UNIVERSITY OF TWENTE

MASTERS IN HEALTH SCIENCES

ASSOCIATION BETWEEN MUCINOUS OVARIAN TUMORS AND SECONDARY GASTROINTESTINAL TUMORS

Author
Yomi Okegunna

Supervision University of Twente
First supervisor : Prof Sabine Siesling, PhD
Second supervisor : Brenda Bergink-Voorthuis, MSc

Supervision external organization
Netherlands Comprehensive Cancer Organization (IKNL)
First supervisor : Prof Maaike Van Aa, PhD
Second supervisor : Prof Hans Wezel, PhD

ABSTRACT

Aim: Secondary gastrointestinal (sGI) tumors can occur after the diagnosis of mucinous ovarian tumors (mOTs) and often have a bad prognosis. This study examined the occurrence of sGI tumors in women who were previously diagnosed with mOTs and its behavioral subtypes, the invasive mucinous ovarian tumors (imOTs) and mucinous borderline ovarian tumors (mBOTs). Besides, risk factors associated with occurrence of a sGI tumor and the risk factors on the survival of mOT patients with sGI tumors were investigated.

Methods: Women diagnosed with mOTs and sGI tumors between 1989 and 2021 were identified from the Netherlands Cancer Registry(NCR). Of the women with mOTs, those with the subtypes imOTs or mBOTs were identified. The interaction term between mOTs (imOT and mBOT) and the laterality of tumors was investigated using linear regression. Multivariable logistic regression analysis was used to identify risk factors associated with having a sGI tumor. Kaplan-Meier analysis was used to estimate the survival of imOT and mBOT women with a sGI tumor. Log-rank analysis was used to indicate the equality of survival functions of both subtypes. A graphical hazards proportionality assessment and Schoenfeld residuals were performed for proportional-hazards assumption. Cox proportion hazard regression model was applied to examine the risk factors on the survival among mOT patients with sGI tumors.

Results

Of 8992 mOT patients, 4730 (53%) had an imOT and 4624 (47%) had a mBOT. A total of 277 women (3%) developed a sGI tumor, which was found more often in patients with imOTs, compared to those with mBOTs (4% vs. 3%, p=0.003). The Lower sGI tumors (60%) were the most frequent in both groups. Age (OR 1.02; 95% CI [1.01-1.02]; P <.001), morphological characteristics of mOTs such as mucinous cystadenoma (OR 2.67; 95% CI [1.67-4.26]; p <0.001), papillary mucinous cystadenoma (OR 3.02; 95% CI [1.43-6.39]; P = 0.004), and invasiveness compared to borderline behavioral subtypes of mOTs (OR 2.14; 95% CI [1.53- 2.99]; P <.001) emerged as significant risk factors of having a sGI tumor. In addition, age (HR 1.04; 95% CI [1.02-1.06]; P <.001), hepatobiliary tumors (HR 2.43; 95% CI [1.46-4.92] , p = 0.001), < 1 year of sGI diagnosis from mOTs diagnosis (HR 47.04; 95% CI [13.47-164.29], P <.001), 1-8 year interval of sGI diagnosis from mOTs diagnosis (HR 19.27; 95% CI [5.98-61.85], P <.001), 9-16 year interval of sGI diagnosis from mOTs diagnosis (HR 6.11; 95% CI [1.93-18.65], P = 0.002),

and advanced disease stage (HR 2.38; 95% CI [1.33-4.25], P = 0.003) emerged as significant risk factors of death of mOT patients with sGI tumors.

Conclusion

There is low occurrence of sGI tumors among women who were previously diagnosed with mOTs or its subtypes, the imOTs or mBOTs. However, this is clinically significant because the percentage of mOT patients being alive decreases every year after the diagnosis of a sGI tumor. In addition, imOT patients have a lower risk of death than patients with mBOTs. The results of the study indicated some factors such as the age of patient, the morphological types, and the behavioral subtypes of mOTs, as risk factors of having a sGI tumor. These factors could help lead to personalisation of diagnostic work-up of patients at high risk for a sGI tumor. The results also revealed age, laterality of mOTs, location of sGI tumor diagnosis, the time interval of sGI tumor diagnosis after mOT diagnosis, and the disease stage of mOTs, as bad prognostic factors of survival from having mOT with sGI tumor. These factors could also lead to personalization of treatment methods of patients based on the degree of influence each factor has on the outcome of treatment.

Keywords: Metastasis, mucinous ovarian tumors (mOTs), mucinous invasive ovarian tumours (imOTs), mucinous borderline ovarian tumor(mBOTs), secondary gastrointestinal (sGI) tumors.

1. INTRODUCTION

Mucinous ovarian tumors (mOTs) account for 6% of all ovarian tumors that affect women all over the world. In the Netherlands, 7600 women are diagnosed yearly with ovarian tumours, of which 3% are mOTs [1]. mOTs are tumors that have mucus coated around their cells. These types of tumors have three behavioral subtypes, the benign mOTs, the borderline mOTs or mBOTs, and the invasive mOTs or imOTs [1]. The benign mOTs are known to have more differentiated cells than both the mBOTs and imOTs, but the imOTs are the only behavioral subtype with a stromal invasion. In general, the mBOTs are known to be more common. They are approximately 67% of all mOTs [2]. They more often occur in women in either ovary (79%) than in both ovaries (5%) [2]. They are diagnosed in women at any age, but occur mostly in women after the age of 45 [3]. Also, 80% of mucinous tumor of the ovary are metastatic in nature [2].

Secondary tumors constitute 15-20% of all tumors diagnosed in the world. One of their common location is in the gastrointestinal tract [5]. The sGI tumor can be located anywhere in the GI tract from the mouth to the anus [6]. Although, sGI tumors are very rare in women, they can occur after

mOTs. [7]. Recent literatures reported cases where mOTs were discovered to have metastasized to the GI tract [3, 8, 9]. In general, the most commonly reported sites of sGI tumors are the small intestines and the stomach [10]. They are said to have poor prognosis as they are diagnosed late and are detected incidentally during investigative and therapeutic procedures for unrelated diseases [11, 12]. The aim of this study is to examine the occurrence of sGI tumors in women who were previously diagnosed with imOTs or mBOTs. This is relevant because it indicates the influence of a sGI tumor diagnosis on the prognosis of these women. Besides, risk factors associated with occurrence of a sGI tumor, and the risk factors on the survival of mOT patients with sGI tumors were investigated.

2. RESEARCH DESIGN METHODS

Study design and patient selection

A retrospective study was performed by analyzing data obtained from the Netherlands Cancer Registry (NCR). This is a population-based registry which consists of patients diagnosed with new malignancies in the Netherland since 1989. The NCR is hosted by the Netherlands Comprehensive Cancer Organization (IKNL) which is an independent institution responsible for registering data from all Dutch hospitals. The registration clerks frequently extract the information of patients from medical records available within hospitals. All of these clerks undergo the same training which involved the use of a coding manual specifically made for each malignancy. This ensures uniformity in the interpretation and entry of data. The data analyzed for this research was for all women diagnosed with mOTs from 1989 till 2021 [13]. Data on the behavioral subtypes (imOTs and mBOTs), age, location and presence of sGI tumors, morphology, topographical site and subsite and differential grade was collected through the municipality registry. The vital status of all mOT patients were also collected.

Statistical Analysis

Descriptive statistics were used to characterize sGI patients with imOTs and mBOTs. The qualitative variables were expressed as absolute frequencies and percentages while the quantitative variables were reported using mean and standard deviation. The non-normal distributed data were reported using median and interquartile range.

The interval between mOT and sGI tumors diagnosis was categorized as <1 year, within 1-8 years,9-16 years,17-24 years, and 25-32 years. The types of sGI tumors present in patients with an imOTs or mBOTs were compared. Furthermore, in the NCR, the classification of tumors is not

according to the FIGO (The international federation of gynecology and obstetrics) staging system. Thus, the TNM (tumor, node and metastasis) stages of tumor were converted into FIGO stages to fit the NCR classification and grouped into early (IA-IIA) and advanced (IIB-IVB).

Associations between the qualitative variables of patient and tumor characteristics were assessed using Pearson chi squared test. Multivariable logistic regression analysis was used to identify risk factors associated with having a sGI tumor after a mOT diagnosis. Kaplan-Meier analysis was used to estimate the survival of mOT patients with sGI tumors. A log rank was used to test for equality in the survival functions of both groups. A Cox regression model was used to examine risk factors associated with death and to calculate the hazard ratios (HR) and 95% confidence intervals (CI) in patients with mOTs and sGI tumors. In addition, a Cox regression was performed separately for imOT patients with an sGI tumor and mBOT patients with an sGI tumor to examine risk factors associated with death in each behavioral subtypes. A graphical hazard proportionality assessment and Schoenfeld residuals were performed to assess the proportional-hazards assumptions in imOTs and mBOTs patients with sGI tumors. The predictors used in the Cox regression model were selected based on predictors sited in the literature (i.e. clinical outcomes among women with mOTs) [14] .All of the analyses were effectuated using Stata/SE version 14.2 (Stata Corporation, College Station, TX, USA). Predictors from univariable analyses were included in the multivariable analysis if $P < 0.1$. Statistical tests were considered to be significant for the multivariable analysis if $P < 0.05$.

3. RESULTS

Study population

A total of 8,992 women were identified with mOTs in the NCR. Of these, 277 (3%) patients were reported with sGI tumors. Topographical site and subsite, laterality of tumor, disease stages, and differentiation grade of mOTs are summarized in Table 1. The imOTs were more often diagnosed at a more advanced disease stage than the mBOTs among women with mOTs (30% vs 0% respectively). There were also more patients reported with mOTs in either the left (45%) or the right ovary (43%) than in both ovaries (8%).

Table 1 - Characteristics of mOTs and its behavioral subtypes, mBOTs and imOTs

Characteristics, n (%)	mOTs	mBOTs	imOTs	P
Mean age at diagnosis* (SD)	54 (16)	53 (16)	56 (16)	
Topographical site and subsite	n = 8992	n = 4262	n = 4730	0.001
Ovary	8922 (99)	4246 (100)	4676 (99)	
Specified parts of the peritoneum	31 (0)	8 (0)	23 (0)	
Not specified parts of the peritoneum	31 (0)	7 (0)	24 (0)	
Fallopian tube	8 (0)	1 (0)	7 (0)	
Laterality of tumor	n = 8704	n = 4204	n = 4500	<.001
Left only	4077 (47)	2165 (51)	1912 (42)	
Right only	3862 (44)	1947 (46)	1915 (43)	
Both	703 (8)	77 (2)	626 (14)	
Unknown	62 (1)	15 (0)	47 (0)	
Disease stage	n = 8992	n = 4262	n = 4730	<.001
Early (IA-IIA)	3215 (36)	841 (20)	2374 (50)	
Advanced (IIB-IVB)	1436 (16)	10 (0)	1426 (30)	
Unknown	4341 (48)	3411 (80)	930 (20)	
Differentiation grade	n = 8992	n = 4262	n = 4730	<.001
Well	1434 (16)	37 (1)	1397 (30)	
Moderately	845 (9)	0 (0)	845 (18)	
Poorly	486 (5)	1 (0)	485 (10)	
Undifferentiated	14 (0)	0 (0)	14 (0)	
Unknown	6213 (69)	4224 (99)	1989 (42)	

***** of primary tumor; **mOTs** mucinous ovarian tumors; **mBOTs** mucinous borderline ovarian tumors; **imOTs** invasive mucinous ovarian tumors; The summation of percentages might not sum to 100% because of rounding

The lower sGI tumors (60%) were the most frequent sGI tumors among the 277 mOT patients who had sGI tumors (Table 2). Over half of the sGI tumor diagnosis (61%) were recorded between year 1-16 after the diagnosis of mOTs. In addition, sGI tumor diagnosis among patients with imOTs (53%) was less when compared to those with mBOTs (75%) between year 1-16 (Table 2). Overall, there are 187 (68%) patients reported dead and 90 (32%) patients reported alive among women with both mOTs and sGI tumors. Also, the interaction value between mOTs and the laterality of tumor diagnosed as a predictor of survival of patients reported no significance (P = 0.314).

Table 2 - sGI tumor characteristics present in mOTs and its behavioral subtypes, the mBOTs and the imOTs

Characteristics, n (%)	mOTs	mBOTs	imOTs	P
Mean age at diagnosis* (SD)	57 (12)	57 (12)	58 (12)	0.612
Location of sGI tumors present	n = 277	n = 107	n = 170	0.858
Upper sGI-tumors	34 (12)	12 (11)	22 (13)	
Lower sGI-tumors	165 (60)	62 (58)	103 (61)	
Hepatobiliary tumors	58 (21)	24 (22)	34 (60)	
Other sGI-tumors	20 (7)	9 (8)	11 (6)	
sGI diagnosis based on intervals (years) after the initial diagnosis of a mOT	n = 255	n = 98	n = 157	<.001
< 1 year	42 (16)	11 (11)	31 (20)	
1-8 years	89 (35)	47 (48)	42 (27)	
9-16 years	81 (32)	33 (34)	48 (30)	
17-24 years	36 (14)	5 (5)	31 (20)	
25-32 years	7 (3)	2 (2)	5 (3)	

* of sGI patients**, sGI** secondary gastrointestinal; **mOTs** mucinous ovarian tumors; **mBOTs** mucinous borderline ovarian tumors; **imOTs** invasive mucinous ovarian tumors; The summation of percentages might not sum to 100% because of rounding.

Risk analysis for sGI

The results of the logistic regression analysis of risk factors associated with the occurrence of sGI tumors in women with mOTs are reported in Table 3. The result of the stratified analysis for the tumor behavioral subtype imOT is reported in Table S1 (see supplementary materials section).

In the logistic regression univariable analysis, age (P = 0.002), morphological characteristics (P = 0.002), bilaterality of tumors (P = 0.077), imOT behavior (P = 0.003), poor differentiation grade (P = 0.052), ovary (P = 0.004), and non-specified parts of the peritoneum as a topographical site (P = 0.077), were associated as risk factors for the occurrence of a sGI tumor among the population of women with mOTs.

In the logistic regression multivariable analysis, age (OR 1.02; 95% CI [1.01-1.02]; P <.001), morphological characteristics of mOTs such as mucinous cystadenoma (OR 2.67; 95% CI [1.67-4.26]; p <0.001), papillary mucinous cystadenoma (OR 3.02; 95% CI [1.43-6.39]; P = 0.004), and invasiveness compared to borderline behavioral subtypes of mOTs (OR 2.14; 95% CI [1.53- 2.99]; P <.001) emerged as significant risk factors of having a sGI tumor.

Table 3 - Univariable and multivariable logistic regression analysis of risk factors for the occurrence of a sGI tumor in the mOT population

	mOTs	Univariable			Multivariable		
		OR	95% CI	P	OR	95% CI	P
Age at diagnosis*, years (SD)	54 (16)	1.01	1.00-1.02	0.002	1.02	1.01-1.02	<.001
Morphology, n (%)	**n = 8992**			0.002			
Mucinous cystadenocarcinoma	1851 (21)	1.58	1.19-2.10		2.67	1.67-4.26	<.001
Papillary mucinous cystadenoma	233 (3)	1.74	0.93-3.26		3.02	1.43-6.39	0.004
Mucinous cystic tumor of borderline malignancy	4759 (53)	Reference			Reference		
Cystadenoma borderline malignancy	120 (1)	2.50	1.20-5.24		2.07	0.98-4.37	
Mucinous adenocarcinoma	1576 (18)	0.89	0.62-1.28		1.53	0.87-2.71	
Mucin-producing adenocarcinoma	351 (4)	0.51	0.21-1.25		1.16	0.41-3.28	
Mucinous adenocarcinoma, endocervical type	17 (0)	2.19	0.29-16.64		4.30	0.54-34.46	
Metastatic signet ring cell carcinoma	61 (1)	-			-		
Mucinous adenocarcinofibroma	24 (0)	1.52	0.20-11.37		1.90	0.25-14.33	
Laterality, n (%)	**n = 8642**						
Unilateral	7939 (92)	Reference			Reference		
Bilateral	703 (8)	0.61	0.36-1.05	0.077	0.57	0.32-1.02	
Tumor behavior, n (%)	**n = 8992**						
mBOTs	4262 (47)	Reference			Reference		
imOTs	4730 (53)	1.45	1.13-1.85	0.003	2.14	1.53-2.99	<.001
Disease stage, n (%)	**n = 8992**						
Early IA-IIA	3215 (36)	Reference			Reference		
Advanced IIB-IVB	1436 (16)	0.80	0.53-1.94	0.273	0.92	0.58-1.46	
Unknown	4341 (48)	1.23	0.95-1.60	0.120	3.12	1.94-5.02	
Differentiation grade, n (%)	**n = 8992**						
Well	1434 (16)	Reference			Reference		
Moderately	845 (9)	1.04	0.66-1.65	0.867	1.18	0.73-1.91	
Poorly	486 (5)	0.47	0.22-1.00	0.052	0.60	0.27-1.35	
Undifferentiated	14 (0)	-			-		
Unknown	6213 (69)	0.89	0.65-1.23	0.482	1.20	0.80-1.82	
Topographical site and subsite	**n = 8992**						
Ovary	8922 (99)	0.10	0.02-0.47	0.004	0.07	0.01-0.44	
Specified parts of the peritoneum	31 (0)	-			-		
Non-specified parts of the peritoneum	31 (0)	0.10	0.01-1.29	0.077	0.06	0.02-1.32	
Fallopian tube	8 (0)	Reference			Reference		

OR Odds Ration; **CI** Confidence Interval; * mean (SD); The summation of percentages might not sum to 100% because of rounding and missing results. (-) no result

In the logistic regression multivariable analysis of imOT patients (Table S1), ovary as the topographical site of mOT (OR 0.47; 95% CI [0.01-0.31]; P = 0.001) emerged as an independent predictor of the risk of having sGI tumors.

Survival analysis for survival of mOT patients with sGI tumors

After 5 years of the diagnosis of sGI tumors among patients with mOTs, the survival rate was 81.07%. After 30 years, the survival rate became 13.22%. In general, the percentage of patients being alive decreases with every year from the diagnosis of a sGI tumor. The median survival time for imOT and mBOT patients with an sGI tumor were 16 years (interquartile range 0-32) and 12 years (interquartile range 0-32) respectively.

Differences in the survival rates were observed between imOT and mBOT patients with sGI tumors. After 5 years, the survival rates was 79.32% and 83.87% respectively. The percentages decreased to 9.73% and 16.27% after 30 years. Log rank analysis indicated the survival functions of both groups are not equal (P <.001).

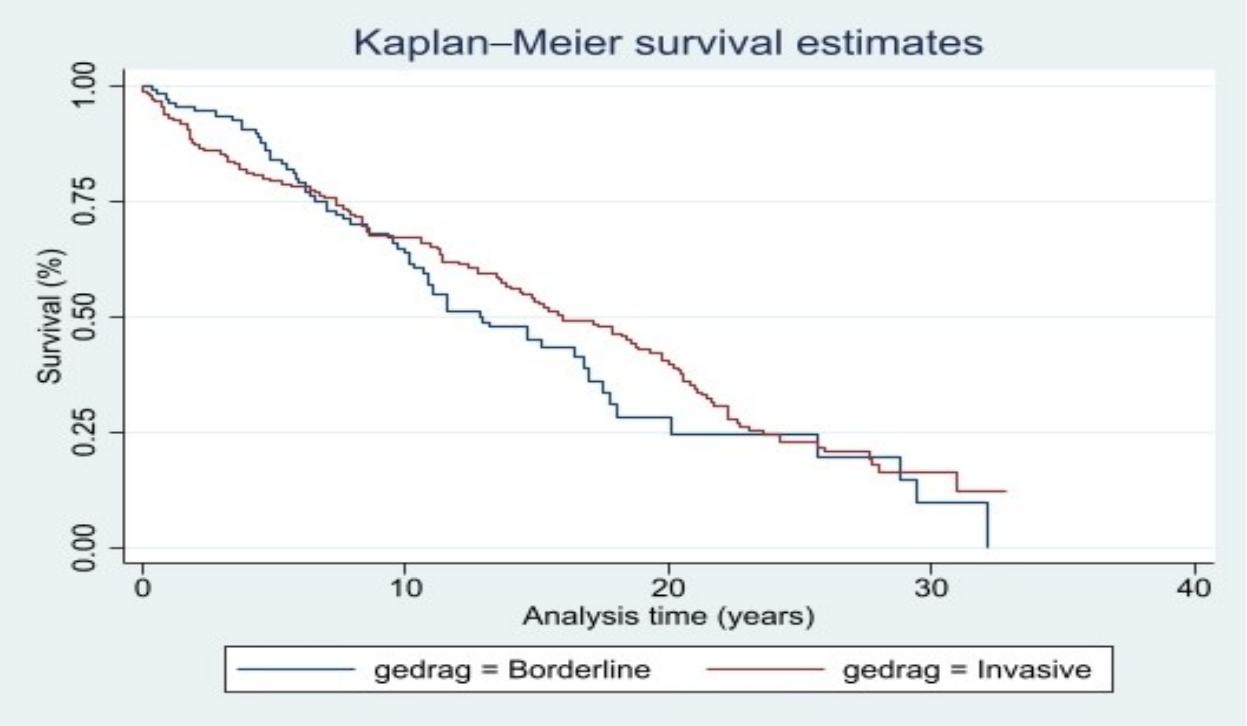

Figure 1. Kaplan-Meier survival curve estimates for patients with imOTs and mBOTs and sGI

Analysis in Figure 2 show non-parallel curves between sGI patients in imOTs and mBOTs. This indicates that the survival probability of patients with a sGI tumor in either of the behavioral subtypes is dependent on the time of diagnosis. Schoenfeld residuals also indicated a non-significant association between imOT and mBOT patients with sGI tumors (P = 0.276).

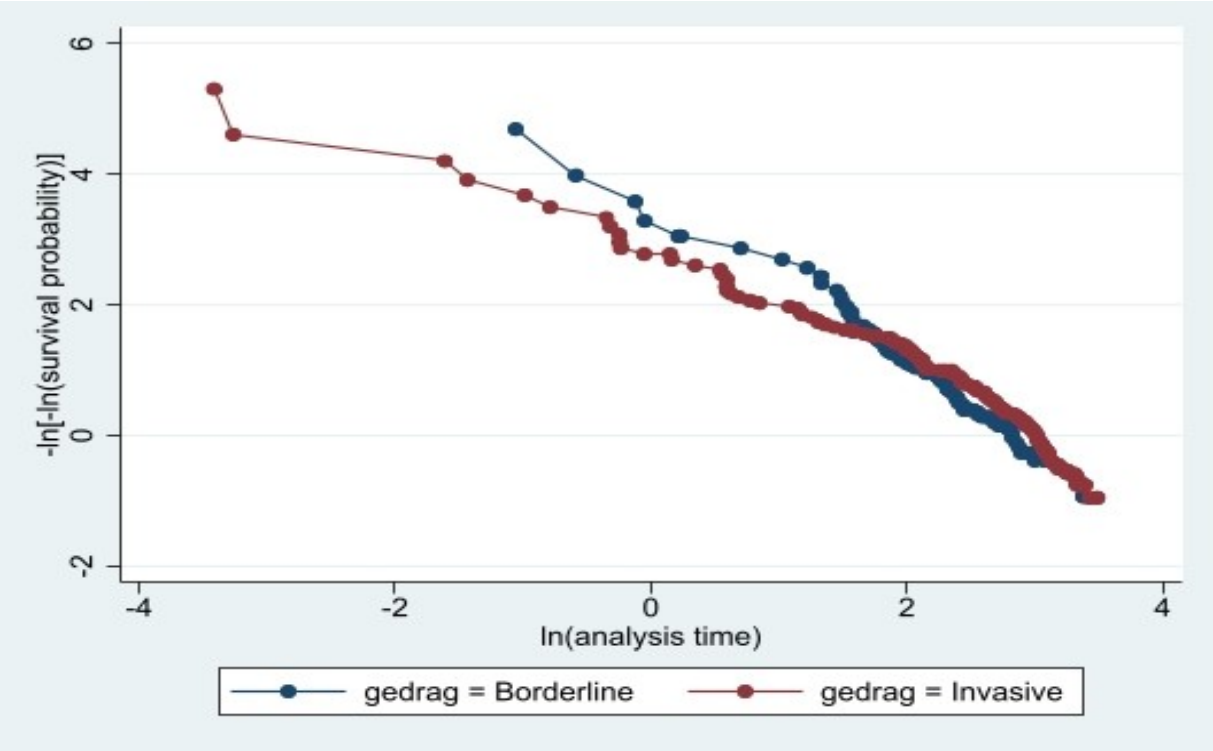

Figure 2. Graphical assessment of proportional hazards assumption

The Cox regression analysis for mOT patients with sGI tumors (Table 4) showed age (HR 1.04; 95% CI [1.02-1.06]; P <.001), hepatobiliary tumors (HR 2.43; 95% CI [1.46-4.92] , p = 0.001), < 1 year of sGI diagnosis from mOTs diagnosis (HR 47.04; 95% CI [13.47-164.29], P <.001), 1-8 year interval of sGI diagnosis from mOTs diagnosis (HR 19.27; 95% CI [5.98-61.85], P <.001), 9-16 year interval of sGI diagnosis from mOTs diagnosis (HR 6.11; 95% CI [1.93-18.65], P = 0.002), and advanced disease stage (HR 2.38; 95% CI [1.33-4.25], P = 0.003) emerged as significant risk factors on the survival of mOT patients with sGI tumors.

Also, the Cox regression analysis for only imOT patients with sGI tumors in supplementary Table S2 showed age (HR 1.05; 95% CI [1.03-1.07]; P <.001), hepatobiliary tumors (HR 2.40; 95% CI [1.09-5.27] , p = 0.029), < 1 year of sGI diagnosis from imOTs diagnosis (HR 38.60; 95% CI [7.57-196.68], P <.001), 1-8 year interval of sGI diagnosis from imOTs diagnosis (HR 11.97; 95% CI [2.52-56.86], P <.001), and advanced disease stage (HR 2.04; 95% CI [1.13-3.69], P = 0.018) emerged as significant risk factors on the survival of imOT patients with sGI tumors.

In addition, the Cox regression analysis for only mBOT patients with sGI tumors in supplementary Table S3 showed age (HR 1.04; 95% CI [1.01-1.07]; P < 0.013), hepatobiliary tumors (HR 4.11; 95% CI [1.50-11.29] , p = 0.006), < 1 year of sGI diagnosis from imOTs diagnosis (HR 103.61; 95% CI [7.56-1419.22], P 0.001), 1-8 year interval of sGI diagnosis from imOTs diagnosis (HR

79.93; 95% CI [7.58-843.11], P <.001), 9-16 year interval of sGI diagnosis from imOTs diagnosis (HR 13.68; 95% CI [1.45-128.63], P = 0.022), and advanced disease stage (HR 19.30; 95% CI [2.40-155.41], P = 0.005) emerged as significant risk factors on the survival of mBOTs patients with sGI tumors.

Table 4 - Univariable and multivariable Cox regression analysis on risk factors on the survival of mOT patient with sGI tumors (n=277)

	Univariable			Multivariable		
Risk factors	HR	95% CI	P	HR	95% CI	P
Age, years	1.04	1.03-1.06	<.001	1.04	1.02-1.06	<.001
Laterality						
Unilateral	Reference			Reference		
Bilateral	1.13	0.58-2.23	0.715	1.39	0.64-3.02	
Location of sGI tumors present						
Upper sGI-tumors	Reference			Reference		
Lower sGI-tumors	0.74	0.50-1.09	0.126	0.47	0.31-0.77	0.001
Hepatobiliary tumors	1.88	1.10-3.18	0.020	2.43	1.46-4.92	0.001
Other sGI-tumors	-			-		
sGI diagnosis based on intervals (years) after the initial diagnosis of a mOT						
< 1 year	15.85	5.23-47.99	<.001	47.04	13.47-164.29	<.001
1-8 years	13.28	4.58-38.53	<.001	19.27	5.98-61.85	<.001
9-16 years	3.75	1.32-10.66	0.013	6.11	1.93-18.65	0.002
17-24 years	2.28	0.78-6.66	0.130	2.46	0.77-7.82	
25-32 years	Reference			Reference		
Differentiation grade, n (%)						
Well	Reference			Reference		
Moderately	1.61	0.91-2.86	0.100	0.75	0.36-1.59	
Poorly	2.18	0.96-4.99	0.064	2.16	0.86-5.46	
Unknown	1.41	0.94-2.11	0.096	2.95	1.69-5.17	
Disease stage, n (%)						
Early IA-IIA	Reference			Reference		
Advanced IIB-IVB	1.84	1.16-2.92	0.010	2.38	1.33-4.25	0.003
Unknown	0.10	0.72-1.37	0.977	0.69	0.46-1.10	

sGI secondary gastrointestinal; **HR** Hazard Ratio; **CI** Confidence Interval; (-) no result

4. DISCUSSION

In this nationwide multicenter observational study in the Netherlands, only 3% of women had sGI tumors among women with mOTs. According to the results, this is still clinically significant because the percentage of mOT patients being alive decreases every year after the diagnosis of a sGI tumor. Conversely, imOT patients diagnosed with sGI tumors after 30 years have worse survival rates when compared to mBOT patients with sGI tumors after the same time period (9.73% vs 16.27%).

Age, morphological types, and the tumor behavioral subtypes of women with mOTs were found to be significant risk factors for the occurrence of a sGI tumor in mOT patients (P <.001). In addition, recent studies suggest that those with a first and second degree family history of GI tumors are also of significant risk of having a sGI tumor [15, 17, 18]. About 1 in every 3 persons with a history of sGI tumors have other family members with the same diagnostic history [17] . In this research, the most frequently diagnosed sGI tumors are the lower sGI tumors which were higher among the imOTs compared to those with mBOTs. The most frequent lower sGI tumors diagnosed were the colon and rectal tumors (colorectal tumors). Although, there is reportedly wide variation in geography of incidence and mortality of colorectal tumors across the world, they still rank third position among the most worldwide diagnosed tumors [19]. They are also third place in most occurring malignancy in the Netherlands [9]. Therefore, it is not surprising they are the most frequent sGI types among the mOT population.

In addition, the results also indicate that the risk factor on the survival of both groups depend on the time of diagnosis of a sGI tumor. Thus, the closer the diagnosis of a sGI tumor from the primary mOT diagnosis, the higher the risk of death of the patient. Also, this risk is higher in imOT patients than it is in mBOT patients. A cox regression was performed for the risk factors on the survival of sGI tumor patients in the whole mOTs population and also for each of its behavioral subtypes. The results obtained showed the intervals between < 1 year, 1-8 years
9-16 years as the years of diagnosis of a sGI tumor from mOTs which has a significant risk on the survival of patients with mOTs (P<.001). This reveals that patients with sGI tumor diagnosis much later after the mOTs diagnosis might have more influence of risk factors which reduces the chance of survival from both diseases, such as advanced age [22].Some studies reveal later consequences such as neighboring and distant organ metastasis of sGI tumor detected much later in life [24, 25].

Although, GI tumors are the secondary tumors in this research, they could have remained non-symptomatic and undetected for years in the GI tract [22]. This could have resulted in their late

diagnosis years after the primary mOTs. Conversely, it can also be suggested that the years where GI tumors remained undetected might have occurred even before the diagnosis of mOTs in some women. In this group of women, the tumor could have metastasized during this period to the ovaries to cause mOT as a primary tumor. In this case, the GI tumor would be the primary tumor if it had been detected much earlier before the diagnosis of mOT.

We identified imOT patient as having higher risk for the diagnosis of a sGI tumor in comparison to a mBOT patient ($P < .001$). This is also in accordance with multiple reviews on the ability of imOT to metastasize to neighboring and distance organs such as the GI tract [7, 8, 22]. Although, in the studies under ovarian tumors metastasis, only imOTs were measured. Whereas in our study, since there was no information on benign mOTs and they are not expected to influence the risk of sGI tumors, the focus was on data reported for both the imOTs and mBOTs [3, 7]. Also, the data for the FIGO classification of mBOT patients in this study only started from 2007 till date. This is in contrast to that of the imOT patients recorded since 1989. In addition, missing values are due to registration practice. Also, other literature suggests empty and omitted results in a data might be due to multicollinearity [23].

The supplementary results on imOT and mBOT patients showed age, location of sGI tumor, the time interval of sGI tumor diagnosis, and the disease stage as important risk factors of survival of imOT and mBOT patients with sGI tumor diagnosis. A study in accordance showed that advanced stage of sGI tumor diagnosis in older imOT women when compared to mBOT women is the cause of worse prognosis and lower survival rate among this group [27]. Thus, in clinical practice, early diagnostic measures of a sGI tumor such as early screening among women with first and second degree family history of sGI tumors should be examined [14, 25].

The strength of this study was the use of nationwide data from NCR. This ensures the provision of data from clinical practice from selected hospitals. In addition, the high-quality data from NCR is a large sample size that has close to complete nationwide coverage, by this including every region of the country. Furthermore, the data provided can be investigated to identify areas of improvement in sGI tumor diagnosis and treatment among mOT patients. The data also included the behavioral subtypes of mOTs, the imOTs and the mBOTs.

A limitation of an observational research is its dependency on the quality and completeness of data present in the medical record. There were missing values in the data analyzed for this research. One major limitation is the absence of information on other possible diseases present in

mOT patients other than sGI tumors such as hypertension and diabetes. These are common with increase in age [26]. The presence of these other diseases might also be influential in the mortality outcomes of mOT patients with sGI tumors.

6. CONCLUSION

There is low occurrence of sGI tumors among women who were previously diagnosed with mOTs or its subtypes, the imOTs or mBOTs. However, this is clinically significant because the percentage of mOT patients being alive decreases every year after the diagnosis of a sGI tumor. In addition, imOT patients have a lower risk of death than patients with mBOTs. The results of the study indicated some factors such as the age of patient, the morphological types, and the behavioral subtypes of mOTs, as risk factors of having a sGI tumor. These factors could help lead to personalisation of diagnostic work-up of patients at high risk for a sGI tumor. The results also revealed age, laterality of mOTs, location of sGI tumor diagnosis, the time interval of sGI tumor diagnosis after mOT diagnosis, and the disease stage of mOTs, as bad prognostic factors of survival from having mOT with sGI tumor. These factors could also lead to personalization of treatment methods of patients based on the degree of influence each factor has on the outcome of treatment. This could be by the adopting either pharmaceutical or/and non-pharmaceutical treatments such as chemotherapy, radiation therapy or surgery for different patients based on presenting risk factors. In addition, the focus of clinical practice should be on early screening and diagnosis for possible mOTs and GI tumors. One way of achieving this is encouraging women to be aware of their first and second degree family history with mOTs and GI tumors. This will help determine their level of risk towards having these tumors.

REFERENCES

[1] S. Christopher, "A resident's perspective of ovarian cancer," *Diagnostics,* vol. 7, no. 2, p. 24, 2017.

[2] G. Abdulaziz and B. Prafull, "Mucinous Cancer of the Ovary: Overview and Current Status," *National Library of Medicine,* vol. 10, no. 1, p. 52, 2020.

[3] P. Barbora and N. S. Dundr, "Primary mucinous ovarian tumors vs. ovarian metastases from gastrointestinal tract, pancreas and biliary tree: a review of current problematic," *National Library of Medicine,* vol. 20, 11 March 2021.

[4] L. M. Morton, . K. Onel and R. . E. Curtis, "The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults," pp. 57-67, 2014.

[5] M. T. Jr and R. P. Abreu, "Gastrointestinal malignancy and the microbiome," *National Library of Medicine,* vol. 146, no. 6, pp. 1534-1546, 2014.

[6] N. CBS, "Deaths: Cause of death (extensive list), age and sex," *CBS Open data Statline,* 2022.

[7] D. S. M. Felipe and K. V. Antonina, "A distinct role for Lgr5 + stem cells in primary and metastatic colon cancer," *National Library of Medicine,* vol. 543, no. 7647, pp. 676-680, 2017.

[8] B. M. Bhutani and G. Guillermo, "Large solitary ovarian metastasis from colorectal cancer diagnosed by endoscopic ultrasound," *Pubmed,* vol. 14, no. 32, pp. 5096-5097, 2008.

[9] Y. Z. Zhang and H. Y. Weibin, "Long non-coding RNA H19 promotes colorectal cancer metastasis via binding to hnRNPA2B1," *National Library of Medicine,* vol. 39, no. 1, p. 141, 2020.

[10] S. Irani, "Emerging Insights into the biology of metastasis: A review article," *National Library of Medicine,* vol. 22, no. 8, pp. 833-847, 2019.

[11] A. Agaimy, P. . H. Wünsch, L. H. Sobin and . J. Lasota, "Occurrence of other malignancies in patients with gastrointestinal stromal tumors," vol. 23, no. 2, pp. 120-9, 2006.

[12] N. C. Registry, "cijfersoverkanker," 2021. [Online]. [Accessed 17 6 2022].

[13] L. S. Massad, G. Feng and H. Ian, "Clinical Outcomes among Women with Mucinous Adenocarcinoma of the Ovary," pp. 411-5, 2018.

[14] A. . N. Wilkinson and D. Lieberman, "Colorectal cancer screening for patients with a family history of colorectal cancer or adenomas," vol. 65, no. 11, pp. 784-789, 2019.

[15] S. A , . M. D. Bi and F. SR , "Family History as a Risk for Upper Gastrointestinal Tract Cancer: A Case Control Study," vol. 3, no. 4, pp. 114-118, 2011.

[16] A. J , W. D. P and K. P , "Family history as a risk factor for colorectal cancer in inflammatory bowel disease," vol. 120, no. 6, pp. 1356-62, 2001.

[17] E. H. Kuipers and A. R. Schreuders, "Colorectal cancer screening: A global overview of existing programmes," *PubMed National Librabrary of Medicine,* vol. 64, no. 10, pp. 1637-49, 2015.

[18] M. S. Brandt and V. A. Piet, "Meditarranean diet adherence and risk of colorectal cancer: the prospective Netherlands Cohort Study," *National Library of Medicine,* vol. 35, pp. 25-35, 2020.

[19] H. Scherübl, S. Faiss and W.-T. Knoefel, "Management of early asymptomatic gastrointestinal stromal tumors of the stomach," vol. 6, no. 7, pp. 266-271, 2014.

[20] G. Karpathiou, C. Chauleur and . S. Hathroubi, "Secondary Tumors of the Gynecologic Tract: A Clinicopathologic Analysis," vol. 38, no. 4, pp. 363-370, 2019.

[21] M. G. Magdalena and G. Hans-Peter , “Secondary tumors of the GI tract: origin, histology, and endoscopic findings,” vol. 88, no. 1, pp. 151-158, 2018.

[22] M. WG, “Immunohistochemistry in the distinction between primary and metastatic ovarian mucinous neoplasms,” *J Clin Pathol,* no. 65, p. 596–600, 2012.

[23] K. P. Vatcheva, L. MinJae and M. . B. Joseph, “Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies,” vol. 2, no. 6, p. 227, 2016.

[24] S. S. J. Seong, . D. . H. Kim and . M. K. Kim, “Controversies in borderline ovarian tumors,” vol. 26, no. 4, pp. 343-349, 2015.

[25] T. Matsuda, . A. Ono, . Y. Kakugawa and . M. Matsumoto , “Impact of screening colonoscopy on outcomes in colorectal cancer,” vol. 45, no. 10, pp. 900-5, 2015.

[26] A. Jindal, A. Whaley-Connell and J. R. Sowers, “Type 2 diabetes in older people; the importance of blood pressure control,” vol. 7, no. 3, pp. 233-237, 2013.

[27] C. G. Smith, “A Resident's Perspective of Ovarian Cancer,” *National Library of Medicine,* vol. 7, no. 2, p. 24, 2017.

[28] D. K. Tulunay and I. U. Comert, “Mucinous Borderline Ovarian Tumors: Analysis of 75 patients from a single center,” *National Library of Medicine,* vol. 17, no. 2, pp. 96-100, 2016.

[29] E. D. Wallace and T. J. Pieter, “Colorectal cancer,” *National Library of Medicine,* vol. 394, no. 10207, pp. 1467-1480, 2019.

[30] . L. Neven, P. Goran and A. Nataša , “OPPORTUNISTIC SCREENING FOR COLORECTAL CANCER IN HIGH-RISK PATIENTS IN FAMILY MEDICINE PRACTICES IN THE REPUBLIC OF CROATIA,” vol. 60, no. 2, pp. 17-21, 2021.

[31] C. Ludwick, C. B. Gilks and . D. Miller, “Aggressive behavior of stage I ovarian mucinous tumors lacking extensive infiltrative invasion: a report of four cases and review of the literature,” vol. 24, no. 3, pp. 205-17, 2005.

[32] P. Dundr, N. Singh and B. Nožičková, “Primary mucinous ovarian tumors vs. ovarian metastases from gastrointestinal tract, pancreas and biliary tree: a review of current problematics,” pp. 16-20, 2021.

[33] A. Babaier and P. Ghatage, “Mucinous Cancer of the Ovary: Overview and Current Status,” vol. 10, no. 1, p. 52, 2020.

[34] M. Galanopoulos, F. Gkeros, . C. Liatsos and C. Pontas, “Secondary metastatic lesions to colon and rectum,” vol. 31, no. 3, pp. 282-287, 2018 .

[35] Q. Tian, B. Lu, . J. Ye and . W. Lu, “Early stage primary ovarian mucinous carcinoma: Outcome-based clinicopathological study in comparison with serous carcinoma,” vol. 44, no. 2, p. 357–366, 2016.

SUPPLEMENTARY MATERIALS

The results of the logistic regression analysis on risk factors associated with the occurrence of a sGI tumor in imOTs is reported in Table S1. Variables that are associated with the risk factors of a sGI tumor were entered into a multivariable logistic regression. Ovary as the topographical site ((OR 0.47; 95% CI [0.01-0.31]; P = 0.001) emerged as an independent predictor of the risk of sGI tumors in ImOTs patients.

Table S1 - Univariable and multivariable logistic regression table for risk of occurrence of sGI tumour in imOT patients

	imOTs	Univariable			Multivariable		
		OR	95% CI	P	OR	95% CI	P
Age at diagnosis*, years (SD)	56 (16)	1.01	0.10-1.02	0.210	1.01	1.00-1.02	
Laterality, n (%)	**n = 4453**						
Unilateral	3827 (86)	Reference			Reference		
Bilateral	626 (14)	0.47	0.26-0.86	0.013	0.57	0.30-1.09	
Disease stage, n (%)	**n = 4730**						
Early IA-IIA	2374 (50)	Reference			Reference		
Advanced IIB-IVB	1426 (30)	0.62	0.41-0.92	0.019	0.80	0.50-1.27	
Unknown	930 (20)	1.44	1.01-2.07	0.044	3.12	1.94-5.02	
Differentiation grade, n (%)	**n = 4730**						
Well	1397 (30)	Reference			Reference		
Moderately	845 (18)	1.01	0.64-1.61	0.958	1.14	0.71-1.85	
Poorly	485 (10)	0.46	0.22-0.98	0.045	0.54	0.24-1.22	
Undifferentiated	14 (0)	-			-		
Unknown	1989 (42)	1.20	0.27-0.48	<.001	1.15	0.75-1.75	
Topographical site and subsite	**n = 4730**						
Ovary	4676 (99)	0.10	0.02-0.48	0.005	0.47	0.01-0.31	0.001
Specified parts of the peritoneum	23 (0)	-			-		
Non-specified parts of the peritoneum	24 (0)	0.11	0.01-1.45	0.093	-		
Fallopian tube	7 (0)	Reference			Reference		

OR Odds Ration; **CI** Confidence Interval; * mean (SD); The summation of percentages might not sum to 100% because of rounding and missing results. (-) no result

Table S2 - Univariable and multivariable Cox regression analysis on risk factors on the survival of imOT patient with sGI tumors (n=170)

	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age, years	1.05	1.03-1.07	<.001	1.04	1.02-1.07	<.001
Laterality						
Unilateral	Reference			Reference		
Bilateral	1.07	0.52-2.22	0.837	1.57	0.64-3.62	
Location of sGI tumors present						
Upper sGI-tumors	Reference			Reference		
Lower sGI-tumors	0.62	0.38-0.10	0.049	0.56	0.31-0.77	0.034
Hepatobiliary tumors	1.11	0.55-2.25	0.776	2.40	1.09-5.27	0.029
Other sGI-tumors	-			-		
sGI diagnosis based on intervals (years) after the initial diagnosis of a mOT						
< 1 year	21.77	4.92-96.39	<.001	38.60	7.57-196.68	<.001
1-8 years	17.15	3.98-73.88	<.001	11.97	2.52-56.86	<.001
9-16 years	4.65	1.11-19.56	0.013	4.15	0.94-18.36	
17-24 years	2.93	0.68-12.56	0.130	1.88	0.41-8.63	
25-32 years	Reference			Reference		
Differentiation grade, n (%)						
Well	Reference			Reference		
Moderately	1.56	0.88-2.77	0.127	0.77	0.36-1.66	
Poorly	2.12	0.92-4.85	0.075	2.16	0.85-5.48	
Unknown	1.26	0.82-1.96	0.295	2.95	1.49-4.71	
Disease stage, n (%)						
Early IA-IIA	Reference			Reference		
Advanced IIB-IVB	1.81	1.13-2.88	0.013	2.04	1.13-3.69	0.018
Unknown	0.10	0.53-1.21	0.292	0.73	0.41-1.31	

sGI secondary gastrointestinal; **HR** Hazard Ratio; **CI** Confidence Interval; (-) no result

Table S3 - Univariable and multivariable Cox regression analysis on risk factors on the survival of mBOT patient with sGI tumors (n=107)

	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Age, years	1.04	1.01-1.07	0.004	1.04	1.01-1.07	0.013
Laterality						
Unilateral	Reference			Reference		
Bilateral	2.13	0.29-15.55	0.457	1.91	0.20-18.68	
Location of sGI tumors present						
Upper sGI-tumors	Reference			Reference		
Lower sGI-tumors	1.05	1.39-2.13	0.901	0.29	0.31-0.66	0.003
Hepatobiliary tumors	5.56	2.18-14.16	<.001	4.11	1.50-11.29	0.006
Other sGI-tumors	-			-		
sGI diagnosis based on intervals (years) after the initial diagnosis of a mOT						
< 1 year	12.30	1.39-108.67	0.024	103.61	7.56-1419.22	0.001
1-8 years	12.87	1.72-96.25	0.031	79.93	7.58-843.11	<.001
9-16 years	3.40	0.47-24.73	0.226	13.68	1.45-128.63	0.022
17-24 years	1.50	0.25-9.10	0.658	6.56	0.91-47.19	
25-32 years	Reference			Reference		
Disease stage, n (%)						
Early IA-IIA	20.62	3.39-125.37	0.001	19.30	2.40-155.41	0.005
Advanced IIB-IVB	Reference			Reference		
Unknown	-			-		

sGI secondary gastrointestinal; **HR** Hazard Ratio; **CI** Confidence Interval; **(-)** no result