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The clinical significance of occult gynecologic primary tumours in metastatic cancer

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ABSTRACT

Objective We estimated the frequency of occult gynecologic primary tumours (GPTs) in patients with metastatic cancer from an uncertain primary and evaluated the effect on disease management and overall survival (OS).

Methods We used Manitoba administrative health databases to identify all patients initially diagnosed with metastatic cancer during 2002–2011. We defined patients as having an "occult" primary tumour if the primary was classified at least 6 months after the initial diagnosis. Otherwise, we considered patients to have "obvious" primaries. We then compared clinicopathologic and treatment characteristics and 2-year OS for women with occult and with obvious GPTs. We used Cox regression adjustment and propensity score methods to assess the effect on OS of having an occult GPT.

Results Among the 5953 patients diagnosed with metastatic cancer, occult primary tumours were more common in women (n = 285 of 2552, 11.2%) than in men (n = 244 of 3401, 7.2%). In women, GPTs were the most frequent occult primary tumours (n = 55 of 285, 19.3%). Compared with their counterparts having obvious GPTs, women with occult GPTs (n = 55) presented with similar histologic and metastatic patterns but received fewer gynecologic diagnostic examinations during diagnostic work-up. Women with occult GPTs were less likely to undergo surgery, waited longer for radiotherapy, and received a lesser variety of chemotherapeutic agents. Having an occult compared with an obvious GPT was associated with decreased OS (hazard ratio: 1.62; 95% confidence interval: 1.2 to 2.35). Similar results were observed in adjusted analyses.

Conclusions In women with metastatic cancer from an uncertain primary, GPTs constitute the largest clinical entity. Accurate diagnosis of occult GPTs early in the course of metastatic cancer might lead to more effective treatment decisions and improved survival outcomes.

Key Words Cohort studies, data linkage, gynecologic cancers, matched groups, metastasis, occult primary neoplasms, propensity score

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INTRODUCTION

The Canadian Cancer Society estimates that, annually, approximately 10,000 women in Canada are diagnosed with a primary gynecologic cancer involving the cervix and body of the uterus, fallopian tubes, ovaries, vagina, or vulva[1]. Of all gynecologic cancers, only cervical cancer can be found early through effective screening tests (Pap cytology and DNA testing for the human papillomavirus), when treatment can be most effective[2]. Lack of screening tests means that gynecologic cancers, especially those of the ovary and fallopian tube, tend to present at an advanced stage[2].

Women with metastatic gynecologic cancers sometimes present with clinical and pathologic findings that do not indicate a gynecologic origin ("occult gynecologic tumour")[3]. A recent series of gene expression profiling analyses predicted a gynecologic site of origin in 10%–23% of women initially diagnosed with metastatic cancer of unknown origin[4–7].

The clinical and pathologic features of metastatic gynecologic primary tumours (GPTs) can mimic metastatic disease from other sites[8–11], complicating the task of effectively managing affected patients—for example, by quickly referring them to specialized gynecologic oncology

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services. Accurate diagnosis of GPT cancers might improve survival by allowing patients to benefit from a growing arsenal of effective site-specific (targeted) therapies[4,12].

In the present study, we used health administrative databases from the Canadian province of Manitoba to estimate the frequency of occult GPTs and to assess disease management and patient survival in affected patients compared with their counterparts having obvious (that is, readily diagnosed) GPTs.

METHODS

Study Design and Data Sources

Our historical cohort study used data obtained by linking the databases of the Manitoba Cancer Registry (MCR) and the Provincial Pharmacy Program at CancerCare Manitoba (CCMB) with Manitoba Health's administrative databases, including the Hospital Discharge Database, the Physician Claims Database, and the Drug Program Information Network. A full description of those databases, their contents, and the linkage process has been reported elsewhere[13–16].

The MCR is a provincial database that contains records for more than 99.5% of all cancer cases in Manitoba[17]. Information on cancer staging, based on the American Joint Committee on Cancer staging system (version 5), has been routinely collected for all cancer sites since January 1995[18]. The MCR also collects patient demographics, diagnostic confirmation methods, clinical characteristics of primary and secondary tumours [tumour site, histology, size, grade differentiation; progression of primary and secondary tumours (including local, regional, and distant progressions), progression sites, progression confirmation methods; death; and most cancer treatments (surgery, radiotherapy, and systemic therapy)]. The recorded diagnosis is based on decisions made by the clinical team; the registry does not interpret pathology reports except when based on an autopsy report. The MCR continues to update patient records as new information becomes available during the course of the disease after initial case registration. The MCR routinely takes monthly snapshots of its files, permitting the construction of monthly time-series of documented updates to a patient's diagnosis.

Since January 2004, all provincial budgets for intravenous oncology drugs have been consolidated at the CCMB for centralized purchase, administration, and review under the Provincial Oncology Drug Program. The Provincial Pharmacy Program at the CCMB maintains an electronic database of patient and treatment information about the use of systemic therapies for which reimbursement is being sought through the Provincial Oncology Drug Program or for which information is being collected by Investigational Drug Services when a drug is provided as part of a clinical trial. The pharmacy dataset contains the date, agent name, dose, fee for each agent given, and clinical data such as the patient's height, weight, body surface area, age, and diagnosis information.

The Hospital Discharge Database contains inpatient information, including admission date, length of hospital stay, and diagnoses and interventions during the entire hospital stay. The Physician Claims Database contains the date, numeric tariff index (a service-specific code used for physician compensation), and fee for each service provided by physicians. The Drug Program Information Network contains the date, dose, fee, and drug identification number for each drug claim.

Data collection and analyses were approved by the University of Manitoba Health Research Ethics Board, the Manitoba Health Information Privacy Committee, and the University of Western Ontario Health Sciences Research Ethics Board.

Identification of Study Population

First, all patients diagnosed with metastatic cancer (defined as an initial diagnosis of stage IV disease or distant metastasis within 4 months of initial diagnosis) during the period 1 January 2002 to 31 December 2011 were identified. The analysis was then limited to Manitoba residents 18–90 years of age with no history of malignancy before the initial diagnosis, whose metastatic disease was histologically confirmed and who survived at least 6 months after diagnosis. The 6-month window was used to ensure that patients would have had reasonable time early during the course of their disease to undergo all necessary clinical and pathology diagnostic evaluations (that is, diagnostic work-up) and to receive a diagnosis of the primary tumour site[5].

Then, to determine the time at which the most up-to-date identification of each patient's primary tumour was obtained during the disease course, we used linking (based on both tumour-specific identification number and scrambled health number) to the historical records routinely created by the MCR (the monthly snapshots of tumour files after the initial tumour registration). We searched for the earliest historical tumour-specific record that matched the up-to-date primary tumour site. We defined a patient as having an "obvious" primary tumour if the earliest historical record matching the up-to-date primary tumour site was found within less than 6 months after the initial cancer diagnosis or as having an "occult" primary tumour if the earliest historical record was found at 6 months or more after the initial diagnosis (that is, metastatic cancer of uncertain primary). This 6-month window for the definition of an occult primary tumour is considered conservative compared with other attempts to identify occult primary tumours using only a 2-month window[5]. Full details about the identification of occult primary tumours in our metastatic patient population are also reported elsewhere[19,20].

Within the cohort, we then identified all women diagnosed with metastatic GPTs including those of labium, vulva, vagina, cervix, isthmus uteri, endometrium, unspecified uterus, ovary, fallopian tube, placenta, overlapping lesion of female genital organs, and unspecified female genital tract. We stratified that group into two main subgroups: women with occult GPTs, and women with obvious GPTs. Because the end of the accrual period was 2011, at least 2 years of follow-up information from the time of initial diagnosis was available for each patient in the two subgroups. Follow-up information included diagnosis of a second primary, cancer treatments (for example, therapeutic surgical and radiology procedures, systemic therapies, and palliative care), and death.

Database Linkages

We linked all women in the final identified cohort with the Provincial Pharmacy Program database at the CCMB and administrative databases held by Manitoba Health, including the Hospital Discharge Database, the Physician Claims Database, and the Drug Program Information Network.

To protect confidentiality, linkages in the study were performed using a scrambled unique Personal Health Identification Number to access anonymized versions of the databases. Wherever possible, the results were cross-validated using multiple databases and further data about therapies were collected. For instance, data about chemotherapy and targeted biologic therapy captured by the MCR (recorded as *International Classification of Diseases,* 9th Revision, Clinical Modification procedure codes) were validated by linking the study population with the Provincial Pharmacy Program database and the Physician Claims Database to verify the MCR data and to collect additional information about therapeutic agents. We used comorbidity diagnoses coded using the method developed by Charlson *et al.*[21], excluding cancer diagnoses, to measure comorbidity based on information in the Hospital Discharge Database and the Physician Claims Database for the period from 1 year before to 6 months after the cancer diagnosis.

We also used the Physician Claims Database to collect information about gynecologic diagnostic examinations undertaken during the diagnostic work-up (defined as the period from 6 months before to 6 months after the cancer diagnosis) for all identified women in the final cohort. The gynecologic diagnostic tests recorded in the Physician Claims Database included gynecologic clinical and physical examinations, gynecologic surgical examinations (that is, biopsies of gynecologic sites, conization, dilation and curettage, taking of cytologic smears from the cervix, colposcopy, hysteroscopy, laparoscopy, or laparotomy), pelvic ultrasonography, and computed tomography and magnetic resonance imaging of the pelvis.

Statistical Analysis

We calculated descriptive statistics using the Fisher exact and chi-square tests for categorical variables and t-tests for continuous variables. All statistical tests were 2-sided and considered significant if p was less than 0.05. The statistical analysis was performed using the SAS software application (version 9.3: SAS Institute, Cary, NC, U.S.A.).

The primary outcome of this analysis was overall survival (OS) at 2 years. We used the Kaplan–Meier method to estimate cumulative OS probabilities and the log-rank test to assess the statistical significance of differences between the subgroups. We used Cox proportional hazards regression to calculate hazard ratios (HRS) and 95% confidence intervals (CIS) for women with occult compared with obvious GPTS. To adjust the HRS for differences in baseline tumour and patient characteristics, we used both multivariate standard Cox proportional hazards models and propensity score methods[22].

In the multivariate Cox model, we adjusted for age, score on the Charlson comorbidity index, number of metastatic sites, grade differentiation, primary tumour site, histology, and year of initial diagnosis, regardless of the individual statistical significance of those variables. The proportional hazards assumption for each covariate in the model was tested, and the assumption was appropriate in all cases.

We also conducted a propensity score analysis[22] by fitting multiple logistic regression models that included the same set of variables to predict the likelihood that a given woman would have an occult GPT. We used three approaches to the propensity score to adjust for differences in baseline characteristics between the patient subgroups. First, we included the propensity score in the Cox model to generate an adjusted HR. Second, we used a weighted Cox proportional hazards model wherein the weight assigned for each patient was based on the stabilized inverse propensity score as previously described[23]. Third, we matched, on estimated propensity score, each woman who had an occult GPT with one who had an obvious GPT (that is, a matched-pair analysis). To avoid a poor-quality match, only observations that were within ±0.01 of the propensity score for the occult GPT subject were considered to be matches, and the closest match was selected without replacement (that is, caliper matching without replacement)[22].

We also examined the potential effect of treatments on the calculated HRS for women with occult compared with obvious GPTS. We included receipt of surgical resection (no vs. yes), radiation therapy [RT (no vs. yes)], and chemotherapy (no vs. yes) as covariates in all Cox proportional hazards models. We also tested the interactions between those covariates and the status of the primary GPT (occult vs. obvious).

RESULTS

We identified 5953 patients whose initial diagnosis during the period of interest was metastatic cancer. Of those 5953 patients, 2552 (43%) were women, and 3401 (57%) were men. We found 285 women and 244 men who had a metastatic cancer of uncertain primary origin (that is, they had an occult primary tumour), respectively accounting for 11.2% of all women and 7.2% of all men diagnosed with metastatic cancer (mean difference: 4%; 95% CI: 2.5% to 5.5%; $p < 0.0001$).

In 320 women, a GPT was found to be the primary for their metastatic cancer (Table I). Of those 320 women, 55 (17.2%) had an occult GPT, accounting for 19.3% of all women with metastatic cancer of uncertain primary (Table I). Of those 55 women, 26 (47.3%) had an initial classification of unknown primary, and 29 (52.7%) had an initial classification of a primary site different from the GPT identified later during the course of their disease.

Patient, Tumour, and Treatment Characteristics

Age, year of diagnosis, primary tumour site, histology, grade differentiation, number and type of metastatic tumour sites, second primary tumours, and comorbidities did not significantly differ between women having an occult compared with an obvious GPT (Table II). Receipt of RT, endocrine therapy, and chemotherapy, and time to surgical resection and systemic therapy did not differ significantly between the subgroups (Table III).

Compared with their counterparts having an obvious GPT, women having an occult GPT were less likely to undergo a gynecologic clinical and physical examination (mean

TABLE I Primary tumour site in 2552 women diagnosed with metastatic cancer

Site of primary tumour	Study group [*n* (%)]		
	Obvious primary (*n*=2267)	Occult primary (*n*=285)	All metastatic (*n*=2552)
Gastrointestinal	613 (27)	40 (14)	653 (25.6)
Lung and pleural	604 (26.6)	21 (7.3)	625 (24.5)
Gynecologic	265 (11.7)	55 (19.3)	320 (12.5)
Breast	280 (12.3)	4 (1.4)	284 (11.1)
Lymphoma	211 (9.3)	10 (3.5)	221 (8.6)
Unknown[a]	—	129 (45.2)	129 (5)
Urologic	89 (3.9)	6 (2.1)	95 (3.7)
Head and neck	91 (14)	3 (0.3)	94(3.7)
Endocrine	44 (1.9)	4 (1.4)	48 (1.8)
Bone and soft-tissue sarcoma	41 (1.8)	6 (2.1)	47 (1.8)
Melanoma (skin)	25 (1.1)	6 (2.1)	31 (1.2)
Ophthalmic	4 (0.2)	0	4 (<0.16)
Ill-defined	0	1	1 (<0.1)

[a] Primary tumour never diagnosed.

difference: 42%; 95% CI: 28.5% to 55.9%; $p \leq 0.0001$), a gynecologic surgical examination (mean difference: 22.7%; 95% CI: 9% to 36.3%; $p = 0.002$), pelvic ultrasonography (mean difference: 15%; 95% CI: 2% to 28%; $p = 0.03$), or computed tomography imaging of the pelvis (mean difference: 28%; 95% CI: 14.2% to 42.1%; $p = 0.0001$) during the diagnostic work-up (Table II).

Compared with women having an obvious GPT, those with an occult tumour experienced, on average, a longer wait time of 11.4 months after the initial cancer diagnosis to the identification of their primary tumour (Table II). Women with an occult tumour were also less likely than their counterparts with an obvious tumour to undergo surgical resection (mean difference: 17.9%; 95% CI: 13.2% to 21.7%; $p = 0.01$; Table II). Of women who received RT, those with an occult GPT experienced a longer wait time to RT than did women with an obvious GPT (mean difference: 2.8 months; 95% CI: 2.6 to 5.3 months; $p = 0.03$; Table III). Among women who received chemotherapy, those with an occult GPT were less likely than their counterparts with an obvious GPT to receive 3 or more chemotherapeutic agents (mean difference: 20.2%; 95% CI: 5.9% to 34.5%; $p = 0.02$); they were also less likely to receive chemotherapy regimens other than a platinum–taxane combination (mean difference: 23.7%; 95% CI: 6.5% to 40.7%; $p = 0.02$; Table III).

TABLE II Baseline patient and tumour characteristics for 320 women diagnosed with metastatic gynecologic cancer

Characteristic	Study group [*n* (%)]				
	Obvious primary (*n*=265)	Occult primary (*n*=55)	*p* Value[a]	Matched controls[b] (*n*=55)	*p* Value[c]
Age at initial diagnosis (years)					
Mean	61±12.8	63±13.9	0.1	62±12.6	0.5
Range	24–87	40–89		25–82	
Year of initial diagnosis [*n* (%)]					
2002–2003	74 (28)	17 (31)	0.5	18 (32.7)	0.9
2004–2005	68 (25.6)	11 (20)		11 (20)	
2006–2007	59 (22.3)	10 (18.2)		9 (16.4)	
2008–2009	33 (12.5)	11 (20)		13 (23.6)	
2010–2011	31 (11.7)	6 (11)		4 (7.3)	
Gynecologic diagnostic examination received[d] [*n* (%)]					
Clinical and physical	237 (89.4)	26 (47.3)	<0.0001	51 (92.7)	<0.0001
Surgical[e]	142 (53.6)	17 (30.9)	0.002	29 (52.7)	0.02
Pelvic ultrasonography	112 (42.3)	15 (27.3)	0.03	26 (47)	0.03
Pelvic computed tomography imaging	171 (64.5)	20 (36.4)	0.0001	36 (65)	0.002
Pelvic magnetic resonance imaging	6 (2.3)	1 (1.8)	0.9	2 (3.6)	0.9
Gynecologic primary tumour site [*n* (%)]					
Cervix	36 (13.6)	4 (7.2)	0.05	4 (7.2)	0.9
Uterus	66 (24.9)	7 (12.7)		7 (12.7)	
Ovary	145 (54.7)	37 (67)		38 (69)	
Other female genital system	18 (6.7)	7 (12.7)		6 (11)	
Differentiation [*n* (%)]					
Well or moderately differentiated	50 (19)	6 (11)	0.2	5 (9)	0.9
Poorly differentiated or undifferentiated	215(81)	49 (89)		50 (91)	

TABLE II Continued

Characteristic	Study group [*n* (%)]				
	Obvious primary (*n*=265)	Occult primary (*n*=55)	*p* Value[a]	Matched controls[b] (*n*=55)	*p* Value[c]
Histology [*n* (%)]					
Squamous	36 (13.6)	4 (7.3)	0.4	4 (7.3)	0.9
Mucinous and serous	98 (37)	16 (29)		17 (31)	
Other adenocarcinomas	97 (36.6)	26 (47.3)		24 (44)	
Other and unspecified epithelial	22 (8.3)	6 (11)		6 (11)	
Other non-epithelial or undifferentiated	12 (4.5)	3 (5.5)		4 (7.3)	
Interval between initial cancer diagnosis and identification of primary tumour (months)					
Mean	0.20±0.93	11.6±4.7	<0.0001		<0.0001
Range	0–5.9	6–23.1			
Interval group [*n* (%)]					
0 to <3 months	254 (95.8)	0		51 (93)	
3 to <6 months	11 (4.2)	0		4 (7)	
6 to <9 months	0	20 (36.4)		0	
9 to <12 months	0	15 (29.1)		0	
12 to <15 months	0	8 (14.5)		0	
15 to <24 months	0	12 (22)		0	
Metastasis [*n* (%)]					
Number of sites					
1	122 (46)	21 (38)	0.1	21 (38)	0.9
2	64 (24.2)	20 (36.4)		21 (38)	
3	46 (17.4)	11 (20)		10 (19)	
≥4	33 (12.5)	3 (5.5)		3 (5.5)	
Anatomic site					
Digestive system	210 (42.7)	46 (45.1)	0.7	49 (42.6)	0.9
Respiratory system	70 (14.2)	15 (14.7)		19 (16.5)	
Breast	2 (0.4)	0		1 (0.9)	
Female genital system	27 (5.5)	7 (6.7)		5 (4.3)	
Bladder	3 (0.6)	1 (0.9)		2 (1.7)	
Brain	14 (2.9)	5 (4.9)		5 (4.3)	
Endocrine	1 (0.2)	1 (0.9)		0	
Bones and joints	9 (1.8)	1 (0.9)		2 (1.7)	
Soft tissue (including heart)	10 (2)	4 (3.9)		3 (2.6)	
Lymph nodes	79 (16)	11 (10.8)		9 (7.8)	
Skin	2 (0.4)	0		0	
Hematopoietic and reticuloendothelial systems	7 (1.4)	0		1 (0.9)	
Others and ill-defined	58 (11.8)	11 (10.8)		14 (12.2)	
Second primary tumour [*n* (%)]	14 (5.3)	1 (1.8)	0.5	1 (1.8)	1
Charlson comorbidity index[f]					
Score (*n*)					
Mean	0.24±0.68	0.41±1	0.2	0.4±1.1	0.9
Range	0–8	0–6		0–8	
Score > 0 [*n* (%)]	49 (18.5)	13 (23.6)	0.4	12 (21.8)	0.8
Score 0	216	42		43	
Score 1	41	8		9	
Score ≥2	8	5		3	

[a] Occult group (*n*=55) compared with entire obvious group (*n*=265) by the Fisher exact or chi-square test.
[b] Women with obvious gynecologic primary tumours matched based on estimated propensity score.
[c] Occult (*n*=55) compared with matched controls (*n*=55) by the Fisher exact or chi-square test.
[d] Diagnostic workup was defined as the period from 6 months before to 6 months after the metastatic cancer diagnosis.
[e] Includes biopsies obtained from gynecological sites, conization, dilation and curettage, cytology smears obtained from cervix, colposcopy, hysteroscopy, laparoscopy, or laparotomy.
[f] Comorbidities were considered present if they were found during the 1 year before and 6 months after the initial diagnosis with cancer.

TABLE III Treatments received by 320 women diagnosed with metastatic gynecologic cancer

Characteristic	Study group [*n* (%)]				
	Obvious primary (*n*=265)	Occult primary (*n*=55)	*p* Value[a]	Matched controls[b] (*n*=55)	*p* Value[c]
Surgical resection [*n* (%)]	192 (72.4)	31 (56)	0.01	41 (74.6)	0.04
Interval between initial cancer diagnosis and surgical resection (months)					
Mean	1.9±2.2	2.1±2.2	0.6	1.5±2.2	0.2
Range	0–11.9	0–6.7		0–9.8	
0 to < 3 months	133	18		33	
3 to < 6 months	48	10		6	
6 to < 12 months	11	3		2	
Radiotherapy [*n* (%)]	107 (40)	18 (34)	0.29	20 (36.3)	0.8
Interval between the initial cancer diagnosis and start of radiotherapy (months)					
Mean	5.4±4.8	8.2±6.3	0.03	6.4±5.8	0.38
Range	0–21	0.7–22.5		0.7–20.4	
0 to <3 months	43	5		7	
3 to <6 months	25	4		4	
6 to <12 months	30	4		4	
12 to <24 months	9	5		5	
Type of radiotherapy [*n* (%)]					
Teletherapy	42 (39.3)	9 (50)	0.19	14 (70)	0.4
Brachytherapy	16 (15)	3 (16.7)		2 (10	
Teletherapy and brachytherapy	36 (33.6)	2 (11.1)		3 (15)	
Unknown	13 (12.2)	4 (22.2)		1 (5)	
Endocrine therapy [*n* (%)]	15 (5.6)	2 (3.6)	0.74	5 (9)	0.4
Chemotherapy [*n* (%)]	223 (84.2)	49 (89.1)	0.41	49 (89.1)	1
Interval between the initial cancer diagnosis and start of chemotherapy (months)					
Mean	2±3.3	1.3±1.2	0.13	1.7±3.4	0.4
Range	0–23.6	0–4.7		0–23.6	
0 to <3 months	186	45		44	
3 to <6 months	24	4		4	
6 to <24 months	13	0		1	
Information about systemic agents available [*n* (%)]	149 (66.8)	30 (61.2)	0.5	28 (50)	0.7
Agents received [*n* (%)]					
Single	14 (9.4)	3 (10)	0.02	3 (10)	0.01
Double	85 (56.3)	23 (76.6)		15 (53.5)	
Triple or more	50 (33.5)	4 (13.3)		10 (35.7)	
Type of chemotherapeutic agents received [*n* (%)]					
Platinum and taxanes[d]	79 (53)	23 (76.7)	0.02	15 (53.6)	0.05
Other combination of agents[e]	70 (47)	7 (23.3)		13 (46.4)	
Type of biologic agents received [*n* (%)]					
Bevacizumab or trastuzumab	2 (1.3)	0	0.9	0	
Support agents [*n* (%)]	43 (28.8)	10 (33.3)	0.6	9 (32.1)	0.9

[a] Occult group (*n*=55) compared with entire obvious group (*n*=265) by the Fisher exact or chi-square test.
[b] Women with obvious gynecologic primary tumours matched based on estimated propensity score.
[c] Occult (*n*=55) compared with matched controls (*n*=55) by the Fisher exact or chi-square test.
[d] Platinum-based agents included carboplatin and cisplatin. Taxanes included paclitaxel and docetaxel.
[e] Includes taxanes, platinum, and doxorubicin; nucleotide analogs (gemcitabine and methotrexate IV); cyclophosphamide; topotecan; etoposide; vincristine; and vinorelbine.
[f] Given to control side effects or conditions associated with chemotherapy. Includes ondansetron, filgrastim, alteplase, mannitol, furosemide, zoledronic acid, fondaparinux, and dexamethasone.

Survival Outcomes

In an unadjusted 2-group analysis, OS was worse for women with an occult GPT than for those with an obvious GPT (2-year OS: 34.5% vs. 51.7%; $p = 0.01$; median OS: 18 vs. >24 months; Figure 1; HR: 1.62; 95% CI: 1.2 to 2.35; $p = 0.01$; Table IV).

In a Cox proportional hazards regression analysis adjusted for all baseline patient and tumour characteristics, having an occult compared with an obvious GPT was independently associated with decreased survival (HR: 1.53; 95% CI: 1.14 to 2.25; $p = 0.02$; Table IV). When we used the estimated propensity score as a covariate to adjust for baseline patient and tumour characteristics, having an occult compared with an obvious GPT was also significantly associated with a survival disadvantage (HR: 1.46; 95% CI: 1.1 to 2.13; $p = 0.02$; Table IV). Results were similar when we used a weighted Cox proportional hazards model (HR: 1.72; 95% CI: 1.2 to 2.44; $p = 0.002$; Table IV).

Based on estimated propensity score, we matched the 55 women having an occult GPT with an equal number of women having an obvious GPT. This matched-pair analysis eliminated differences in age, comorbidity score, number of metastatic sites, grade differentiation, primary tumour site, histology, and year of initial diagnosis (Table II) and, as in the other survival analyses, revealed a survival disadvantage for women having an occult compared with an obvious GPT (2-year OS: 34.5% vs. 58.2%; $p = 0.01$; median OS: 18 vs. >24 months; Figure 1; HR: 1.86; 95% CI: 1.2 to 3.1; $p = 0.02$; Table IV).

In additional Cox proportional hazards analyses, having an occult compared with an obvious GPT became a nonsignificant independent predictor of OS when controlling for the use of surgery, RT, and chemotherapy (Table IV). In those analyses, receipt of surgical resection was a significant independent predictor of OS (Table IV). Otherwise, none of the interactions between receipt of a given treatment and primary tumour status (occult vs. obvious) was significant. In subgroup analyses, the wait time after initial diagnosis to receive RT was not a significant independent predictor of OS in women treated with RT in either patient group (data not shown). Similarly, the type of chemotherapeutic agents received (platinum and taxanes vs. other combinations) was not a significant independent predictor of OS in women treated with chemotherapy in either patient group (data not shown).

DISCUSSION

In a population-based analysis, we found that metastatic cancer of uncertain primary site was significantly more frequent in women than in men. In this population, GPTs were the most frequent occult primaries detected in women (19.2%). Compared with their counterparts having metastatic cancer from obvious GPTs, women having metastatic cancer arising from occult GPTs presented with similar histologies and metastatic patterns, but underwent fewer gynecologic clinical and physical examinations, gynecologic surgical examinations, and gynecologic diagnostic imaging procedures during the diagnostic work-up. Moreover, even after the use of multiple approaches to address potential biases that might be introduced by nonrandom selection of the patient subgroups being compared, the

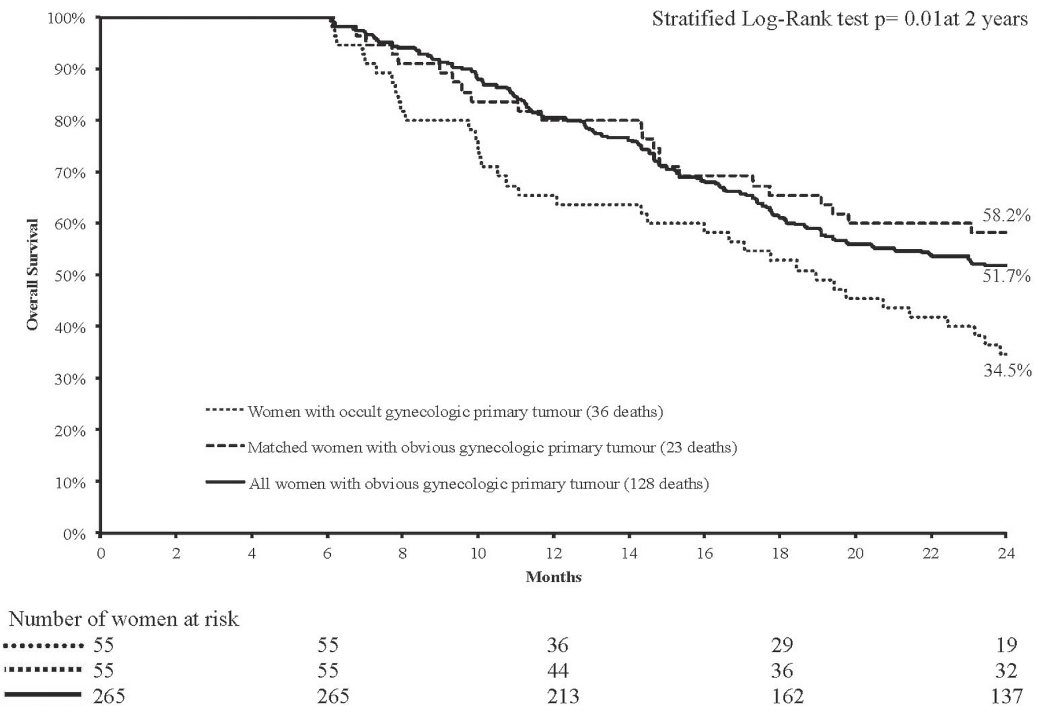

FIGURE 1 Analysis of overall survival, comparing women having occult gynecologic primary tumours with women having obvious gynecologic primary tumours.

TABLE IV Adjusted and unadjusted proportional hazards models[a] for death

Model		Unadjusted			Adjusted[b]										
		Occult vs. obvious			Occult vs. obvious			Surgical resection (no vs. yes[c])			Radiation therapy (no vs. yes[c])			Chemotherapy (no vs. yes[c])		
		HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
All women with metastatic gynecologic cancer (*n*=320)	Unadjusted	1.62	1.2 to 2.35	0.01	1.42	0.96 to 2.08	0.07	2.82	2.05 to 3.88	<0.0001	0.94	0.66 to 1.26	0.66	1.35	0.88 to 2.08	0.16
	Adjusted for patient and disease characteristics	1.53	1.14 to 2.25	0.02	1.42	0.95 to 2.12	0.08	2.76	1.9 to 3.9	<0.0001	0.82	0.53 to 1.29	0.4	1.37	0.84 to 2.22	0.19
	Adjusted for estimated propensity score	1.46	1.1 to 2.13	0.02	1.32	0.89 to 1.97	0.15	2.69	1.94 to 3.73	<0.0001	0.84	0.60 to 1.19	0.34	1.38	0.89 to 2.14	0.13
	Adjusted for patient and disease characteristics[d] using inverse probability weighting	1.72	1.2 to 2.44	0.002	1.45	0.9 to 1.98	0.1	2.75	2.06 to 3.66	<0.0001	0.88	0.69 to 1.13	0.4	1.17	0.88 to 1.65	0.98
For the 55 pairs (*n*=110) of women with metastatic gynecologic cancer matched on estimated propensity score		1.86	1.2 to 3.1	0.02	1.52	0.87 to 2.65	0.13	3.54	2.04 to 6.15	<0.0001	0.86	0.503 to 1.45	0.56	4.04	1.96 to 8.3	0.0001

[a] To test proportionality, time-dependent covariates were created through interactions of the covariates with a function of survival time. When time-dependent covariates were nonsignificant, the covariates were considered proportional. The proportionality assumption was appropriate for all covariates.
[b] Adjusted for receipt of surgical resection, radiation therapy, and chemotherapy.
[c] The interaction between receipt of a given treatment (no vs. yes) and status of the primary tumour (occult vs. obvious) was tested for significance. No significance was found.
[d] Included age, comorbidity, number of metastatic sites, tumour differentiation, histology, primary tumour site, and year of initial diagnosis.
HR = hazard ratio; CI = confidence interval.

women with occult GPTs were observed to experience a 17.2% decrease in OS at 2 years (Figure 1) and a 46%–86% increase in risk of mortality (Table IV). The main difference between the two patient groups was in certain cancer treatments. In particular, women with occult GPTs were significantly less likely to receive surgical interventions, they waited longer after the initial diagnosis to receive RT, and they received a lesser variety of chemotherapeutic agents. The independent effect on OS of underutilization of surgery was significant and appeared to account for a large proportion of the observed increase in risk of mortality for women with occult GPTs (Table IV).

To our knowledge, the present study is the first to use population-based data that reflect real-world clinical practice in evaluating occult primary tumours in a female patient population initially diagnosed with metastatic cancer. Given the high incidence of occult GPTs observed in our study, oncologists and pathologists should take our findings into consideration when conducting clinical, surgical, pathology, and radiologic evaluations of women presenting with metastatic cancer of uncertain primary site. For instance, immunohistochemistry (IHC) stains for the initial diagnostic biopsy are chosen based not only on clinical findings and histologic diagnosis, but also on a knowledge of common potential tumour types with relatively diagnostic IHC profiles[24]. Several IHC staining profiles are highly specific and suggestive (that is, diagnostic) of GPT types[24,25], and one possible barrier to an accurate early diagnosis of a GPT site in the course of metastatic disease is simply not considering and applying the most appropriate IHC profiles[26,27]. That scenario is a possibility because an indiscriminate approach of multiple IHC tests is currently not recommended. Such an approach frequently exhausts the biopsy specimen and often is not more revealing than a measured and rational stepwise approach[24,28]. Given our findings, oncologists and pathologists could ensure the selection of one or more proper IHC panels for women presenting with metastatic cancer of uncertain primary. Similarly, they could ensure a quick referral for such women to early and full physical examination and imaging of the pelvis. Such action might potentially enable the diagnosis of a GPT[24–27], leading to the quick referral of women for specialized gynecologic oncology services and appropriate therapy early in the course of their metastatic disease. Thus, our data are relevant in generating and designing optimal referral and triage guidelines for patients presenting with metastatic cancer of uncertain primary at cancer care centres.

Having an occult GPT was associated with less surgical intervention and decreased OS. However, our analysis does not prove that the observed association is causal. Patients with occult primary tumours might have had a higher disease burden at diagnosis or a reduced functional status, rendering them unsuitable for surgical intervention. Higher disease burden is usually associated with worse prognosis. Those patients might also have a more aggressive tumour biology, associated both with worse prognosis and with earlier metastatic spread from a smaller and less symptomatic primary tumour. Nevertheless, the hypothesis that more surgical intervention might be beneficial for such patients is of interest to potentially improve survival, as supported by clinical data reported elsewhere[29]. However, induction chemotherapy to reduce the tumour burden or to improve functional status, or both, might be necessary first.

Although a lesser use of systemic treatment was not associated with survival outcomes in our study, it might be more important in the near future[4,24,25]. Novel chemotherapeutic agents and targeted biologic therapies are being identified for the treatment of advanced gynecologic cancers[30–35]. For instance, angiogenesis inhibitors such as bevacizumab have been tested in phase III trials for women with metastatic ovarian[36,37], cervical[38], and uterine cancer[34,39] and appear to improve survival. Those therapies have been tested and approved, and are reimbursed in many jurisdictions within the context of primary tumour type.

Overall, our data suggest that identification of occult GPTs early in the course of metastatic cancer is currently important and will continue to be important, because identification might enable more effective treatment decisions. Thus, diagnostic tools that are more accurate are currently needed. For instance, gene expression profiling assays for the identification of primary tumours in metastatic cancer[6,40–46] have recently emerged to complement traditional diagnostic procedures (for example, IHC analyses and computed tomography imaging) and are particularly useful when dealing with diagnostic difficulties[24,25,28].

The main limitations of our study relate to its retrospective nature and the limitations of administrative data. For example, the types of systemic therapy agents given were not collected by the Provincial Pharmacy Program before 2004, and thus that information was unknown for women diagnosed in 2002 and 2003. The MCR and the administrative databases held by Manitoba Health also do not collect certain relevant information about factors associated with the diagnostic work-up or about biologic markers. Examples include the type and location of health care facilities, specialist referrals, and type and frequency of IHC tests. Thus, we were unable in this study to examine the actual diagnostic barriers in women with an occult GPT. However, the identification of real-life patients with occult GPTs permits future investigation by retrospective chart review or health record review of more detailed and expensive risk factors associated with an occult GPT. Future studies can further link such real-life patients with specimens from banks of tumour tissue samples to study the potential utility of IHC and gene expression profiling assays.

CONCLUSIONS

Metastatic cancer of uncertain primary origin is more common in women than in men. The most common occult primary tumours identified in women were GPTs. Compared with their counterparts having an obvious metastatic GPT, women with an occult GPT have similar clinicopathologic features, but receive fewer gynecologic diagnostic examinations and surgical interventions, and experience decreased OS. Early and full physical examination and imaging of the pelvis in women presenting with metastatic cancer of uncertain primary site could potentially enable early diagnosis of an occult GPT and thus contribute to more effective treatment decisions and improved survival outcomes.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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