Overview of non-epithelial ovarian tumours

European Journal of Cancer 118 (2019) 97–104

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Overview of non-epithelial ovarian tumours: Incidence and survival in the Netherlands, 1989–2015

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Received 4 December 2018; received in revised form 7 June 2019; accepted 12 June 2019
Available online 18 July 2019

KEYWORDS
Ovarian neoplasms;
Incidence;
Histology;
Rare cancer;
Ovarian germ cell tumours;
Sex cord-stromal tumours;
Ovarian sarcoma;
Overall survival

Abstract ***Introduction:*** About 5% of ovarian tumours have a non-epithelial histology, including germ cell tumours (GCTs), sex cord-stromal tumours (SCSTs) and sarcomas. Because these non-epithelial ovarian tumours are rare and population-based studies are scarce, the aim of this population-based study is to describe trends in the incidence, treatment and survival of women with these tumours in the Netherlands.
Methods: All women diagnosed with non-epithelial ovarian malignant tumours in the Netherlands between 1989 and 2015 were identified from the Netherlands Cancer Registry. Data on demographics, tumour characteristics and initial treatment were collected, and overall survival was analysed.
Results: A total of 1258 non-epithelial ovarian tumours were identified comprising 752 GCTs (60%), 341 SCSTs (27%) and 165 sarcomas (13%). The European age-standardised incidence rate (ESR) was 0.4 per 100,000 persons per year for GCTs, 0.2 for SCSTs and 0.1 for sarcomas. Approximately 97% of patients underwent surgical resection for the primary tumour, 31% received systemic treatment and 3% radiotherapy. Between the late 1980s and 2015, five-

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https://doi.org/10.1016/j.ejca.2019.06.005

year overall survival improved for all histologic subtypes: GCTs rose from 73% to 88% (p = 0.03), SCSTs from 64% to 81% (p = 0.57) and sarcomas from 20% to 29% (p = 0.14). ***Conclusion:*** Malignant GCTs and SCSTs are rare, and their incidence has not significantly changed over recent decades. They have a good prognosis, which also improved slightly during this period. Primary sarcomas of the ovary are extremely rare and still have a poor prognosis.

1. Introduction

About 5% of women diagnosed with malignant ovarian tumours present with non-epithelial histology, including germ cell tumours (GCTs), sex cord-stromal tumours (SCSTs) and sarcomas. These subtypes account for 3.0%, 1.0% and 0.8% of all ovarian tumours, respectively [1,2]. These tumours can be classified as rare (defined as an annual incidence of <6 per 100,000) [1].

GCTs arise from primordial germ cells and are classified into two groups: dysgerminoma and non-dysgerminoma [3,4] which include yolk sac tumours, immature teratomas, pure embryonal carcinomas, non-gestational choriocarcinomas and mixed GCTs. GCTs are mostly unilateral, often grow rapidly and have specific tumour markers that can aid in initial diagnosis and management [3]. These tumours typically present during adolescence and early adulthood. The first choice of treatment is surgery. Currently, a staging procedure followed by chemotherapy is advised, with the exception of stage IA pure dysgerminoma and stage IA grade I immature teratoma [3]. It has been suggested that chemotherapy subsequent to a surgical staging laparotomy may improve survival in this subgroup, although this treatment is controversial [5,6].

SCSTs of the ovary originate from theca cells, granulosa cells, Sertoli and Leydig cells and fibroblasts [7]. SCSTs constitute a heterogeneous group and are classified into three subgroups: pure sex cord tumours, pure stromal tumours and mixed SCSTs. These tumours occur over a wide range of age and are generally found in peri-menopausal and postmenopausal women [8]. The first choice of treatment is surgery. Again, there is controversy about the need for complete surgical staging (including lymph node sampling) in clinical early stage disease because the prevalence of lymph node metastases in these cases is very low [9]. The choice for subsequent chemotherapy in patients with granulosa cell tumours must be individualised, and any marginal benefit must be balanced against possible serious adverse effects [10,11].

Primary sarcomas of the ovary, including leiomyosarcoma, fibrosarcoma, angiosarcoma and liposarcoma are of mesenchymal origin and develop in soft tissues and viscera. These tumours often present at later stages, are aggressive and have a poor prognosis. They occur over a wide range of age, except for leiomyosarcoma which occurs mainly in postmenopausal women [12]. The role of adjuvant treatment is unclear because of limited experience and the lack of comparative studies [12–14].

Because these non-epithelial ovarian tumours are rare and population-based studies are scarce, the aim of this population-based study is to describe trends in the incidence, treatment and survival of women with these tumours in the Netherlands.

2. Methods

Patients were selected from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry which includes all newly diagnosed malignancies in the Netherlands since 1989 [15]. Notification is based on an automated nationwide network and registry of histopathology and cytopathology in the Netherlands [16], and the National Registry of Hospital Discharge Diagnosis. Dedicated registration clerks routinely extract patient information from hospital medical records. Owing to thorough training of the registration teams and regular consistency checks, the quality of the data is high. Information on vital status and date of death was obtained from municipal demographic registries in the Netherlands.

2.1. Study population

All women diagnosed with non-epithelial ovarian malignant tumours in the Netherlands between 1989 and 2015 were selected from the NCR. Information was available on date of birth, date of diagnosis, International Classification of Disease-Oncology (ICD-O), both clinical and pathological tumour-node-metastasis (TNM) stage, differentiation grade, type of tumour, the number of dissected lymph nodes, the number of positive lymph nodes, primary treatment and follow-up date [17,18]. Since 1999, information on the number of lymph nodes removed has also been collected. Therefore, analyses of lymph node removal were restricted to the period 1999–2015. The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 2014 stage [19] was derived from the TNM stage, which was based on

postoperative pathology findings. If patients had not undergone surgery, clinical tumour stage was used.

2.2. Statistical analysis

Patients were allocated to groups according to their date of diagnosis to analyse differences over time for the following time periods: 1989–1993, 1994–1998, 1999–2003, 2004–2009, 2010–2015 (3 5-year periods and 2 6-year periods). Overall survival (OS) was defined as the date of diagnosis until date of death or until date of last follow-up for patients who were still alive (February 1st 2018). OS was analysed using Kaplan-Meier survival curves, and multi-variable Cox regression models were used to adjust for age, period of diagnosis and FIGO stage. Log-rank tests were performed to calculate differences in survival curves for different stages and periods.

3. Results

In total, 1258 women were diagnosed with non-epithelial ovarian malignant tumours in the Netherlands between 1989 and 2015, of which 752 were diagnosed with GCTs (60%), 341 with SCSTs (27%) and 165 with sarcomas (13%) (Tables 1–3).

3.1. Germ cell tumours – overall

The absolute numbers of GCTs increased over time from 132 in 1989–1993 to 194 in 2010–2015. The European age-standardised incidence rate (ESR) varied between 0.3 and 0.4 per 100,000 person years. More than half of the GCTs were FIGO stage I tumours and were treated surgically (97%), and around 40% received adjuvant chemotherapy, which was constant over time (Table 1). Women with FIGO stage I tumours received less adjuvant chemotherapy (25%) than women with FIGO stage IV tumours (69%) (data not shown). Since 1999, 268 women with GCTs at clinical stages I or II have undergone surgery. Of those women, 68 underwent lymph node removal, 19 of whom had positive lymph nodes (28%). Sixteen of these 19 women (84%) received additional chemotherapy. In the group with negative lymph nodes, 49% received chemotherapy (24/49). Five-year OS was comparable in groups both with and without lymph node removal, at 86% and 90% ($p = 0.53$), respectively.

Survival was strongly related to FIGO stage, 5-year OS for FIGO stages I and IV being 91% and 59%, respectively ($p < 0.01$, Table 4). Five-year OS in GCTs increased from 73% in 1989–1993 to 88% in 2010–2015 ($p = 0.03$). This effect persisted after adjustment for age, histology and FIGO stage (hazard ratio [HR]: 0.4, 95% confidence interval [CI]: 0.3–0.7; Table 4).

3.2. Subgroups of GCTs

Seventy-seven percent ($n = 578$) of all GCTs were diagnosed as non-dysgerminomas, 18% ($n = 135$) were dysgerminomas and the remaining 39 tumours were classified as 'dysgerminoma not otherwise specified'

Table 1
The number of patients diagnosed in the Netherlands between 1989 and 2015 with GCTs per subtype of tumour, baseline characteristics and therapy per period of diagnosis.

	1989–1993 (n, %)	1994–1998 (n, %)	1999–2003 (n, %)	2004–2009 (n, %)	2010–2015 (n, %)	Total (n, %)
Type of GCTs						
Dysgerminoma	25 (19)	21 (17)	30 (21)	29 (18)	30 (16)	135 (18)
Non-dysgerminoma	104 (79)	98 (79)	106 (74)	118 (75)	152 (78)	578 (77)
Dysgerminoma NOS	3 (2.3)	5 (4.0)	8 (5.6)	11 (7.0)	12 (6.2)	39 (5.2)
Age (years)						
<20	35 (27)	33 (27)	36 (25)	48 (30)	47 (24)	199 (27)
21–40	50 (38)	43 (35)	54 (38)	52 (33)	67 (35)	266 (35)
41–60	23 (17)	13 (11)	34 (24)	30 (19)	47 (24)	147 (20)
61–80	22 (17)	33 (27)	19 (13)	21 (13)	26 (13)	121 (16)
>80	2 (1.5)	2 (1.6)	1 (0.7)	7 (4.4)	7 (3.6)	19 (2.5)
FIGO stage						
I	73 (55)	72 (58)	75 (52)	96 (61)	137 (71)	453 (60)
II	14 (11)	15 (12)	19 (13)	16 (10)	17 (8.8)	81 (11)
III	17 (13)	17 (14)	31 (22)	30 (19)	29 (14)	123 (16)
IV	10 (7.6)	13 (11)	11 (7.6)	9 (5.7)	8 (4.1)	51 (6.8)
Unknown	18 (14)	7 (5.7)	8 (5.6)	7 (4.4)	4 (2.1)	44 (5.9)
Therapy						
Surgery	83 (63)	63 (51)	81 (56)	87 (55)	117 (60)	431 (57)
Surgery and chemotherapy	44 (33)	56 (45)	61 (42)	69 (44)	69 (36)	299 (40)
Chemotherapy	4 (3.0)	3 (2.4)	1 (0.7)	2 (1.3)	7 (3.6)	17 (2.3)
Other[a], none or unknown	1 (0.8)	2 (1.6)	1 (0.7)	0	1 (0.5)	5 (0.7)
Total	132	124	144	158	194	752

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; GCTs, germ cell tumours; NOS, not otherwise specified.
[a] Radiotherapy, hormonal therapy and other palliative therapy.

Table 2
The number of patients diagnosed in the Netherlands between 1989 and 2015 with SCSTs per subtype of tumour, baseline characteristics and therapy per period of diagnosis.

	1989–1993 (n, %)	1994–1998 (n, %)	1999–2003 (n, %)	2004–2009 (n, %)	2010–2015 (n, %)	Total (n, %)
Type of SCSTs						
Pure sex cord tumour	69 (86)	83 (89)	51 (81)	43 (71)	34 (77)	280 (82)
Pure stromal tumour	4 (5.0)	5 (5.4)	4 (6.4)	5 (8.2)	3 (6.8)	21 (6.2)
Mixed sex cord-stromal tumour	7 (8.8)	5 (5.4)	8 (13)	13 (21)	7 (16)	40 (12)
Age (years)						
<20	2 (2.5)	3 (3.2)	4 (6.4)	4 (6.6)	1 (2.3)	14 (4.1)
21–40	16 (20)	19 (20)	6 (9.5)	8 (13)	5 (11)	54 (16)
41–60	26 (33)	40 (43)	34 (54)	31 (51)	19 (43)	150 (44)
61–80	30 (38)	27 (29)	16 (25)	14 (23)	15 (36)	103 (30)
>80	6 (7.5)	4 (4.3)	3 (4.8)	4 (6.6)	3 (6.8)	20 (5.9)
FIGO stage						
I	51 (64)	67 (72)	42 (67)	40 (66)	25 (57)	225 (66)
II	10 (13)	13 (14)	9 (14)	10 (16)	6 (14)	48 (14)
III	13 (16)	11 (12)	9 (14)	7 (12)	8 (18)	48 (14)
IV	4 (5.0)	1 (1.1)	1 (1.6)	3 (4.9)	3 (6.8)	12 (3.5)
Unknown	2 (2.5)	1 (1.1)	2 (3.2)	1 (1.6)	2 (4.6)	8 (2.4)
Therapy						
Surgery	66 (83)	83 (89)	53 (84)	49 (80)	38 (86)	288 (85)
Surgery and chemotherapy	11 (14)	9 (9.7)	8 (13)	12 (20)	4 (9.1)	45 (13)
Chemotherapy	1 (1.3)	1 (1.1)	0	0	1 (2.3)	3 (0.9)
Other[a], none or unknown	2 (2.5)	0	2 (3.2)	0	1 (2.3)	5 (1.5)
Total	80	93	63	61	44	341

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; SCSTs, sex cord-stromal tumours.
[a] Radiotherapy, hormonal therapy and other palliative therapy.

Table 3
The number of patients diagnosed in the Netherlands between 1989 and 2015 with sarcomas per baseline characteristics and therapy per period of diagnosis.

	1989–1993 (n, %)	1994–1998 (n, %)	1999–2003 (n, %)	2004–2009 (n, %)	2010–2015 (n, %)	Total (n, %)
Mesenchymal tumours	24	38	37	41	25	165
Age (years)						
0–20	0	1 (2.6)	1 (2.7)	0	0	2 (1.2)
21–40	0	6 (16)	1 (2.7)	6 (15)	0	13 (7.8)
41–60	8 (33)	11 (29)	14 (38)	16 (39)	11 (44)	60 (36)
61–80	14 (58)	19 (50)	16 (43)	18 (44)	12 (48)	79 (48)
>80	2 (8.3)	1 (2.6)	5 (14)	1 (2.4)	2 (8.0)	11 (6.7)
FIGO stage						
I	8 (33)	7 (18)	12 (32)	18 (44)	7 (28)	52 (32)
II	5 (21)	10 (26)	7 (19)	5 (12)	8 (32)	35 (21)
III	1 (4.0)	3 (7.9)	8 (22)	10 (24)	7 (28)	29 (18)
IV	5 (21)	5 (13)	4 (11)	5 (12)	3 (12)	22 (13)
Unknown	5 (21)	13 (34)	6 (16)	3 (7.3)	0	27 (16)
Therapy						
Surgery	17 (71)	29 (76)	29 (79)	29 (71)	19 (76)	123 (75)
Surgery and chemotherapy	2 (8.3)	4 (11)	3 (8.1)	8 (20)	3 (12)	20 (12)
Chemotherapy	0	0	0	0	0	0
Other[a], none or unknown	5 (21)	5 (13)	5 (14)	4 (9.8)	3 (12)	22 (13)
Total	24	38	37	41	25	165

FIGO, Fédération Internationale de Gynécologie et d'Obstétrique.
[a] Radiotherapy, hormonal therapy and other palliative therapy.

(NOS) (5%). The median age at diagnosis was higher for non-dysgerminomas (38 years) than for dysgerminomas (21 years). The 5-year OS was 98% for dysgerminomas and 78% for non-dysgerminomas ($p < 0.01$, Table 4). The 5-year OS for the non-dysgerminoma group increased from 67% in the period 1989–1993 to 85% in the period 2010–2015 ($p = 0.04$). For dysgerminomas, the 5-year OS remained constant, at 100% in the period 1989–1993 and 97% in the period 2010–2015 ($p = 0.55$).

In the dysgerminoma subgroup ($n = 135$), 58 patients were diagnosed with FIGO stage IA. Six (10%) of these patients received adjuvant chemotherapy, and no lymph nodes were removed in four of these six women (data on lymph node removal were unknown in two women). Five-year OS in FIGO stage IA patients was 100%, irrespective of whether or not chemotherapy was given. Of the 77 patients with FIGO stage IB or higher, 53 (69%) received chemotherapy. The 5-year OS of this group was different

Table 4
Crude observed 5-year overall survival (OS) and adjusted hazard ratios (HRs) for all patients diagnosed in the Netherlands between 1989 and 2015 by period of diagnosis, stage at diagnosis and different histology.

	GCTs (n = 752)		SCSTs (n = 341)		Sarcomas (n = 165)	
	5-year OS (95% CI)	HR (95% CI)[a]	5-year OS (95% CI)	HR (95% CI)[a]	5-year OS (95% CI)	HR (95% CI)[a]
Time period						
1989–1993	73% (63–79)	Ref	64% (52–74)	Ref	20% (8–39)	Ref
1994–1998	79% (71–86)	0.64 (0.40–1.02)	75% (64–82)	1.01 (0.68–1.50)	39% (24–54)	1.15 (0.60–2.21)
1999–2003	82% (75–88)	0.71 (0.44–1.12)	79% (66–87)	1.03 (0.66–1.60)	40% (25–56)	0.92 (0.47–1.79)
2004–2009	83% (77–88)	0.58 (0.35–0.95)	73% (60–82)	0.96 (0.58–1.60)	51% (35–65)	0.58 (0.31–1.11)
2010–2015	88% (82–92)	0.43 (0.25–0.74)	81% (66–90)	0.48 (0.21–1.10)	29% (13–49)	0.91 (0.46–1.81)
FIGO stage						
I	91% (88–93)	Ref	82% (76–86)	Ref	67% (53–78)	Ref
II	70% (59–79)	1.82 (1.16–2.85)	72% (56–82)	1.82 (1.15–2.86)	31% (16–46)	2.35 (1.34–4.12)
III	64% (55–72)	4.42 (3.00–6.52)	47% (32–60)	3.09 (2.07–4.60)	13% (3–28)	4.78 (2.71–8.45)
IV	59% (44–71)	4.81 (2.97–7.79)	25% (6–50)	6.86 (3.37–13.9)	0%	10.1 (5.31–19.2)
Histology						
Dysgerminoma	98% (93–99)	Ref	–			
Non-dysgerminoma	78% (74–81)	3.45 (1.49–8.00)	–			
Pure sex cord	–		77% (71–81)	Ref		
Pure stromal	–		47% (25–66)	1.85 (1.02–3.35)		
Mixed	–		62% (45–75)	1.68 (1.06–2.67)		

CI, confidence interval; FIGO, Fédération Internationale de Gynécologie et d'Obstétrique; GCTs, germ cell tumours; SCSTs, sex cord-stromal tumours.
[a] Adjusted for age, stage at diagnosis, period of diagnosis, and histology (where applicable).

from that of the group that did not receive chemotherapy, at 98% and 91%, respectively (p = 0.08).

In the non-dysgerminoma subgroup (n = 578), 20 patients were diagnosed with FIGO stage IA grade I immature teratoma, of whom 18 (90%) did not receive adjuvant chemotherapy. The 5-year OS was 100% which was the same in the group (n = 2) that received chemotherapy. Of the remaining 558 patients with FIGO stage IB or higher, 226 patients (40%) received chemotherapy. The 5-year OS of this group was not significantly different from that of the group that did not receive chemotherapy, being 73% and 80%, respectively (p = 0.36). This effect remained after adjustment for age and FIGO stage (HR: 1.1, 95% CI: 0.8–1.7).

3.3. Sex cord-stromal tumours – overall

The absolute number of SCSTs decreased over time from 80 in 1989–1993 to 44 in 2010–2015. The ESR changed from 0.2 per 100,000 person years during 1989–1993 to 0.1 during 2009–2015. More than half of the SCSTs were FIGO stage I tumours; most patients were treated surgically (98%) and around 10% received adjuvant chemotherapy; these percentages remained constant over time (Table 2). From 1999, 91 patients with clinical stage I or II SCSTs underwent surgery. Of these women, 19 (21%) underwent lymph node removal, and lymph node metastases were not identified in any of them. Overall, the 5-year OS in SCSTs increased from 64% in 1989–1993 to 81% in 2010–2015 (p = 0.57). After adjustment for age, histology and FIGO stage, the effect was less pronounced (HR: 0.5, 95% CI: 0.2–1.1; Table 4). Survival was strongly related to FIGO stage, the 5-year OS being 82% for FIGO stage I and 25% for FIGO stage IV (p < 0.01, Table 4).

3.4. Subgroups of SCSTs

More than 80% (n = 280) of the SCSTs were diagnosed as pure sex cord tumours, 6% (n = 21) were pure stromal tumours and 12% (n = 40) were mixed SCSTs. The five-year OS in these subgroups was 77%, 47% and 62%, respectively (p < 0.02). When corrected for age, FIGO stage and period, on comparison with the pure sex cord group, the HR was 1.9 (95% CI: 1.0–3.4) for the pure stromal group and 1.7 (95% CI: 1.1–2.7) for the mixed group. All women with FIGO stage IA granulosa cell tumours (n = 70) underwent surgery only without adjuvant chemotherapy; the 5-year OS was 89% (95% CI: 79%–95%). Of the remaining group, 31 of 196 (15%) received chemotherapy after surgery. The 5-year OS of this group was significantly different from that of the group without chemotherapy, at 55% and 76%, respectively (p = 0.02). This difference disappeared after adjustment for age and FIGO stage (HR: 1.2, 95% CI: 0.7–2.2).

3.5. Sarcomas

The absolute number of sarcomas was 24 in the period 1989–1993 and 25 in the period 2010–2015. The ESR changed from 0.6 per 100,000 person years during 1989–1993 to 0.4 during 2009–2015. The median age at diagnosis for the total group was 62; this was similar in all periods. Most patients were treated surgically (87%, Table 3). The 5-year OS for all sarcomas was 39% (95%

CI: 31%–46%). Looking at the various time periods, the 5-year OS changed from 20% in the period 1989–1993 to 29% in the period 2010–2015 ($p = 0.14$; Table 4). Survival was strongly related to FIGO stage, the 5-year OS being 67% for FIGO stage I and 0% for FIGO stage IV ($p < 0.01$; Table 4).

4. Discussion

This population-based study focussing on non-epithelial ovarian tumours shows that the ESR for GCTs, SCSTs and sarcomas is low. The main form of treatment of these tumours continues to be surgery. Survival rates have improved slightly over time for most subtypes, in particular for dysgerminomas and SCSTs.

The 5-year OS of GCTs in our study was 82%, at 98% for dysgerminomas and 78% for non-dysgerminomas. This is comparable with survival rates in an earlier study in the US (100% for dysgerminomas and 85% for non-dysgerminomas [3]). In contrast, in a Japanese study, the 5-year OS for GCTs was only 67% [20]. The total number of included patients was lower in the Japanese study [20]. An overview of population-based studies on incidence and survival data is given in Table 5. In these studies, incidence either decreased or remained stable, while survival remained stable or increased in women with non-epithelial ovarian tumours.

When the incidence and survival data are compared with data from the Netherlands on epithelial ovarian tumours, the incidence shows a decline [21], while the long-term survival in women with these tumours has not improved over the last 25 years, despite intensified treatment [22].

The more recent European guidelines on treatment of non-epithelial ovarian cancer recommend surgery without adjuvant chemotherapy for FIGO stage IA pure dysgerminoma and immature teratoma, after an appropriate staging procedure [23]. However, a recent Dutch guideline (2016) states that a surgical staging procedure including lymph nodes is not required because GCTs are extremely chemosensitive and excellent survival rates are also seen in salvage chemotherapy [24]. This is confirmed in our study, as in this particular group of patients, survival was not affected by adjuvant chemotherapy. The same is true for immature teratomas, although the number of patients is rather low. Regarding the completeness of the staging procedure, we only have data lymph node sampling from 1999 onwards. In a review, Kleppe *et al.* [9] found a fairly high incidence of lymph node metastasis in patients with GCTs at clinical stages I and II, with a mean of 11%. In our study, we found an incidence of 28% in the same patient group. Comparing these studies is difficult, and conclusions should be drawn with caution because the percentages depend on the number and extensiveness of lymphadenectomy procedures. Unfortunately, we are not aware of the reasons for lymph node removal. Physicians may have been triggered by intra-operative findings which persuaded them to perform lymphadenectomy or debulking of a lymph node metastasis, thus explaining the rather high incidence of lymph node metastasis in patients with GCTs undergoing lymphadenectomy.

The five-year OS was similar in patients with immature teratomas receiving and not receiving adjuvant chemotherapy, and survival improved over time in the total GCT group. Moreover, the 5-year OS was comparable in patients who did or did not undergo lymph node removal. These findings may contribute to the debate about the necessity of surgical staging and/or adjuvant chemotherapy [5,6,25]. Furthermore, owing to the extreme chemosensitivity of GCTs, not giving adjuvant chemotherapy to all patients but treating only those patients who have recurrences with chemotherapy could be considered.

The largest group of the SCSTs comprised granulosa cell tumours (78%). This was confirmed by a study in the USA which reported that malignant granulosa cell tumours accounted for approximately 75% of all SCSTs [2].

In our study, the 5-year OS of SCSTs was 78%, which is higher than that previously reported in a Japanese study (5-year OS: 55%) [20]. As stated earlier, the number of patients in the Japanese study was low. In patients with SCSTs with FIGO stage 1B or higher, 55% received chemotherapy. After controlling for age and FIGO stage, no difference was shown in survival between the groups that received and did not receive chemotherapy. In addition, survival improved in the total group of SCSTs. This supports the view that adjuvant chemotherapy does not contribute to a better prognosis.

Table 5
Overview of the literature on population-based studies on incidence and survival of non-epithelial ovarian tumours.

Reference	Country	Period	Tumour	Results Incidence	Survival
Smith 2006 [29]	9 SEER registers, USA	1973–2002	GCT	Incidence ↓	Survival ↑
Ioka 2003 [20]	Japan	1975–1994	GCT	Incidence ↔	Survival ↑
			SCST	Incidence ↓	Survival ↑
Ray Coquard 2019 [1]	RARECARE net Europe (27 countries)[a]	1995–2007	GCT	Incidence ↔	Survival ↔
			Sex cord tumours	Incidence ↓	Survival ↔

GCT, germ cell tumour; SCST, sex cord-stromal tumour; SEER Surveillance, Epidemiology, and End Results; ↓ decreased ; ↔ remained stable; ↑ increased.

[a] Online analysis tool was used. http://www.rarecarenet.eu/analysis.php [Accessed Feb 2019].

International guidelines state that FIGO stage IA granulosa cell tumours have an excellent prognosis after surgery alone and do not require adjuvant therapy, and lymph node dissection should be reserved for patients with evidence of nodal abnormality [8,23]. Since 1999, only a minority of these patients underwent a staging procedure that included lymph node dissection, and in those cases where lymph nodes were removed, no lymph node metastases were found – which is in accordance with the literature. A recent review showed that no lymph node metastases were found in clinical stage I and II SCSTs [9].

A literature review on ovarian sarcoma revealed only limited data. It mostly describes subgroups of ovarian sarcomas, i.e. leiomyosarcoma [26], fibrosarcoma [14] and angiosarcoma [13]. Generally, treatment is surgical and any additional treatment depends on FIGO stage at initial diagnosis. The prognosis is still poor, although it might have improved a little over time. A study on rare endometrial sarcomas also showed that the incidence has remained stable at approximately 7 per 1,000,000 person years and that in the Netherlands, survival did not improve in the period 1989–2008 [27]. More generally, an article focussing on recently published data on the management of gynaecological sarcomas revealed that as yet, there has been no improvement in the early diagnosis of, and therapeutic strategies to transform, the poor prognosis of these tumours [28].

The strength of this study is its population-based character and the extensive study period. Some limitations should also be noted. Because of the rarity of these tumours, pathological classification may be difficult and the expertise of the pathologists may vary greatly between hospitals. In addition, a tumour can be heterogeneous and contain different histological subtypes, a subtype of which may be overlooked by the pathologist. Unfortunately, the original histological reports were not revised. In addition, over the years, the classification has changed slightly. At present, because of the increasing degree of centralisation of patients with these tumours, pathologists or even a panel of pathologists specialised in gynaecology classify these tumours.

Unfortunately, the NCR contains no detailed information on the recurrence of these tumours or their treatment, nor on surgical and staging procedures. Therefore, data on lymph nodes should be interpreted with caution.

In conclusion, among the malignant ovarian tumours, malignant GCTs and SCSTs are rare and their incidence has not significantly changed over recent decades. In contrast to epithelial ovarian tumours, the majority are diagnosed in an early stage. This is one explanation of their good prognosis, which has also improved slightly. Primary sarcomas of the ovary are extremely rare, and patients with this tumour type face a poor prognosis.

Conflict of interest statement

None declared.

Acknowledgement

The authors thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data from the Netherlands Cancer Registry. This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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