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Thromboembolic events in patients with cervical carcinoma: Incidence and effect on survival☆

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ABSTRACT

Objectives. The purpose of this study was to determine whether thromboembolic events (TE) in cervical cancer patients are associated with survival by comparing the survival of patients with and without thromboembolic events over a seven year period.

Methods. Utilizing a retrospective chart review we identified patients with any diagnosis of a TE, associated risk factors for TE development and overall survival. We also collected clinico-pathological data including stage, histology, height, weight, smoking history, radiation and chemotherapy treatment data and the temporal relationship of the development of TE to the time of cancer diagnosis. Data sources included the University of Iowa Hospitals and Clinics (UIHC) Tumor Registry and the UIHC Gynecologic Oncology Tumor Data Base as well as a search of UIHC medical record data bases using ICD-9 codes to initially identify all patients diagnosed with cervical carcinoma.

Results. In this study, the incidence of TE in cervical cancer patients was 11.7%. There was a clear and significant difference in survival between patients with and without TE. We identified an association between TE and stage, chemotherapy, brachytherapy, and radiation therapy.

Conclusions. The major findings of our study are a significant incidence of thromboembolism in patients with cervical cancer, and a significant decrease in survival in patients who experience thromboembolism at presentation or during treatment. Deaths in these patients were overwhelmingly related to progressive cancer rather than the TE itself, suggesting that this adverse prognostic event may be related to aggressive tumor biology.

Introduction

We have previously reported on a higher than average (16.7%) incidence of (TE) in patients treated at our institution with chemoradiation for invasive cervical cancer [1]. Studies examining thromboembolic events in other malignancies including breast, colon and ovary have indicated that they are associated with advanced disease, metastases, and decreased survival in all cancer types studied [2–6]. Many risk factors for TE have been identified and include the classic triad of venous stasis, hypercoaguable states and endothelial injury. It is currently unclear whether the development of TE is associated with survival in patients diagnosed with cervical carcinoma and if there are other risk factors unique to this population. To determine whether TE in cervical cancer patients is associated with survival we performed a retrospective study of patients diagnosed with cervical cancer over a seven-year period and compared the survival of patients with and without TE. Our cohort of patients was either treated at our institution or a known referring hospital. They all had reliable, close follow up during and after treatment.

Materials and methods

After acquiring Institutional Review Board approval, medical records were reviewed to identify patients diagnosed with cervical cancer from January 1997 until December 2003 who were seen at the University of Iowa Hospitals and Clinics (UIHC). Patients were included if they received the majority of their care at UIHC or had their treatment plan formulated at UIHC, received treatment elsewhere, but then returned to UIHC for at least 6 months of follow up from the time of diagnosis. Routine follow-up notes were mandatory from the treating institution describing not only the treatment details, but also the general health and physical characteristics of each patient as they underwent treatment in order for them to be included in the study.

☆ Preliminary data for this study were presented in the abstract: "Decreased survival in cervical cancer patients with thromboembolic events", ASCO 2007.

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We identified cervical cancer patients with any diagnosis of a TE, associated risk factors for TE development and overall survival. Thromboembolic events were defined as pulmonary emboli, deep vein thromboses, and arterial thromboses. These were confirmed by review of the relevant radiology documents. We also collected clinico-pathological data including stage, histology, height, weight, smoking history, radiation and chemotherapy treatment data and the temporal relationship of the development of the TE to the time of cancer diagnosis. Data sources included the UIHC Tumor Registry and the UIHC Gynecologic Oncology Tumor database as well as a search of UIHC medical record databases using ICD-9 codes to initially identify all patients diagnosed with cervical carcinoma.

Patients were excluded if they were seen only at UIHC for consultation and then referred back to the referring physician for treatment and follow up or if they did not have at least six months of follow up at UIHC after their date of cancer diagnosis, regardless of their treatment location. This exclusion criterion was imposed so treatment related complications would not be missed as patients were receiving their primary treatment locally. At our medical center there are many patients who present for an initial consultation, receive their treatment locally, and then are referred back to UIHC for their long term follow up. In these instances we ensured the communication from referring physicians was frequent enough to avoid missing treatment related side effects.

Patients with a diagnosis of invasive cervical cancer at UIHC are offered treatment based on stage, occasionally modified by performance status or medical co-morbidity. Patients with stage IB1 or lower are typically treated with a radical hysterectomy and pelvic lymph node dissection. Patients with Stage IB2 or higher, are typically treated with pelvic radiation and brachytherapy. Since 1999 these patients were treated with concurrent cisplatin chemotherapy, at 40 mg/m^2 given weekly in addition to the radiation regimen. Prior to 2005, the time period of this study, brachytherapy was administered at a low dose rate, using 1–2 insertions to deliver 40 Gy to point A. Patients hospitalized for abdominal surgery or low dose rate brachytherapy typically received subcutaneous heparin during their admission, in addition to antiembolism stockings and sequential compression devices for the lower extremities. These therapies were continued until the patient regained mobility and/or was discharged. It is the policy of the division of gynecologic oncology to not use erythropoietin stimulating agents nor growth factors to maintain hemoglobin or to treat neutropenia. Patients undergoing chemoradiation who develop significant anemia are transfused with packed red blood cells. In cases of neutropenia, chemotherapy is delayed until hematopoietic recovery. Growth factors are specifically excluded in patients undergoing concurrent chemotherapy and radiation.

Statistical analyses included the Pearson chi-squared test for categorical variables, and the two-sample *t*-test for continuous variables. Log–rank tests were used for survival analysis along with Kaplan–Meier survival curves. Multivariate analysis was performed with a Cox proportional hazards regression to assess the effect of TE on survival rates after adjusting for age, stage and cell type. This was also

Table 1
Demographic data for patients with and without thromboembolism ($n=436$)

Factor	Number of patients (%)					
	With TE ($n=51$)		Without TE ($n=385$)		Total	*p*-value
Age (years)						
Median	51.5		52.4			0.69
Range	25.2–81.3		18.8–97.3			
	n	%	*n*	%		
Stage						
I	26	(51.0)	260	(67.5)	286	0.001
II	6	(11.8)	62	(16.1)	68	
III	10	(19.6)	44	(11.5)	54	
IV	9	(17.6)	19	(4.9)	28	
Histology						
Squamous	31	(60.8)	253	(65.7)	284	0.75
Adenocarcinoma	16	(31.4)	109	(28.3)	125	
Other[a]	4	(7.8)	23	(6.0)	27	
External beam radiation						
Yes	40	(78.4)	201	(52.2)	241	0.0004
No	11	(21.6)	184	(47.8)	195	
Brachytherapy						
Yes	32	(62.7)[b]	163	(42.3)[c]	195	0.0059
No	19	(37.3)	222	(57.7)	241	
Chemotherapy treatment						
No chemotherapy	12	(23.5)	217	(56.4)	229	<0.0001
Platinum	38	(74.5)[d]	165	(42.8)[e]	203	
Other	1	(2.0)[f]	3	(0.8)[g]	4	
Thromboembolic disease[h]						
DVT only	39	(76.5)	–	39	–	
PE only	6	(11.7)	–	6		
DVT and PE	4	(7.8)	–	4		
Arterial	1	(2.0)	–	1		
DVT and A	1	(2.0)	–	1		

[a] Other histologies include adenoid basal (2), carcinosarcoma (2), clear cell carcinoma (3), leiomyosarcoma (1), neuroendocrine (2), papillary serous (7), small cell (9) and undifferentiated (1).
[b] 30 patients received brachytherapy implants, 2 received interstitial implants.
[c] 152 patients received brachytherapy implants, 11 received interstitial implants.
[d] Cisplatin alone was used in 35 patients and a carboplatin combination was used in 3 patients.
[e] Cisplatin alone was used in 159 patients and a carobplatin combination was used in 6 patients.
[f] Patient received vinblastine and methotrexate.
[g] Patients received 5-Fluorocil (1), etoposide (1) and topotecan (1).
[h] DVT = deep vein thrombosis, PE = pulmonary embolism.