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Does diabetes mellitus have an impact on the prognosis for patients with cervical cancer?

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HIGHLIGHTS

- We evaluated the impact of diabetes mellitus on the prognosis of cervical cancer.
- Diabetes mellitus was not a poor prognostic factor for such patients

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ABSTRACT

Objective. To evaluate the impact of comorbid diabetes mellitus (DM) on prognoses among patients with cervical cancer.

Methods. We analyzed cervical cancer outcomes in patients who treated in two hospitals retrospectively. Patients were divided into those with DM and those without. Clinicopathologic parameters, disease-free survival (DFS), and overall survival (OS) rates were evaluated.

Results. Of the 494 patients, 50 had DM. These were more likely to be older than those in the non-DM group and their body mass index (BMI) was higher. They showed higher levels of tumor markers and had more combined diseases. They were less likely to have had surgical treatment. Among these patients, 12 (24%) experienced a recurrence (hazard ratio, HR, 1.484; 95% confidence interval, CI, 0.746–2.951). Differences in DFS did not show statistical significance. In the OS analysis, 11 (22%) in the DM group and 62 (14%) in the non-DM group died (HR, 1.239; 95% CI, 0.606–2.533). No statistically significant differences were also observed for cancer-specific death (HR, 1.246; 95% CI, 0.567–2.737). Those with DM and an adenocarcinoma tended to have an increased risk of dying compared with the non-DM patients with an adenocarcinoma (HR, 3.673; 95% CI, 0.990–13.625), but this difference was not statistically significant ($p = 0.0518$).

Conclusion. Diabetes mellitus did not have an impact on the prognosis for patients with cervical cancers. In those with an adenocarcinoma, patients with diabetes tended to have an increased risk of dying compared with the non-DM group, but this difference was not statistically significant.

1. Introduction

Overall, 8–18% of patients with cancer have diabetes mellitus (DM) as a comorbid medical condition [1]. Despite the rising prevalence rates of type 2 DM and cancer that have occurred with aging of the population, there is limited information on the short- and long-term outcomes for patients with cancer and DM. Type 2 DM is characterized by insulin resistance, inappropriate hepatic production of glucose, and aberrant growth hormone production. These anomalies in glucose metabolism can lead to abnormal cellular growth and regulation [2]. Pancreatic, hepatic, colorectal, breast, urinary tract, and endometrial cancers have shown increased frequencies in patients with diabetes. In various studies examining the relationship between cancer and DM, the highest risks have been demonstrated for hepatocellular and pancreatic cancers [3]. Both the liver and pancreas are involved in glucose homeostasis and are exposed to high insulin concentrations. Continuous exposure to hyperglycemia and the subsequent elevated concentrations of circulating insulin might stimulate cancer growth or its progression, leading to a worse prognosis [4–7]. Many patients with diabetes and cancers have pre-existing chronic renal insufficiency, cardiovascular diseases, myocardial infarction, a risk of heart failure, and peripheral neuropathy, which are the types of organ system damage most relevant to the choice of chemotherapy and drug delivery. Dose reduction and the use of alternative agents during chemotherapy frequently need to be adjusted for patients with DM and cancer, and diabetes might reduce the effects of chemotherapy. Patients with

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hyperglycemia are also more likely to have infections leading to sepsis and severe complications during chemotherapy [8]. Among those with gynecologic cancers, DM was associated with decreased long-term survival in patients with endometrial and ovarian cancers [9,10]. However, no studies to date have investigated the impact of DM on cervical cancer outcomes. Therefore, the aim of this study was to evaluate the impact of comorbid DM on survival among patients with cervical cancers.

2. Materials and methods

We retrospectively analyzed 543 consecutive patients who had been treated for cervical cancer between 2000 and 2013 at Bucheon St. Mary's Hospital and Seoul St. Mary's Hospital in Republic of Korea. This study was approved by the Institutional Review Board. Exclusion criteria were patients with histopathologically diagnosed neuroendocrine carcinomas or sarcomas, those who had inadequate treatment or follow-up, and patients who had another malignancy at the same time. Three patients had a neuroendocrine carcinoma but none of them had DM. Because of old age or advanced stage, eight patients abandoned treatment and one of them had DM. Thirteen patients moved to different hospitals after the diagnosis of cervical cancer, and two of them had DM. Twenty-two patients were lost to follow-up after treatment and two of them had DM. Two patients had breast cancer and one patient had colon cancer together with cervical cancer. None of these three patients had DM. After excluding patients, 494 of the 543 patients were selected for this study. The International Federation of Gynecology and Obstetrics (FIGO) 2008 staging system was used for cervical cancer. Patients were divided according to their diabetic status into a DM group and non-DM group. Patients in the former group were defined as having a diagnosis of DM at the time of treatment. The clinicopathologic parameters evaluated and compared were: age, body mass index (BMI), cancer stage, histological subtype, tumor markers, treatment method, and any combined disease. For the combined disease category, cardiovascular diseases included hypertension, arrhythmia, and congestive heart failure. For the patients with DM, we also collected other variables: fasting blood sugar level, hemoglobin type A1C (HgbA1C) percentage at the time of cancer diagnosis, treatment method for DM, and complications of DM. Disease-free survival (DFS) and overall survival (OS) were recorded for both groups. DFS was calculated from the date of diagnosis until the date of a recurrence of cervical cancer. Patients without recurrence were censored at the last follow-up. OS was calculated from the date of diagnosis until death or the observation was censored as of the date of the last follow-up. We also checked cancer-specific survival for those deaths resulting from cervical cancer only.

Chi-squared, Fisher's exact, or Wilcoxon rank-sum tests were applied to evaluate the association between categorical variables. Kaplan–Meier estimates for DFS and OS were obtained according to DM status, and the differences were examined by the log-rank test. A Cox proportional hazards model was used to estimate hazard ratios (HRs) for DFS and OS while adjusting for age, stage, and cancer cell type. Statistical significance in this study was defined as $p < 0.05$. All statistical analyses were performed using the software package SAS Enterprise Guide 5.1 (SAS Institute, Inc., Cary, NC, USA) or MedCalc software version 12.7 (https://www.medcalc.org).

3. Results

Of the 494 patients with cervical cancer, 50 (10.1%) were in the DM group. Baseline characteristics of both groups are given in Table 1. Overall, the mean age was 49.8 years. Patients with diabetes were more likely to be older and their BMI was higher. They also showed higher levels of tumor markers and had more combined diseases. They were also less likely to have surgical treatment methods compared with the non-DM group. For glucose control among the patients with diabetes, three used dietary control, 37 took oral hyperglycemic agents, six received insulin injections, and four used oral hyperglycemic agents and insulin injections combined. Ten of them had combined complications: five had nephropathy including chronic renal failure, three had coronary or cerebral arteriosclerosis, and two had retinopathy. Median values of fasting blood sugar and HgbA1C in the DM group were 122 mg/dL (range 73–361 mg/dL) and 7.0% (range 3.3–12.7%). Among patients without DM, 72 (16.2%) had a recurrence. Among those with DM, 12 (24%) experienced a recurrence (adjusted HR, 1.484; 95% CI, 0.746–2.951). Differences in DFS between two groups did not show statistical significance in the Kaplan–Meier analysis (log-rank test, $p = 0.131$; Fig. 1). In the OS analysis, 11 (22%) of the patients with DM and 62 (14.0%) patients without DM died (adjusted HR, 1.239; 95% CI, 0.606–2.533). Two of the patients with diabetes and five of those without diabetes died of causes other than cervical cancers. However, no statistically significant differences were observed between the groups for all causes of death and cancer-specific death rates (log-rank test; $p = 0.123$ and $p = 0.267$ respectively; Fig. 2). The mean duration of follow-up was 61.6 ± 33.8 months. Diabetes was not implicated in the risk factors for incomplete treatment of cervical cancer (odds ratio, 2.298; 95% CI, 0.626–8.436, $p = 0.2099$) or distant metastasis (odds ratio, 3.167, 95% CI, 0.723–13.871, $p = 0.1261$; Table 2). We also compared the survival of patients with or without DM for each tumor

Table 1
Baseline characteristics of patients with uterine cervical cancer and with or without diabetes mellitus.

Characteristics	Total ($n = 494$)	Diabetes mellitus		p
		No ($n = 444$)	Yes ($n = 50$)	
Age (y)				
Mean ± SD	49.8 ± 12.8	48.3 ± 12.2	62.9 ± 10.8	<0.0001
Median (range)	48 (24–94)	47(24–85)	62 (44–94)	
BMI (kg/m^2)				
Mean ± SD	23.6 ± 3.9	23.4 ± 3.9	25.2 ± 3.1	0.0001
Median (range)	23 (16–58)	23 (16–58)	25 (19–34)	
Stage (% per group):				
I	316 (64)	289 (65.1)	27 (54)	0.0693
II	141 (28.5)	125 (28.2)	16 (32)	
III	18 (3.6)	13 (2.9)	5 (10)	
IV	19 (3.9)	17 (3.8)	2 (4)	
Cell type (% per group):				
Squamous cell carcinoma	408 (82.6)	364 (82.0)	44 (88)	0.3769
Adenocarcinoma	73 (14.8)	67 (15.1)	6 (12)	
Adenosquamous cell carcinoma	13 (2.6)	13 (2.9)	0	
Tumor markers:				
SCC antigen (ng/ml)				
Mean ± SD	5 ± 11.6	4.9 ± 12.1	5.8 ± 7.6	0.0242
Median (range)	1.3 (0.1–127.8)	1.2 (0.1–127.8)	2.3 (0.1–30.7)	
CEA (ng/ml)				
Mean ± SD	5.6 ± 16.3	5.3 ± 16.4	8.4 ± 15.3	0.001
Median (range)	1.6 (0.1–171.9)	1.5 (0.1–171.9)	2.6 (0.1–71.5)	
Treatment (% per group):				
Surgery ± chemotherapy	290 (58.7)	269 (60.6)	221 (42)	0.0003
Surgery + radiotherapy ± chemotherapy	124 (25.1)	113 (25.4)	11 (22)	
Radiotherapy ± chemotherapy	80 (16.2)	62 (14.0)	18 (36)	
Combined disease:				
Cardiovascular disease	98 (19.8)	72 (16.2)	26 (52)	<0.0001
Hepatitis	23 (4.7)	19 (4.3)	4 (8)	
Thyroid disease	5 (1.0)	5 (1.1)	0	
No disease	368 (74.5)	348 (78.4)	20 (40)	

SD, standard deviation: SCC, squamous cell carcinoma: CEA, carcinoembryonic antigen. Data are presented as n (%) and as the mean ± SD, or median and (range). The p values indicate differences between the DM and non-DM groups, by chi-squared, Fisher's exact, or Wilcoxon rank sum tests.