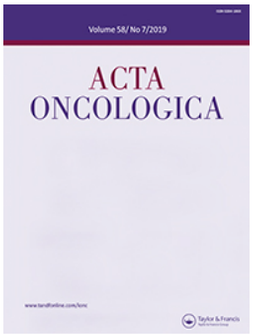
Trends in incidence, treatment and survival of borderline ovarian tumors in the Netherlands



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ORIGINAL ARTICLE

Trends in incidence, treatment and survival of borderline ovarian tumors in the Netherlands: a nationwide analysis

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ABSTRACT

Background: Population-based data on borderline ovarian tumors (BOTs) are scarce and information regarding recent trends in incidence, treatment and survival is lacking. The purpose of this study was to analyze these trends in the Netherlands and to assess the risk of developing a subsequent invasive ovarian tumor.

Material and methods: All consecutive patients diagnosed with BOTs between 1993 and 2016 ($n = 7113$) were identified from the Netherlands Cancer Registry (NCR). Annual age-adjusted incidence rates were calculated. Relative survival (RS) analyses and multivariable analyses estimating excess mortality were conducted. Patients with a subsequent invasive ovarian tumor were identified by the NCR.

Results: Age-adjusted incidence increased from 2.1/100,000 person-years in 1993 to 4.2/100,000 in 2011, after 2011 the incidence declined. The proportion of bilateral tumors decreased over time from 16% in 1993–1998 to 11% in 2005–2010 and remained stable onwards. Survival improved over time (excess mortality ratio$_{adjusted}$ 2011–2016 *versus* 1993–1998: 0.25; 95%CI: 0.13–0.47). Five-year RS increased from 91% in 1993–1998 to 98% in 2011–2016 and 10-year RS from 88% in 1993–1998 to 96% in 2005–2010. Fewer patients were treated with chemotherapy (4.4% in 1993–1998 *versus* 0.7% in 2011–2016). During a median follow-up time of 8 years, 0.9% developed a subsequent invasive ovarian carcinoma.

Conclusions: The incidence of BOTs increased over time from 1993 until 2010 but declined since 2011. This decline may be partly due to changes in the classification of gynecological tumors, as serous BOTs are now more often diagnosed as low grade serous ovarian cancers. Survival is high and has improved since 1993. The risk of a subsequent invasive ovarian carcinoma seems low.

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Introduction

Borderline ovarian tumors (BOTs) are a heterogeneous group of ovarian tumors, comprising 10–20% of all ovarian neoplasms [1–4]. The most common types are the mucinous BOTs (mBOTs) and serous BOTs (sBOTs). Other histological subtypes such as endometrial, clear cell and Brenner tumors are extremely rare (<5%) [5].

BOTs show morphological features of both benign and malignant tumors. In contrast to invasive tumors, they do not show destructive stromal invasion, usually affect younger women, and are generally diagnosed in an earlier stage and have a more favorable prognosis independent of the International Federation of Gynecology and Obstetrics (FIGO) stage [4,6]. Like invasive tumors, BOTs have the ability to metastasize beyond the ovaries. Peritoneal implants are the most frequent type of metastases, approximately 20% of all BOTs being associated with peritoneal implants [6]. Those implants are a major prognostic factor and mainly seen in sBOTs [6–8].

Over the years, the concept of BOTs faced various controversies concerning terminology and diagnostics. Therefore, the diagnosis of BOTs is complicated and a pathologic review of BOTs diagnoses can often result in a change of the original diagnosis, either toward benign or malignant tumors [6,9]. Controversies are also reflected by recent changes in the 2014 WHO classification [10]. In the presence of invasive implants, serous tumors are no longer considered as sBOTs but as low grade serous ovarian carcinomas (LGSOC).

Surgical removal of the tumor is the treatment of choice. Controversies consist regarding the extent of surgery/surgical staging and surgical approach (laparoscopy *versus* laparotomy). Over time, treatment has become less radical [11]. Although associated with an increased risk of recurrences,

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Supplemental data for this article can be accessed here.

fertility-sparing surgery is now generally accepted as a safe treatment option in a large proportion of patients in the reproductive age [7,12,13]. There is no evidence of a beneficial effect of adjuvant therapy on prognosis [14,15].

Follow-up is also a subject of debate. Considering the good prognosis, some advocate no standard follow-up. Others emphasize the need for long follow-up because of the risk of late recurrences [5,11,16].

Since many cancer registries limit their data collection to invasive tumors, only few population-based studies concerning incidence, treatment, survival and subsequent tumors are available. Most reports on BOTs are restricted to small case series. The aim of our study is to describe nationwide trends in incidence, treatment and survival of BOTs in the Netherlands and to assess the risk of developing an ovarian malignancy after a BOT.

Material and methods

Patients selection

All consecutive patients diagnosed with a primary BOT ($n = 7113$) or an invasive epithelial ovarian carcinoma (EOC), including peritoneal and fallopian tube carcinoma (International Classification of Diseases for Oncology (ICD-O) codes C48.1, C48.2, C56.9 and C57.0) ($n = 31{,}564$) in the Netherlands between 1993 and 2016 were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry based on notification by the automated nationwide network and registry of histo- and cyto-pathology (PALGA) and the National Registry of Hospital Discharge Diagnosis. The NCR covers all newly diagnosed malignancies as well as several types of benign tumors and all BOTs. Completeness of the NCR is estimated to be at least 95% [17].

Dedicated registry clerks routinely extract data on patient and tumor characteristics and treatment from the medical files in all Dutch hospitals. Morphology is retrieved from pathology reports, the pathologist's conclusion and coded according to the ICD-O-2 (1993–1999) and ICD-O-3 (2000–2016) [18]. Information on vital status is obtained by annual linkage to the Municipal Personal Records Database and was available up to 1 February 2017.

Unfortunately, FIGO stage and the occurrence of (invasive) implants are not routinely collected for BOTs in the NCR.

Data analyses

Incidence rates per 100,000 person-years (py) were calculated by 5-year age category. Annual European Standardized Incidence Rates (ESR) was calculated by histological subtype.

To evaluate changes in patient and tumor characteristics and provided treatment over time chi-square tests and Kruskal–Wallis tests were performed.

Relative survival (RS) was calculated as an estimation of cause-specific survival according to the Ederer II method [19]. Relative Survival Ratios (RSR) were calculated by period of diagnosis (1993–1998/1999–2004/2005–2010/2011–2016), age category (<60 *versus* ≥ 60 years), histological subtype (serous/mucinous/other) and tumor laterality (unilateral/bilateral/unknown). ICD-O codes 8442, 8462 and 8463 were classified sBOTs and ICD-O codes 8470, 8472 and 8473 as mBOTs.

To identify factors associated with receiving adjuvant chemotherapy we performed multivariable Poisson regression with robust standard error variance. Multivariable Poisson regression adjusted for follow-up time intervals was conducted to identify factors associated with excess mortality due to BOTs.

Survival time was defined as the time from date of diagnosis to date of death or if a patient was still alive to the last date of follow-up (1 February 2017).

Finally, the crude cumulative proportion of patients developing a subsequent invasive ovarian tumor was calculated. A subsequent invasive tumor was defined as a primary EOC diagnosed at least 60 d after the BOT. A patient was considered at risk until the date of first subsequent EOC, or to date of death or last follow-up if a patient did not develop an EOC. If a patient was diagnosed with a synchronous EOC tumor (within 60 d after the initial tumor), this was not considered as having a subsequent invasive tumor and the patient was still considered at risk.

All analyses were performed using STATA/SE version 14.1 (StataCorp, College Station, TX, USA). A two-sided p value of $<.05$ was considered statistically significant.

Results

Between 1993 and 2016, 7113 BOTs were diagnosed, comprising 19% of the non-benign epithelial ovarian tumors. The proportion of BOTs (as part of all non-benign ovarian tumors) increased from 13% in 1993–1998 to 22% in 2011–2016. The majority (57%) of the patients were diagnosed with a mBOT, 39% was diagnosed with a sBOT and the remaining 4% with an endometrioid, clear cell, Brenner or an unspecified BOT. In patients aged <45 years the distribution of histological subtype varied statistically significantly over the time periods (Table 1). In 85% of the patients, the tumor was confined to one ovary, while in 13% the tumor was bilateral. In older patients (aged ≥ 60 years) tumor laterality changed statistically significantly over time ($p < .01$), with more patients being diagnosed with a unilateral tumor (Table 1). The median age at diagnosis for BOTs was 53 years compared to 66 years for EOCs. The median age at diagnosis for BOTs increased from 50 years during 1993–1998 to 55 years in 2011–2016 ($p < .01$) (data not shown).

Incidence

Until the age of 40, the incidence of BOTs was higher than the incidence of EOC. Incidence peaked at the age of 55–59 years with an age-specific incidence rate of 7.3/100,000 py whereas invasive tumors reached the highest incidence rate in patients aged 75–79 years (Supplementary Figure 1).

The ESR of BOTs increased over time from 2.1/100,000 py in 1993 to 4.2/100,000 py in 2011 (Figure 1). After 2011 a

Table 1. Patient and tumor characteristics of patients diagnosed with a borderline ovarian tumor according to period of diagnosis and age category.

	Age category (%)																			
	<45 years					45–59 years					≥60 years					All				
	1993–1998	1999–2004	2005–2010	2011–2016	*p* Value	1993–1998	1999–2004	2005–2010	2011–2016	*p* Value	1993–1998	1999–2004	2005–2010	2011–2016	*p* Value	1993–1998	1999–2004	2005–2010	2011–2016	*p* Value
Number of BOTs[a]	400 (38.1)	578 (51.4)	643 (57.4)	570 (59.0)	<.01	352 (14.3)	604 (21.8)	774 (27.5)	770 (30.8)	<.01	350 (6.7)	545 (10.6)	674 (11.6)	853 (13.2)	<.01	1,102 (12.6)	1,727 (19.1)	2,091 (21.4)	2,193 (22.0)	<.01
Histology					.02					.66					.19					.02
Mucinous	225 (56.3)	199 (34.4)	250 (38.9)	216 (37.9)		209 (59.4)	340 (56.3)	454 (58.7)	445 (57.8)		190 (54.3)	292 (53.6)	272 (40.4)	358 (42.0)		624 (56.6)	995 (57.6)	1,191 (57.0)	1,255 (57.2)	
Serous	167 (41.8)	363 (62.8)	373 (58.0)	350 (61.4)		133 (37.8)	236 (39.1)	295 (38.1)	302 (39.2)		146 (41.7)	213 (39.1)	272 (40.4)	358 (42.0)		446 (40.5)	648 (37.5)	817 (39.1)	876 (40.0)	
Other/NOS	8 (2.0)	16 (2.8)	20 (3.1)	4 (0.7)		10 (2.8)	28 (4.6)	25 (3.2)	23 (3.0)		14 (4.0)	40 (7.3)	38 (5.6)	35 (4.1)		32 (2.9)	84 (4.9)	83 (4.0)	62 (2.8)	
Laterality					.15					.09					<.01					<.01
Unilateral	330 (82.5)	503 (87.0)	568 (88.3)	505 (88.6)		290(82.4)	503 (83.3)	683 (88.2)	663 (86.1)		277 (79.1)	433 (79.5)	566 (84.0)	739 (86.6)		897 (81.4)	1,439 (83.3)	1,817 (86.9)	1,907 (87.0)	
Bilateral	60 (15.0)	65 (11.3)	64 (10.0)	56 (9.8)		54 (15.3)	88 (14.6)	78 (10.1)	96 (12.5)		62 (17.7)	80 (14.7)	91 (13.5)	98 (11.5)		176 (16.0)	233 (13.5)	233 (11.1)	250 (11.4)	
Unknown	10 (2.5)	10 (1.7)	11 (1.7)	9 (1.6)		8 (2.3)	13 (2.2)	13 (1.7)	11 (1.4)		11 (3.1)	32 (5.9)	17 (2.5)	16 (1.9)		29 (2.6)	55 (3.2)	41 (2.0)	36 (1.6)	

[a]Percentage relative to the number of non-benign ovarian tumors within the same period, *p* value shows results of the comparison of distribution of BOT *versus* non-benign ovarian tumors over time.
BOTs: borderline ovarian tumors; NOS: not otherwise specified.

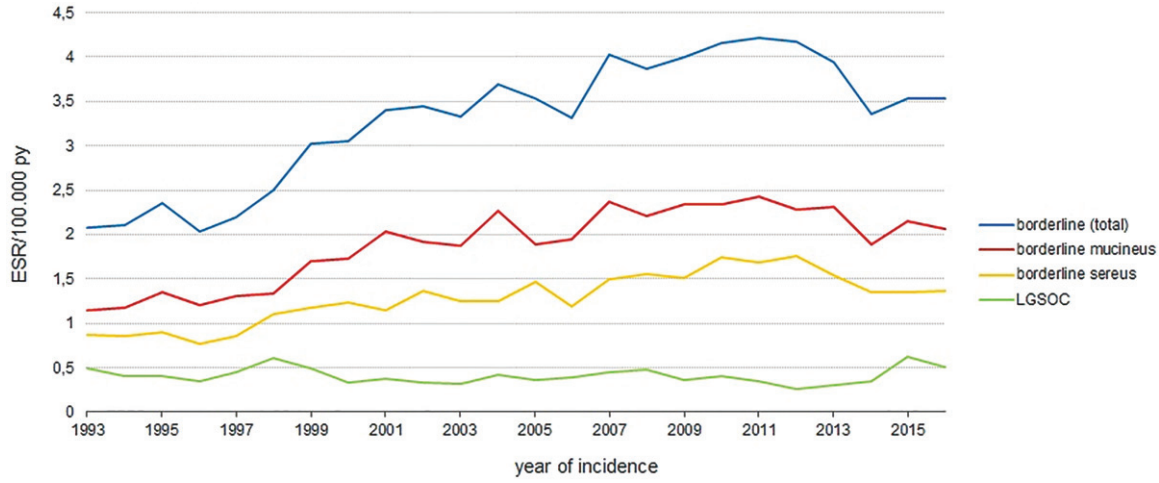

Figure 1. Age-standardized incidence (ESR) of borderline ovarian tumors according to histological subtype and low- grade serous ovarian carcinomas (LGSOC) (1993–2016).

Table 2. Adjusted risk ratios (RR) and 95% confidence intervals (CI) for receiving chemotherapy for borderline ovarian tumors.

	N (%)	RR[a] (95%CI)
Period of diagnosis		
1993–1998	48 (4.4)	1.00 (ref)
1999–2004	46 (2.7)	0.62 (0.43–0.91)
2005–2010	11 (0.5)	0.14 (0.07–0.26)
2011–2016	12 (0.6)	0.13 (0.07–0.25)
Age (in years)		
<45	24 (1.1)	1.00 (ref)
45–59	42 (1.7)	1.63 (1.00–2.65)
60–74	41 (2.3)	2.19 (1.34–3.55)
≥75	10 (1.6)	1.29 (0.63–2.67)
Tumor laterality		
Unilateral	45 (0.7)	1.00 (ref)
Bilateral	62 (7.0)	6.10 (3.91–9.53)
Unknown	10 (6.2)	5.76. (2.97–11.16)
Histology		
Serous	81 (2.9)	1.00 (ref)
Mucinous	31 (0.8)	0.54 (0.33–0.85)
Other/NOS	5 (1.9)	0.80 (0.33–1.94)

[a]Adjusted for all presented variables.
RR: risk ratio; NOS: not otherwise specified; CI: confidence interval.

small decrease in incidence was observed. The increasing trend in incidence was seen in both sBOTs and mBOTs and all age categories (Supplementary Figure 2).

The incidence of EOC decreased continuously from 15.0/100,000 py in 1993 to 10.4/100,000 py in 2016. The incidence of LGSOC was low and fluctuated around 0.5/100,000 py (data not shown).

Treatment

Fewer patients were treated with chemotherapy over time. Between 1993 and1998, 4.4% received chemotherapy *versus* 0.6% between 2011 and 2016. Of the patients with a bilateral tumor, 7.0% received chemotherapy *versus* 0.7% of the patients with a unilateral BOT. In 1993–1998, 18% of the patients with a bilateral BOT received chemotherapy *versus* 2% in 2011–2016 (Supplementary Table 1). Multivariable analyses confirmed the decrease in application of chemotherapy over time in all BOTs (risk ratio [RR] 2011–2016 *versus* 1993–1998: 0.13; 95% CI: 0.07–0.25) and identified the presence of a bilateral tumor as a strong predictor for the application of chemotherapy (RR unilateral *versus* bilateral tumors: 6.1; 95% CI: 3.9–9.5) (Table 2).

Survival

The 5-year RSR of patients with BOTS was 96.0% during the total time period (Figure 2(A)). Survival rates did not reach a plateau but continued to decrease with increasing follow-up time (maximum of 15 years). The 10- and 15-years RSR were 93.7 and 91.6%, respectively. Over time, survival of BOTs improved. Ten-year RSR increased from 88.1% in 1993–1998 to 96.4% in 2005–2010 (Supplementary Table 2).

Large differences in survival rates were observed between uni- *versus* bi-lateral tumors: the 5-year RSR was 96.8% *versus* 91.8%, respectively. After 15 years, survival rates were 93.3 and 83.2%, respectively. Survival rates of sBOTs and mBOTs did not differ, except when stratified by tumor laterality (Figure 2). Five and 15-year RSR were 98.0 and 97.0% for unilateral sBOTs and 96.5 and 92.1% for unilateral mBOTs. For bilateral tumors 5 and 15-year RSR were 95.2 and 86.6% for sBOTs, and 67.3 and 59.2% for mBOTs, respectively.

Multivariable analyses confirmed a lower excess mortality ratio (EMR) in more recent time periods (EMR 2011–2016 *versus* 1993–1998: 0.3;95% CI: 0.1–0.5). Patients with a bilateral tumor had a 3.7 (95%CI: 2.5–5.4) times higher mortality compared to unilateral tumors. Older patients and patients with mBOTs also showed a higher mortality in the adjusted analysis (Table 3).

Subsequent invasive ovarian tumors

Sixty-four patients (0.9%) developed a subsequent invasive ovarian tumor during a median follow-up time of 7.9 years. Compared to the initial BOT, the histological subtype of the invasive tumor was the same in 48 (75.0%) patients. Of the patients diagnosed with a sBOT, 32 (1.2%) patients developed a subsequent EOC, of which 91.6% were invasive serous ovarian carcinomas. Of the patients diagnosed with a

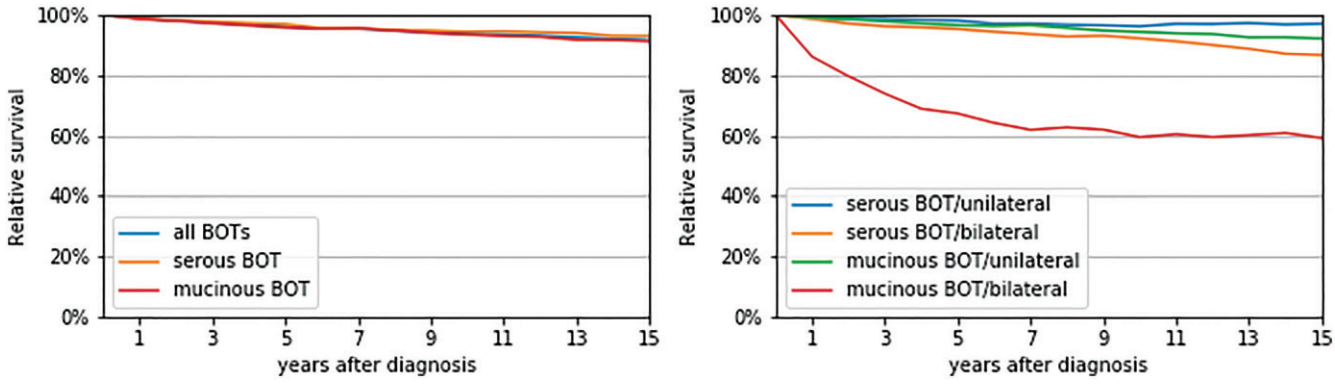

Figure 2. Relative survival ratio up to 15 years after diagnosis with BOT (1993–2016) by (A) histological subtype (B) histological subtype and tumor laterality (1993–2016).

Table 3. Excess mortality ratios for patients diagnosed with borderline ovarian tumor (1993–2016).

	Excess mortality ratio (95%CI)[a]
Period of diagnosis	
1993–1998	1.00 (ref)
1999–2004	0.62 (0.45–0.86)
2005–2010	0.37 (0.25–0.56)
2011–2016	0.25 (0.13–0.47)
Age at diagnosis	
<60 years	1.00 (ref)
≥60 years	2.43 (1.81–3.27)
Histology	
Serous	1.00 (ref)
Mucinous	2.07 (1.40–3.06)
Other/NOS	1.93 (0.99–3.76)
Laterality	
Unilateral	1.00 (ref)
Bilateral	3.66 (2.48–5.39)
Unknown	2.69 (1.46–4.96)

[a]Adjusted for all presented variables.
NOS: not otherwise specified; CI: confidence interval.

mBOT, 29 (0.7%) patients developed an EOC, of which 62.1% were invasive mucinous ovarian carcinomas.

Discussion

Age-standardized incidence rates of BOTs have increased in the Netherlands since 1993. BOTs comprised a larger proportion of all ovarian neoplasms over time. Currently, about one-fifth of the non-benign ovarian neoplasms is a BOT. A rising incidence of BOTs during the past decades (up to 2007) has also been reported in previous population-based studies [1,2,20,21].

However, the incidence in our study was highest in 2011 (4.2/100,000 py), after which incidence slightly decreased. Recent data on trends in incidence of BOTs are scarce. Though a recent report of the Munich Cancer Registry showed the same results: the incidence also peaked in 2011 with an ESR of 4.4/100,000 persons, followed by a decline. In the USA (California) also a declining trend has been observed, but this was an earlier decline (from 2006 to 2010) than we observed [4]. More recent data on trends in incidence of BOTs from other countries are lacking and future studies are needed to determine whether our observation is a real decrease and if the observed decline in incidence continues.

A possible contribution to the declining incidence may be changes in the WHO 2014 classification in which sBOTS with invasive peritoneal were classified as LGSOC. The timing of pathologists adopting the new classification may have varied, possibly explaining the start of the decrease before the publication of the new classification.

Unfortunately, we did not have data on peritoneal implants. Other studies found peritoneal implants in 20–46% of patients with sBOTs, of which the vast majority (83–96%) were non-invasive [22,23]. Considering these percentages, 1–8% of all BOTs would be classified as a sBOT with invasive peritoneal implants before the implementation of the new WHO classification and as a LGSOC afterward. Although this shift will have contributed to the decrease in incidence that we observed during the latter years, definite conclusions are difficult to draw from these data. The low incidence of sBOTs and particularly LGSOC makes it hard to distinguish trends from random fluctuations.

Simultaneously with the increase in incidence of BOTs since 1993, the incidence rate of ovarian carcinoma decreased considerably. Convincing evidence explaining this opposite trend is lacking.

The standard clinical management of BOTs is the surgical removal of the tumor, which cures most patients. According to the current guidelines adjuvant chemotherapy is not indicated. In our population 2% received chemotherapy, these were mainly patients with a bilateral sBOT. The proportion of BOTs treated with chemotherapy decreased from 4.4% in 1993–1998 to <1% in 2011–2016 and is lower than described in most studies. Other studies reported a large variation in the use of chemotherapy varying from 3 to >25% in non-selected series of BOT patients [6,24–30]. Though, comparisons are hampered by a low number of studies reporting the number of BOTs treated with adjuvant chemotherapy, by differences in time periods and by the single institution design of most previous studies.

The decline in adjuvant chemotherapy is in line with the more conservative treatment of BOTs advocated over time. As sBOTs with invasive peritoneal implants are now classified and treated as LGSOC, the role of chemotherapy in the currently classified BOTs is even further limited.

Similar to other studies, BOTs conferred a good prognosis [4,31,32]. However, survival did not reach a plateau, even not

after a long follow-up. This is consistent with previous studies [6,31] and thought to be associated with late recurrences or progression to invasive disease.

Survival of mBOTs and sBOTs appeared to be similar when we did not take prognostic factors into account. Nevertheless, differences in survival were found when stratified by tumor laterality.

The presence of bilateral tumors was a poor prognostic factor in both subtypes, although the strongest impact was seen for mBOTs. However, bilateral mBOTs are extremely rare and the question remains whether these tumors originate from the ovary or present metastatic tumor from another site. Clinicopathological studies have provided evidence that bilateral or advanced stage mucinous tumors are often secondary to appendiceal mucinous tumors and thus should not be classified as primary ovarian tumors [33–36]. Over time, the proportion of bilateral tumors declined in both mBOTs and sBOTs, this can partly explain the improved survival. An earlier detection through enhanced ultrasound as well as an improved distinction between BOTs and invasive gastrointestinal tumors might explain the improved survival rates. Since sBOTs with invasive peritoneal implants are no longer considered as BOTs in the new WHO classification, survival is further expected to rise.

A low number (<1%) of patients developed an EOC after a BOT. This low risk combined with the good prognosis does not plead for intensive follow-up schedules. However, caution is warranted in interpretation of these results. The median follow-up time was 8 years, while recurrences have been detected up to 15 years after initial diagnosis [5].

The major strength of our study is its nationwide character, the large number of BOTs and long follow-up time. The most important drawback is the absence of information on major prognostic factors (such as FIGO stage and the presence of peritoneal implants) and detailed information about surgical treatment (i.e., type of surgery and residual tumor after surgery). Furthermore, no central pathology review was done. The diagnosis of BOTs was made in all Dutch hospitals, by a large number of pathologists. Especially in view of the complexity and controversies that existed in the terminology and diagnosis of BOTs, some variation between pathology laboratories may exist.

Summarized, we observed an increasing incidence of BOTs in the Netherlands between 1993 and 2011, with a declining incidence thereafter. The decline might partly be related to changes in the classification of BOTs. While the proportion of patients treated with adjuvant chemotherapy was already low in the early years, it further decreased over the years. Survival of BOTs is high, especially during the more recent time periods. The improved survival over time might be due to an earlier detection of BOTs, as well as to an improved distinction between BOTs and invasive (gastrointestinal) tumors. The risk of developing an invasive ovarian carcinoma after an BOT was low.

Disclosure statement

The authors declare no conflict of interest.

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