 (9.84)	1.00			1.00
40-45	121 (13.53)	484 (13.53)				
45-50	251 (28.08)	1004 (28.08)				
50-55	434 (48.55)	1736 (48.55)				
55-60				391 (39.30)	1564 (39.30)	
60-65				267 (26.83)	1068 (26.83)	
65-70				155 (15.58)	620 (15.58)	
> 70				182 (18.29)	728 (18.29)	
Urbanization						
1 (least urbanized)	174 (19.46)	696 (19.46)	0.768	229 (23.01)	996 (23.01)	1.00
2	216 (24.16)	867 (24.24)		223 (22.41)	1184 (22.41)	
3	300 (33.56)	1197 (33.47)		296 (29.75)	892 (29.75)	
4	204 (22.82)	816 (22.82)		247 (24.82)	908 (24.82)	
Income-related insurance payment						
1 (lowest)	449 (50.22)	1793 (50.14)	0.600	665 (66.83)	2660 (66.83)	1.00
2	214 (23.94)	856 (23.94)		153 (15.38)	612 (15.38)	
3	146 (16.33)	587 (16.41)		132 (13.27)	528 (13.27)	
4 (highest)	85 (9.51)	340 (9.51)		45 (4.52)	180 (4.52)	
Morbid obesity[1]	44 (4.92)	111 (3.10)	0.010	18 (1.81)	123 (3.09)	0.031
Smoking-related diseases[2]	39 (4.36)	351 (9.82)	< 0.001	73 (7.33)	737 (18.52)	< 0.001
HRT[3]			0.033			0.108
0	548 (61.30)	2200 (61.52)		663 (66.63)	(69.87)	
1-30 d	208 (23.27)	1158 (32.38)		229 (23.02)	774 (19.45)	
31-180 d	113 (12.64)	192 (5.37)		90 (9.05)	350 (8.79)	
> 180 d	25 (2.80)	26 (0.73)		13 (1.31)	75 (1.88)	
Comorbidity						
Hypertension	244 (27.39)	506 (14.15)	< 0.001	473 (47.54)	1779 (44.70)	0.094
Diabetes	164 (18.34)	198 (5.54)	< 0.001	236 (23.72)	816 (20.50)	0.026
Atrial fibrillation	5 (0.56)	11 (0.31)	0.268	12 (1.21)	65 (1.63)	0.312
Hyperlipidemia	95 (10.63)	210 (5.87)	< 0.001	179 (17.99)	750 (18.84)	0.532
Chronic kidney disease	7 (0.78)	15 (0.42)	0.173	11 (1.11)	35 (0.88)	0.511
CLI	8 (0.89)	19 (0.53)		19 (1.91)	66 (1.66)	
Mean follow-up after index date (yr)	4.515	4.535		4.377	4.358	
Incidence per 100000 person-years[4]	198.21	117.17	0.212	436.25	380.54	0.599
Treatment modality						
Surgery alone	727 (81.32)			694 (69.75)		

Surgery + RT	167 (18.68)	301 (30.25)

[1]Morbid obesity (ICD-9 code: 278, 278.00, 278.01, and V778).
[2]Smoking related diagnoses (ICD-9 code: 305.1, 491.2, 492.8, 496, 523.6, 959.84, 649.0, and V15.82).
[3]Number of days of taking hormone replacement therapy (HRT) per year during the follow-up period. HRT was identified according to the Anatomical Therapeutic Chemical classification system and included estrogen only (G03C) and an estrogen-progesterone combination (G03F).
[4]Incidence per 100000 person-years. Data are presented as *n* (%) or mean ± SD.
UC survivors and the comparison group were matched by 5-year age group, sex, urbanization level, and income-related insurance payment. All *P* values were obtained from generalized estimating equations models. UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; CLI: Critical limb ischemia.

Table 2 Crude and adjusted hazard ratios for the occurrence of critical limb ischemia in the younger group using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95%CI)		*P* value	Adjusted HR[1] (95%CI)		*P* value
Group (controls)	1		0.150	1		0.395
UC survivors[2]	1.68	(0.83-3.43)		0.66	(0.25-1.72)	
Surgery alone[3]				0.75	(0.25-2.22)	0.601
Surgery + RT[3]				0.34	(0.10-1.15)	0.083
Morbid obesity	1.36	(0.35-5.37)	0.659			
Smoking	1.83	(0.62-5.35)	0.271			
Diabetes	4.49	(1.76-11.44)	0.002	2.93	(1.09-7.92)	0.033
Hypertension	2.89	(1.33-6.27)	0.007	3.61	(1.43-9.08)	0.006
Hyperlipidemia	3.12	(1.31-7.46)	0.010			
Chronic kidney disease	4.00	(0.40-39.83)	0.237			
HRT						
0 d	1			1		
1-30 d	1.98	(0.82-4.75)	0.127	2.89	(1.06-7.91)	0.038
30-180 d	3.67	(1.16-11.58)	0.027	5.65	(1.62-19.65)	0.006
> 180 d	22.36	(3.43-145.80)	0.001	25.75	(4.72-155.24)	< 0.001

[1]Adjusted HRs and *P* values were obtained from a multiple stratified Cox model, which included treatment modality and significant explanatory variables only.
[2]All UC survivors, regardless of treatment modality.
[3]Treatment modalities (surgery alone and surgery with RT) were examined in the Cox model.
UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; HR: Hazard ratio; CI: Confidence interval; CLI: Critical limb ischemia.

risk of CLI (HR = 6.00, *P* = 0.001; HR = 1.67, *P* = 0.021; HR = 2.24, *P* = 0.002; HR = 5.24, *P* = 0.002, respectively) (left panel, Table 3). Furthermore, the aHRs revealed that the older UC survivors who received RT after surgery had at least a 2-fold higher risk of CLI compared to the matched controls after adjusting for confounders (aHR = 2.12, *P* = 0.019) (right panel, Table 3). In addition, obesity (aHR = 5.55, *P* = 0.003), hypertension (aHR = 2.06, *P* = 0.005) and HRT for ≥ 180 d (aHR = 4.54, *P* = 0.013) were still positively associated with the risk of developing CLI.

The risk of CLI in the UC survivors

Among the 1889 UC survivors, a comparison between treatment modalities revealed that RT increased the risk of CLI by 39%, but this was not significant after adjusting for other confounders (aHR = 1.39, *P* = 0.247). However, the risk of CLI was significantly increased among the survivors who were older (age at the index year > 65 years; aHR ≥ 2.48, *P* < 0.011), had hypertension (aHR = 2.18, *P* = 0.008), and received HRT for longer than 6 mo per year from the diagnosis of UC (aHR = 3.52, *P* = 0.020) (Table 4).

Table 3 Crude and adjusted hazard ratios for the occurrence of critical limb ischemia in the older group using a stratified Cox model with withdrawal as a competing risk

	Crude HR (95%CI)		*P* value	Adjusted HR[1] (95% CI)		*P* value
Group (controls)	1		0.503	1		
UC survivors[2]	1.17	(0.74-1.85)		1.29	(0.80-2.07)	0.299
Surgery alone[3]				0.93	(0.47-1.84)	0.832
Surgery + RT[3]				2.12	(1.13-3.95)	0.019
Morbid obesity	6.00	(2.08-17.29)	0.001	5.55	(1.82-16.94)	0.003
Smoking	0.92	(0.52-1.62)	0.769			
Comorbidity						
Diabetes	1.67	(1.08-2.59)	0.021			
Hypertension	2.24	(1.36-3.68)	0.002	2.06	(1.24-3.43)	0.005
Hyperlipidemia	1.59	(0.98-2.57)	0.062			
Chronic kidney disease	0.800	(0.11-5.63)	0.823			
HRT						
0 d	1			1		
1-30 d	0.68	(0.38-1.24)	0.208	0.60	(1.06-7.91)	0.100
30-180 d	1.01	(0.47-2.15)	0.979	0.82	(1.62-19.65)	0.615
> 180 d	5.24	(1.81-15.23)	0.002	4.54	(1.38-14.91)	0.013

[1]Adjusted hazard ratios and *P* values were obtained from a multiple stratified Cox model, which included treatment modality and significant explanatory variables only.
[2]All UC survivors, regardless of treatment modality.
[3]Treatment modalities (surgery alone and surgery with RT) were examined in the Cox model.
UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; HR: Hazard ratio; CI: Confidence interval; CLI: Critical limb ischemia.

DISCUSSION

In this nationwide study, we found that the risk factors associated with CLI were similar in both cohorts except for adjuvant RT that was negligible in the younger group, but positive in the older group. In our study population, the younger patients accounted for 47% of the total (894/1889), which is much higher than that reported in Western populations[2,5]. Among the survivors, hypertension, advanced age, and HRT for longer than 180 d per year were more hazardous than RT.

PAD in the general population usually appears after the age of 50 years, and the prevalence then increases with age[21]. This trend was also observed in the UC survivors with CLI in the present study. RT is a known cause of cardiovascular morbidity and mortality. The long-term effects on vascular endothelial damage and the possible mechanism of ionizing radiation on the progression of atherosclerotic plaque have been reported[22,23]. Although studies on the late vascular effects induced by RT have been performed in preclinical models, no clear correlations between individual changes and their time course after conventional fractionated RT have been identified. Accordingly, further studies are needed to investigate whether RT for UC increases the risk of CLI. In our analysis, RT did not cause CLI to occur earlier, but it increased the incidence of CLI in the older patients. People over 65 years of age often have multiple cardiovascular risk factors, and atherosclerosis can be accelerated by radiation[24].

In this study, we found that HRT was more associated with an increased risk of CLI than RT. A previous study reported that estrogen can regulate injury-induced chemokines and oxidative stress and that it has a vascular protective effect, but that it has no vascular protective effects on aging blood vessels[25]. The "timing hypothesis" suggests that because the estrogen signaling pathway in older women has changed, estrogen has no vascular protective effect in patients with subclinical vascular diseases[25]. Compared with the slow decline of estrogen levels in natural menopause over time, bilateral oophorectomy for UC treatment can lead to a sudden decrease in estrogen and menopause. This dramatic decline in estrogen has been associated with a higher cardiometabolic risk[26,27]. This may explain why HRT does not have a protective effect in UC patients, and even showed toxic effects on blood vessels in this study.

In this study, the UC survivors all had common risk factors for CLI, such as smoking, obesity, hypertension, and diabetes. Previous studies have reported that hypertension is a major risk factor for

Table 4 Adjusted hazard ratios for the occurrence of critical limb ischemia in the uterine cancer survivors using a Cox proportional hazards model (*n* = 1889)

	Adjusted HR	95%CI	*P* value
Treatment modality			
Surgery alone	1		0.247
Surgery with RT	1.39	(0.80-2.42)	
Age at index year (yr)			
< 55	1		
55-65	0.72	(0.35-1.48)	0.372
65-75	2.48	(1.23-4.99)	0.011
> 75	3.63	(1.55-8.47)	0.003
Hypertension	2.18	(1.23-3.88)	0.008
HRT			
0 d	1		
1-30 d	0.53	(0.25-1.15)	0.108
30-180 d	1.08	(0.45-2.58)	0.864
> 180 d	3.52	(1.22-10.13)	0.020

Adjusted hazard ratios and *P* values were obtained from a multiple Cox model, which included treatment modality and significant explanatory variables only. UC: Uterine cancer; RT: Radiotherapy; HRT: Hormone replacement therapy; HR: Hazard ratio; CI: Confidence interval; CLI: Critical limb ischemia.

PAD regardless of age[2]. In addition, the prevalence of PAD has been shown to increase with age and to be higher in people with metabolic syndrome and diabetes[15]. We also found that the influence of diabetes and hyperlipidemia was more prominent in the younger group. This may be due to the fact that younger UC patients usually have type I endometrial cancer, which is associated with obesity and metabolic syndrome. These are common risk factors for symptomatic PAD and can lead to chronic atherosclerosis[4,15].

The UC survivors in this study were defined as those who were diagnosed with UC between 2000 and 2005, and who survived for longer than 5 years. Although details of the surgical methods were not available in the dataset, we believe that they all underwent traditional surgery. At present, current surgical methods including a laparoscopic or robotic approach and sentinel lymph node evaluation are considered to be minimally invasive surgery which can improve the short-term quality of life. However, no significant difference in overall survival according to the initial surgical management has been reported between traditional laparotomy and these minimally invasive techniques[28]. In addition, sentinel lymph nodes can reduce the risk of lower limb lymphedema, which may influence circulation in the lower limbs. Further studies to evaluate differences in treatment techniques are suggested. In addition, compared with Western women, Asian women have a higher grade of histology, more advanced stage and worse 5-year survival rate. Therefore, Asian women are more likely to receive lymphadenectomy, which may result in more aggressive surgery leading to a higher risk of complications[29,30].

There are several strengths to this study. It is the first study examining RT effect on long-term UC survivors, and the use of a nationwide database allowed for a large sample size, homogeneous population, and long follow-up period. In addition, we could evaluate the temporal relationship regarding the use of HRT. Nevertheless, the major limitation is that data on other covariates including body mass index, use of contraceptives, self-pay medications, reproductive history, smoking status, details of treatment such as volume of radiation are not provided in NHIRD. We also lacked information of histology and staging at the initial diagnosis, which are major factors for survival. However, endometrial adenocarcinoma comprises approximately 90% of all UC[4] and we only included patients who had surgery alone or surgery combined with adjuvant RT, which are the main treatments for loco-regional disease. Finally, limited incidences due to restrict criteria of CLI may cause overfitting in statistical modeling. Using a public dataset for research has inevitable limitations, and therefore we aim to use other data sources for more persuasive comparisons in the future.

CONCLUSION

We used a nationwide population-based database to explore the risk of CLI among long-term UC survivors. Among them, the correlation between adjuvant RT and CLI was far weaker than the correlations of hypertension, diabetes, and long duration of HRT. Therefore, younger patients should pay special attention to monitoring CLI when using HRT. The development of CLI is an important risk factor for severe vascular diseases, such as ischemic stroke and coronary artery disease. Consequently, future survivorship care should include CLI as a late complication to ensure proper prevention and management.

ARTICLE HIGHLIGHTS

Research background

Uterine cancer (UC) is the most common gynecologic malignancy in developed areas. The long-term survivors are commonly defined as patients who are alive for more than 5 years after diagnosis. Peripheral arterial disease (PAD) is a cardiovascular disease and the most prevalent sites of PAD are the lower extremities. In this study, we focused on critical limb ischemia (CLI) which presents a relatively severe clinical syndrome related to PAD.

Research motivation

The risk of CLI which causes ischemic pain or ischemic loss in the arteries of the lower extremities in long-term UC survivors remains unclear, especially in Asian patients, who are younger at the diagnosis of UC than their Western counterparts.

Research objectives

A nationwide population-based study was conducted to assess the risk of CLI in UC long-term survivors, defined as patients who survived for more than 5 years after diagnosis. We also assessed whether age, treatment modality, income level, comorbidities, and hormone replacement therapy (HRT) are associated with the risk of CLI.

Research methods

UC survivors, defined as those who survived for longer than 5 years after the diagnosis, were identified and matched at a 1:4 ratio with normal controls. Stratified Cox models were used to assess the risk of CLI. The data used in this study were sourced from the records from the Taiwan National Health Insurance Research Database.

Research results

From 2000 to 2005, a total of 1889 eligible UC 5-year survivors were identified from the RCI, and 7556 controls were selected. In the younger group, the UC survivors had higher rates of comorbidities including hypertension, diabetes, hyperlipidemia, obesity and duration of HRT than the matched controls. In the younger survivors, the adjusted hazard ratios (aHRs) also revealed that the younger patients with diabetes (aHR = 2.93, P = 0.033), hypertension (aHR = 2.93, P = 0.033), and receiving HRT (aHR ≥ 2.89, P ≤ 0.038) were more likely to develop PAD. Furthermore, the aHRs revealed that the older UC survivors who received radiotherapy (RT) after surgery had at least a 2-fold higher risk of CLI compared to the matched controls. The risk of CLI was significantly increased among the survivors who were older (age at the index year > 65 years; aHR ≥ 2.48, P < 0.011), had hypertension (aHR = 2.18, P = 0.008), and received HRT for longer than 6 mo per year from the diagnosis of UC (aHR = 3.52, P = 0.020).

Research conclusions

We found that the risk factors associated with CLI were similar in both cohorts except for adjuvant RT that was negligible in the younger group, but positive in the older group. Among UC cancer survivors, the correlation between adjuvant RT and CLI was far weaker than the correlations of hypertension, diabetes, and long duration of HRT. Therefore, younger patients should pay special attention to monitoring CLI when using HRT.

Research perspectives

Using a public dataset for research has inevitable limitations, and therefore we aim to use other data sources for more persuasive comparisons in the future.

FOOTNOTES

Author contributions: Chen MC, Chang JJ, Chen CY, and Lee KD designed the research study; Chen MC and Lee KD performed the study concept and collected data; Chen MC analyzed the data; Chen MC, Chang JJ, and Chen CY drafted the manuscript; Chang JJ and Chen CY interpreted the data; Lee KD, Chen MF, Wang TY, and Huang CE edited and reviewed the manuscript; Chen MC and Chang JJ contributed equally to this paper; Lee KD and Chen CY contributed equally to this paper; all authors have read and approved the final manuscript.

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