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ORIGINAL RESEARCH ARTICLE

Stage, treatment and survival of low-grade serous ovarian carcinoma in the Netherlands: A nationwide study

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Abstract

Introduction: Serous ovarian carcinomas constitute the largest group of epithelial ovarian cancer (60%–75%) and are further classified into high- and low-grade serous carcinoma. Low-grade serous carcinoma (LGSC) is a relatively rare subtype (approximately 5% of serous carcinomas) and epidemiologic studies of large cohorts are scarce. With the present study we aimed to report trends in stage, primary treatment and relative survival of LGSC of the ovary in a large cohort of patients in an effort to identify opportunities to improve clinical practice and outcome of this relatively rare disease.

Material and Methods: Patients diagnosed with LGSC between 2000 and 2019 were identified from the Netherlands Cancer Registry (n = 855). Trends in FIGO stages and primary treatment were analyzed with the Cochran–Armitage trend test, and differences in and trends of 5-year relative survival were analyzed using multivariable Poisson regression.

Results: Over time, LGSC was increasingly diagnosed as stage III (39.9%–59.0%) and IV disease (5.7%–14.4%) and less often as stage I (34.6%–13.5%; $p < 0.001$). Primary debulking surgery was the most common strategy (76.2%), although interval debulking surgery was preferred more often over the years (10.6%–31.1%; $p < 0.001$). Following primary surgery, there was >1 cm residual disease in only 15/252 patients (6%), compared with 17/95 patients (17.9%) after interval surgery. Full cohort 5-year survival was 61% and survival after primary debulking surgery was superior to the outcome following interval debulking surgery (60% vs 34%). Survival following primary debulking surgery without macroscopic residual disease (73%) was better compared with ≤1 cm (47%) and >1 cm residual disease (22%). Survival following interval debulking surgery without macroscopic residual disease (51%) was significantly higher than after >1 cm residual disease (24%). Except FIGO stage II (85%–92%), survival did not change significantly over time.

Abbreviations: CI, confidence interval; EHR, excess hazard ratio; HGSC, high-grade serous carcinoma; IDS, interval debulking surgery; LGSC, low-grade serous carcinoma; PDS, primary debulking surgery; RS, relative survival.

Conclusions: Over the years, LGSC has been diagnosed as FIGO stage III and stage IV disease more often and interval debulking surgery has been increasingly preferred over primary debulking in these patients. Relative survival did not change over time (except for stage II) and worse survival outcomes after interval debulking surgery were observed. The results support the common recommendation to perform primary debulking surgery in patients eligible for primary surgery.

KEYWORDS
cytoreductive surgery, debulking surgical procedure, epithelial, ovarian cancer, ovarian epithelial carcinoma, ovarian neoplasms

1 | INTRODUCTION

Epithelial ovarian cancer constitutes the largest group of ovarian malignancies (90%–95%), with serous tumors being the most common histological subtype of epithelial ovarian cancer (60%–75%).[1–4] Serous ovarian carcinomas are further classified into high-grade serous carcinoma (HGSC) or low-grade serous carcinoma (LGSC).[5,6] LGSC is a relatively rare subtype constituting 2% of epithelial ovarian cancer and approximately 5% of serous carcinomas.[7,8] Women with LGSC are often younger at diagnosis (mean 56 years) than women with HGSC (mean 63 years).[7] LGSC has a more indolent nature and milder biological behavior, with more patients being diagnosed with FIGO stage I disease (LGSC 34% and HGSC 9%).[7,9] However, the majority are diagnosed at an advanced stage, with FIGO stage III being the most common (43%).[7] Several studies have shown better survival rates for LGSC than for HGSC, with most recent 5-year survival rates of 89.3% vs 80.8% for early-stage disease and 57.7% vs 35.3% for advanced stage.[7,10,11]

A comprehensive staging procedure in presumed early-stage disease, or debulking surgery for advanced stage disease, followed by adjuvant chemotherapy if indicated, is still the preferred treatment for LGSC.[12] In advanced stage disease, debulking surgery with resection of all macroscopic disease (synonym: cytoreductive surgery) is of pivotal importance because of its relative chemoresistance (response rate of 4%–11%).[12,13] There is a growing and promising body of evidence for the efficacy of endocrine, molecularly targeted and anti-angiogenic treatment modalities in both the front-line and recurrent setting.[14–17]

As LGSC is rare and incidence rates are relatively low, randomized controlled trials and retrospective series including large numbers of patients are scarce. In addition, the available studies generally present (1) primary treatment and survival rates without trends over time, (2) crude survival rates instead of relative survival (RS), (3) survival rates subdivided by early- and advanced stage disease instead of FIGO stage I–IV, and (4) outcomes of debulking surgery without differentiating between the primary and interval approach. To provide more detailed information and to identify opportunities to improve clinical practice and disease outcome, the present study aims to report trends in FIGO stage, primary treatment, and RS of LGSC in a large cohort of patients.

Key message

Neoadjuvant chemotherapy for low-grade serous ovarian carcinoma increased over time. Overall 5-year relative survival was 61% and did not change over time, except for FIGO stage II disease. Survival after primary surgery was superior to interval surgery.

2 | MATERIAL AND METHODS

2.1 | Data selection

All consecutive patients diagnosed with LGSC in the Netherlands between January 2000 and December 2019 were identified from the Netherlands Cancer Registry. The Netherlands Cancer Registry is a population-based registry, primarily based on notification by PALGA (automated Dutch nationwide histo- and cytopathology data network and registry/archive) and supplemented with data from the National Registry of Hospital Discharge Diagnosis.[18] It comprises information on all newly diagnosed cancer patients in the Netherlands, and the completeness is estimated to be at least 95%.[19]

Serous ovarian cancer was classified according to the International Classification of Diseases for Oncology (ICD-O-3 codes 8260, 8441, 8450, 8460, 8461).[20,21] Patients with a Shimizu/Silverberg grade 1 tumor, or LGSC according to the current two-tier system, were included.[5,6,22] Data on patient, tumor and treatment characteristics were routinely extracted from the medical files of all Dutch hospitals by dedicated data managers. Diagnoses were made based on surgically obtained specimens or cytological or histological examination of specimens obtained in patients not eligible for primary surgery (eg ascites or omental cake biopsy). Information on vital status was obtained by annual linkage to the Personal Records Database (BRP) and was available up to January 31, 2022 (last follow-up date). Tumor staging was performed according to the 1988/2014 FIGO classification.[23] FIGO stage was originally not available in The Netherlands Cancer Registry but was derived from the pathological or clinical Union for International Cancer Control Tumor-Node-Metastasis (TNM) classification from the patient file.[24] Editions 5, 6 and 7 (corresponding to FIGO 1988)

and edition 8 (FIGO 2014) were used for the periods 2000–2016 and 2017–2019, respectively. In cases where treatment was started with neoadjuvant chemotherapy, where no surgery was performed or where there was no oncological treatment at all, tumor stage at the time of diagnosis was used (eg tumor-positive omental biopsy or pleural effusion). FIGO stages I–IIA and IIB–IVB were considered early-stage and advanced stage disease, respectively. A staging procedure was recorded in the Netherlands Cancer Registry if any part of the epithelial ovarian cancer staging procedure was performed in addition to the salpingo-oophorectomy with(out) hysterectomy (peritoneal biopsies, omentectomy or omental biopsy or lymph node sampling/dissection). Debulking surgery could not be registered in case of early-stage disease (I–IIA).

Definitions of outcomes of debulking surgery have changed over time in the literature.[28–30] Accordingly, the cutoff value for optimal debulking surgery has been changed in the Netherlands Cancer Registry from ≤2 to ≤1 cm residual disease in January 2007 and macroscopic residual disease >1 cm was denoted as incomplete debulking surgery. In December 2009, "no macroscopic residual disease" was added (complete debulking surgery). Therefore, RS with respect to the outcome of debulking surgery was only analyzed for patients included in the Netherlands Cancer Registry according to the December 2009 manual.

All analyses were conducted using STATA/SE version 16.1 (Stata Corporation). Statistical tests were two-tailed and considered significant at $p < 0.05$.

2.2 | Statistical analyses

Crude incidence rates (ie number of new LGSC cases in the Dutch population during a year) and annual European standardized incidence rates (ESR; age-standardized incidence rate using the European global standard population) were calculated per 100 000 person-years.[25] Patients were grouped by period of diagnosis (2000–2006, 2007–2013 or 2014–2019), and temporal trends in FIGO stage and primary treatment were analyzed with the Cochran–Armitage trend test. Five-year RS, estimating cause-specific survival without requiring cause-of-death information, was calculated using the Ederer II method.[26,27] Differences of RS with respect to outcomes of specific variables (eg FIGO stages) and trends in RS rates were analyzed using uni- and multivariable Poisson regression (adjusting for age, FIGO stage and primary treatment [surgery and chemotherapy]) and presented as both unadjusted and adjusted excess hazard ratios (EHRs) with 95% confidence intervals (CIs).

2.3 | Ethics statement

This study was approved by the Privacy Review Board of the Netherlands Cancer Registry on January 8, 2021 (K20.327).

3 | RESULTS

3.1 | Study population

A total of 855 women were included in this study. The mean age at diagnosis was 59 ± 15 years. Early-stage disease was diagnosed in 213 patients (24.9%) and advanced stage in 586 patients (68.5%; Table 1). Regarding FIGO stage II disease ($n = 85$; 9.9%), nine patients (10.6%) were diagnosed with stage IIA, 43 (50.6%) with stage IIB and 33 (38.8%) with stage IIC disease (data not shown). Stage III disease was the most common ($n = 425$; 49.7%), of which stage IIIC ($n = 304$; 71.5%; data not shown) was the most prevalent. From 2000 to 2019,

TABLE 1 Characteristics of a cohort of 855 patients with low-grade serous carcinoma, grouped as per period of diagnosis.

Characteristics, *n* (%)*	2000–2006	2007–2013	2014–2019	Total
Number of patients diagnosed	263 (30.8)	265 (31.0)	327 (38.2)	855
Age, years (mean ± SD)	60 ± 15	58 ± 15	59 ± 16	59 ± 15
FIGO stage				
I	91 (34.6)	69 (26.0)	44 (13.5)	204 (23.9)
II	21 (8.0)	26 (9.8)	38 (11.6)	85 (9.9)
III	105 (39.9)	127 (47.9)	193 (59.0)	425 (49.7)
IV	15 (5.7)	23 (8.7)	47 (14.4)	85 (9.9)
Early-stage disease (FIGO stage I–IIA)	94 (35.7)	71 (26.8)	48 (14.7)	213 (24.9)
Advanced stage disease (FIGO stage IIB–IV)	138 (52.5)	174 (65.7)	274 (83.8)	586 (68.5)
Missing	31 (11.8)	20 (7.5)	5 (1.5)	56 (6.5)
Follow-up, years, median (interquartile range)	7.49 (2.47–17.30)	6.25 (2.76–10.73)	3.48 (2.32–5.02)	4.59 (2.43–9.42)

*Unless otherwise specified.

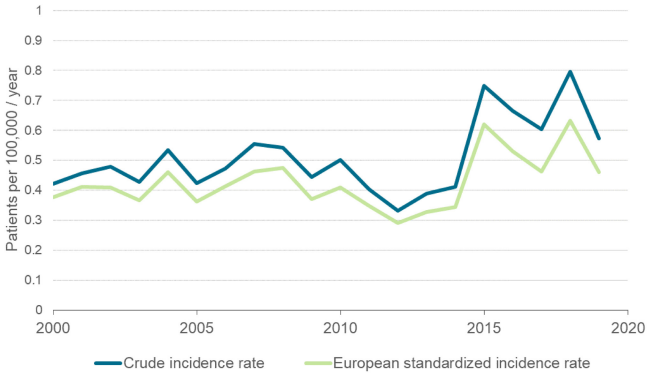

FIGURE 1 Temporal trends of crude and European standardized incidence rates of patients diagnosed with low-grade serous carcinoma in The Netherlands from 2000 to 2019.

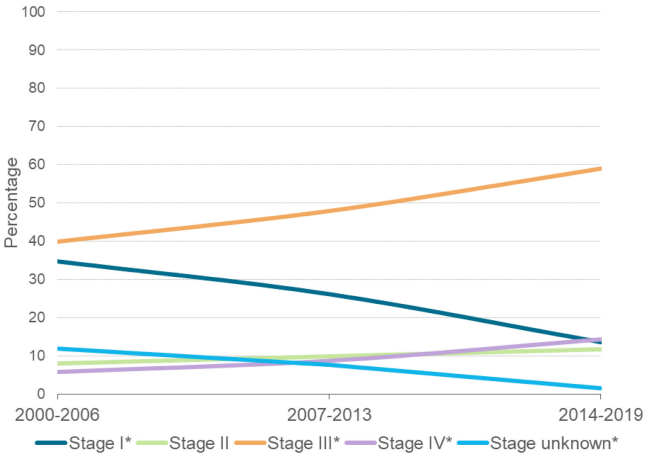

FIGURE 2 Temporal trends in distribution of FIGO stages, grouped as per period of diagnosis. *Significant at $p < 0.05$.

a median of 39 patients (interquartile range 35–47) was diagnosed with LGSC on an annual basis in the Netherlands. Crude incidence rates varied from 0.33 to 0.80/100 000 person-years per year, and ESR varied from 0.29 to 0.63/100 000 person-years per year, with a notable increase in both incidence rates being observed from 2015 onwards (Figure 1). Temporal trends in the distribution of FIGO stages are shown in Figure 2, showing a significant increase over time in stage III (from 39.9% to 59.0%; $p < 0.001$) and stage IV disease (from 5.7% to 14.4%; $p < 0.001$) and a decrease in stage I disease (from 34.6% to 13.5%; $p < 0.001$).

3.2 | Primary treatment

Primary treatment of patients diagnosed with LGSC between 2000 and 2019 is shown in Table 2, and trends are illustrated in Figure 3. Surgery was performed in 763 patients (89.2%), of which the majority ($n = 491$; 64.4%) underwent debulking surgery and 18.3% of the patients ($n = 140$) a staging procedure. Following the staging procedure, 19 of 140 (13.6%) patients were considered to have advanced stage disease (1.4% stage unknown; data not shown). Of 109 patients that only underwent a salpingo-oophorectomy with(out) hysterectomy, 89 (81.7%) had early-stage disease and those with known advanced stage disease ($n = 17$; 15.6%) constituted only 2.9% of all advanced stage disease patients (data not shown). Over time (2000–2006 to 2014–2019), debulking surgery was performed more often (46.8%–64.8%; $p < 0.001$), whereas the percentage of patients who only underwent a salpingo-oophorectomy with(out) hysterectomy decreased (27.8%–4.3%; $p < 0.001$). Primary debulking surgery (PDS) was the most common debulking strategy (374 of 491 patients; 76.2%), although the application of interval debulking surgery (IDS) increased over the years (10.6%–31.1%; $p < 0.001$). A total of 252 of 374 PDS patients (67.4%) and 95 of 117 IDS patients (81.2%) were included in the Netherlands Cancer Registry handling the most recent criteria for the outcome of debulking surgery (no macroscopic, ≤1 or >1 cm residual disease). Regarding the 252 patients who underwent PDS, the outcome was unknown for 26 patients (10.3%), and there was no macroscopic residual disease in 142 patients (56.3%), ≤1 cm residual disease in 69 patients (27.4%) and >1 cm residual disease in 15 patients (6.0%; data not shown). In the IDS group, the outcome was unknown for four patients (4.2%) and no macroscopic, ≤1 cm, and >1 cm residual disease was achieved in 43 (45.3%), 31 (32.6%) and 17 (17.9%) patients, respectively (data not shown). In 92 patients (10.8%), there was no surgical procedure, and this proportion increased over time (8.0%–15.9%; $p = 0.001$).

Chemotherapy was administered in 559 of 855 LGSC patients (65.4%), and the percentage of patients receiving chemotherapy increased over time (59.3%–68.2%; $p = 0.029$; Table 2 and Figure 3). Treatment was started with chemotherapy (whether or not followed by IDS) in 173 patients (30.9% of 559 treated with chemotherapy; 20.2% of the full cohort). Regarding the full cohort, there was an increase in the percentage of patients starting treatment with chemotherapy over the years (9.9%–28.8%; $p < 0.001$). Adjuvant chemotherapy following surgery was administered in 386 patients (69.1% of 559 treated with chemotherapy; 45.1% of the full cohort); considering the full cohort, significantly fewer patients were treated with adjuvant chemotherapy over time (49.4%–39.5%; $p = 0.013$). Of 213 confirmed early-stage disease patients, 29 (13.6%) were treated with chemotherapy (only adjuvant chemotherapy) and it was administered significantly less often over time (22.3%–8.3%; $p = 0.007$). Confirmed advanced stage disease was treated with chemotherapy in 494 of 586 patients (84.3%), and the percentage did not significantly change over time.

3.3 | Relative survival

Five-year RS curves of the full cohort, as well as stratified by FIGO stage and type and outcome of debulking surgery, are illustrated in Figure 4. Five-year RS percentages and results from multivariable analysis are presented in Table 3. Average RS of LGSC patients diagnosed between 2000 and 2019 was 61%. FIGO stage I or II LGSC had similar RS (89% and 87%, respectively), even after covariate

TABLE 2 Primary treatment for patients diagnosed with low-grade serous carcinoma, grouped as per period of diagnosis.

Primary treatment, *n* (%)	2000–2006 (*n* = 263)	2007–2013 (*n* = 265)	2014–2019 (*n* = 327)	Total (*n* = 855)
Surgical treatment	242 (92.0)	246 (92.8)	275 (84.1)	763 (89.2)
Salpingo-oophorectomy ± hysterectomy	73 (27.8)	22 (8.3)	14 (4.3)	109 (12.7)
Staging procedure	34 (12.9)	63 (23.8)	43 (13.1)	140 (16.4)
Debulking surgery	123 (46.8)	156 (58.9)	212 (64.8)	491 (57.4)
PDS	110 (41.8)	118 (44.5)	146 (44.6)	374 (43.7)
IDS	13 (4.9)	38 (14.3)	66 (20.2)	117 (13.7)
Other (eg palliative resection of tumor deposits, surgery not otherwise specified)	12 (4.6)	5 (1.9)	6 (1.8)	23 (2.7)
Chemotherapy	156 (59.3)	180 (67.9)	223 (68.2)	559 (65.4)
Start with chemotherapy ± surgery ± adjuvant chemotherapy	26 (9.9)	53 (20.0)	94 (28.7)	173 (20.2)
NACT, IDS and ACT	6 (2.3)	35 (13.2)	44 (13.5)	85 (9.9)
NACT, IDS, no ACT	7 (2.7)	3 (1.1)	22 (6.7)	32 (3.7)
Palliative chemotherapy/NACT without subsequent surgery	13 (4.9)	15 (5.7)	28 (8.6)	56 (6.5)
ACT following surgery (without prior NACT)	130 (49.4)	127 (47.9)	129 (39.4)	386 (45.1)
No surgery, no chemotherapy	8 (3.0)	4 (1.5)	24 (7.3)	36 (4.2)

Abbreviations: ACT, adjuvant chemotherapy; CT, chemotherapy; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery.

adjustment. Stage III disease patients (RS 49%) had a significantly worse RS than those diagnosed with stage I (EHR 4.99, 95% CI 2.20–11.30) or stage II disease (EHR 4.02, 95% CI 1.96–8.24). Patients with stage IV disease (RS 24.8%) had a significantly worse survival compared with patients with stage I (EHR 8.24, 95% CI 3.57–19.00), stage II (EHR 6.63, 95% CI 3.11–14.15) and stage III disease (EHR 1.65, 95% CI 1.21–2.26).

Adjusted analysis also showed that 5-year RS of patients who underwent PDS (60%) was significantly better (EHR 1.75, 95% CI 1.26–2.43) than RS of those who had IDS (34%). Even a subanalysis that also adjusted for the outcome of debulking surgery showed worse RS following interval debulking surgery (EHR 1.69, 95% CI 1.13–2.51). Furthermore, the degree of residual disease following PDS wass revealed to be an important prognostic factor, with the best RS being observed in patients without any macroscopic residual disease (73%), followed by a significantly worse RS in case of residual disease ≤1 cm (47%; EHR 2.08, 95% CI 1.20–3.60) and residual disease >1 cm (22%; EHR 2.63, 95% CI 1.28–5.39). After covariate adjustment, differences in RS following IDS were significant only for patients without macroscopic residual disease (51%) when compared with residual disease >1 cm (24%; EHR 2.69, 95% CI 1.13–6.39).

3.4 | Trends in relative survival

Temporal trends in 5-year RS rates of the full cohort, FIGO stage I–IV disease and early- and advanced stage disease are illustrated in Figure 5. Overall RS and RS rates per period of diagnosis, as well as results of uni- and multivariable analyses (estimated excess hazard ratios), are provided as supporting information in Table S1. Except for FIGO stage II disease (85%–92%; EHR 0.00, 95% CI 0.00–0.02), RS of patients diagnosed with LGSC did not change significantly over time (2000–2006 and 2014–2019). Furthermore, subgroup survival differences between 2000–2006 and 2007–2013 were not significant.

4 | DISCUSSION

In this study, we report trends in incidence, FIGO stages, primary treatment and RS of LGSC in one of the largest cohorts of patients presented thus far. The present study shows a slight increase in both crude and age-standardized incidence rates around 2015, which might be explained by the fact that a small part of serous carcinomas that were formerly classified as grade 2 (Shimizu/Silverberg criteria/WHO 2004 and earlier) might now be classified as LGSC according to the more recent two-tier system.[31,32] Furthermore, serous borderline ovarian tumors with invasive extra-ovarian implants are considered to be LGSC according to the 2014 WHO classification.[33] Studies exploring trends in incidence are scarce and, unfortunately, recent incidence data covering the same time span are not available for comparison. Interestingly, Matsuo et al. found that the proportion of LGSC patients decreased from the 1970s until 2013, for which they cite the more recent two-tier classification, the renewed classification of borderline ovarian tumors, and aging of the population as possible explanations.[8,34]

Over the years, LGSC has been diagnosed more frequently as stage III and IV disease and less often as stage I disease, which

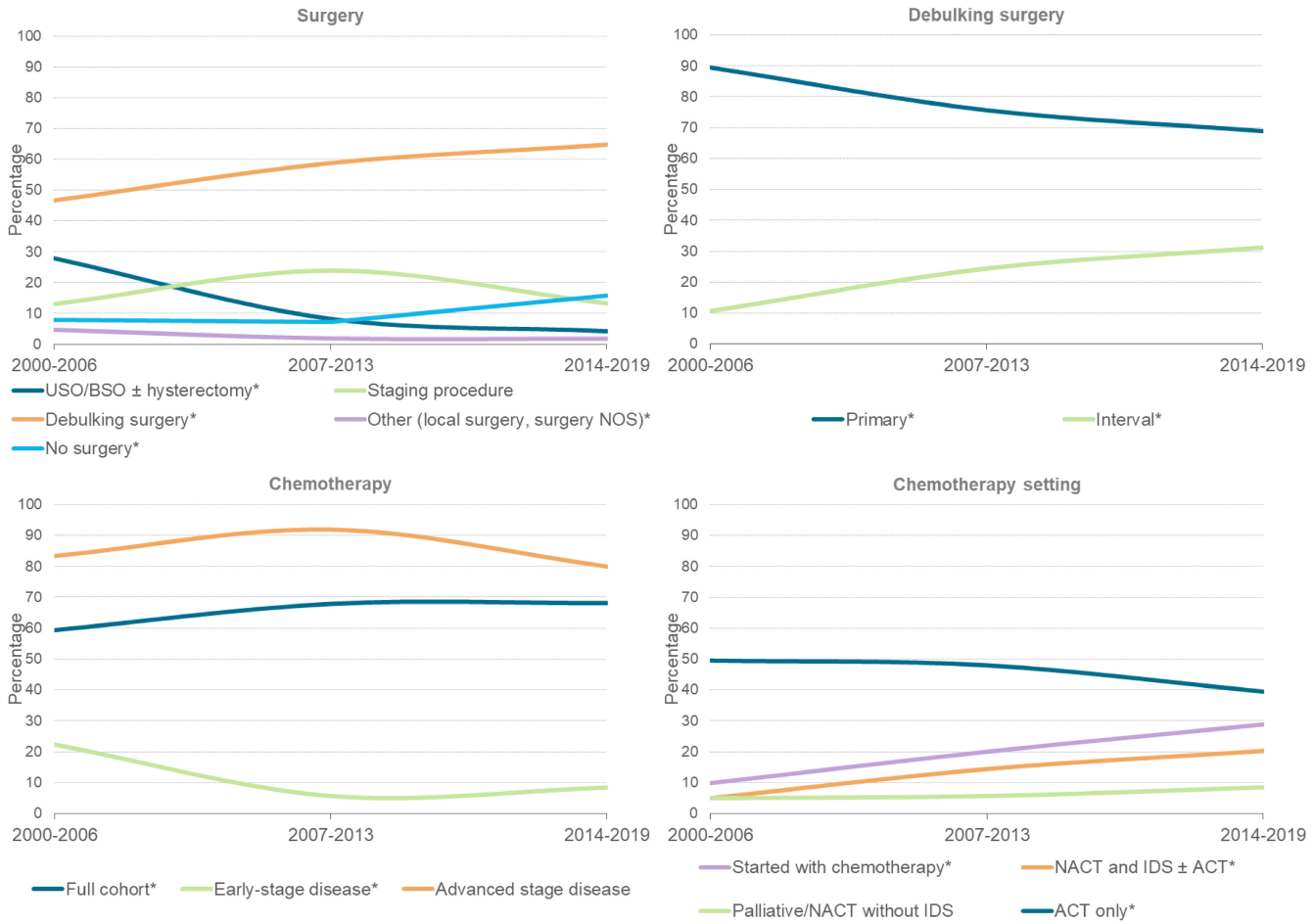

FIGURE 3 Temporal trends in primary treatment of low-grade serous carcinoma patients, shown for overall surgical treatment, debulking surgery, overall application of chemotherapy and setting of chemotherapeutic treatment. ACT, adjuvant chemotherapy; BSO, bilateral salpingo-oophorectomy; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; NOS, not otherwise specified; USO, unilateral salpingo-oophorectomy. *Significant at $p < 0.05$.

might be explained by improved and guideline-based surgical (staging) procedures, more accurate preoperative imaging modalities (eg patients who had no surgery and were diagnosed based on image-guided biopsies) and also the new WHO classification, considering invasive implants in the case of serous borderline ovarian tumors as extra-ovarian LGSC.[7,33,34] To our knowledge, RS rates of LGSC have previously only been published by Plaxe and colleagues in 2008 and were not stratified by FIGO stage I–IV.[11] Overall, the 5-year RS in our study was 61%, whereas Plaxe et al. showed a 5-year RS rate of 75% in their cohort of 793 LGSC patients. This discrepancy may be caused by a different period of inclusion, disparities regarding diagnostic criteria, and other causes of heterogeneity between the cohorts (eg FIGO stage, age). In our study, except for FIGO stage II disease, RS of patients diagnosed between 2000 and 2019 did not improve or deteriorate over time, either for the full cohort or after stratification by FIGO stage. Although it is worrying that RS does not appear to be significantly improved, trends in survival may also be biased to some extent. First of all, overall RS in our cohort might be compromised by the increase in advanced stage disease cases with an associated poorer prognosis, as a result of the aforementioned new classification. Furthermore, we were not able to adjust for adjuvant therapy other than chemotherapy, which has become more common and might improve progression-free and overall survival.[16] Interestingly, Matsuo et al. have shown that 5-year crude overall survival rates for patients diagnosed with advanced stage (III and IV) LGSC between 1988 and 2012 improved over the years (51%–66%).[7] As other-cause mortality is not taken into account in case of crude survival rates, the increase might have been biased by an improved better overall life expectancy.[35] On the other hand, the better and increased survival may also result from differences in treatment protocols, in addition to the aforementioned causes of heterogeneity between study cohorts. However, further studies, exploring novel treatment strategies for LGSC, are warranted.

Analogous to the increase in patients with advanced stage disease, the number of patients who underwent debulking surgery also increased. The outcome of debulking surgery seems to be a prognostic factor in LGSC patients in our study. In the PDS group, relative survival was best following surgery with no macroscopic residual disease and in the IDS group, this applied to patients without macroscopic or ≤1 cm residual disease, in line

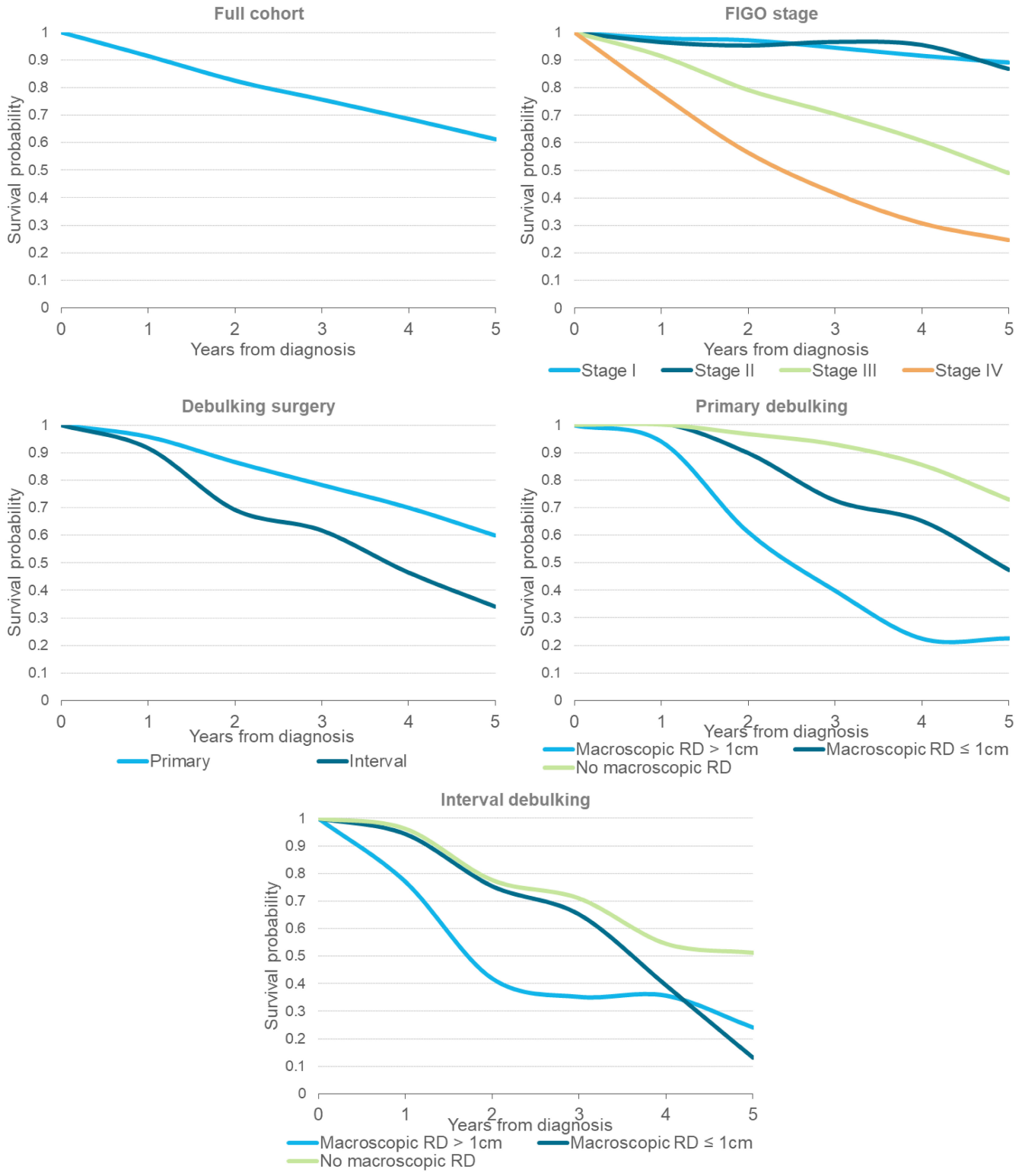

FIGURE 4 Relative survival of the full cohort of low-grade serous carcinoma patients, subdivided by FIGO stage, type of debulking surgery and outcome of primary or interval debulking surgery. RD, residual disease.

with other studies.[10,36–38] Better survival following PDS than after neo-adjuvant chemotherapy followed by IDS was found, which is in accordance with two recent studies, but this was not confirmed in another cohort of stage II–IV LGSC patients.[38–40] It is important to note that these differences might be caused not by the surgery itself but rather by the extent of disease.[13] Despite covariate adjustment, even for the outcome of debulking surgery, the IDS group still might represent patients with poorer prognostic factors that warranted a start with neo-adjuvant chemotherapy (eg multiple hepatic or other visceral metastases and/or impaired

TABLE 3 Five-year relative survival rates (95% CI) and results of uni- and multivariable analyses (estimated excess hazard ratios with 95% CI).

	Five-year relative survival percentage (95% CI)	Unadjusted EHR (95% CI)			Adjusted EHR (95% CI)		
Full cohort	**61 (57–65)**	—	—	—	—	—	—
FIGO stage		II	III	IV	II	III	IV
I	89 (83–94)	1.25 (0.50–3.17)	**6.20 (3.45–11.13)**	**13.66 (7.33–25.48)**	1.24 (0.46–3.33)	**4.99 (2.20–11.30)**	**8.24 (3.57–19.00)**
II	87 (75–94)	—	**4.94 (2.34–10.45)**	**10.89 (5.00–23.73)**	—	**4.02 (1.96–8.24)**	**6.63 (3.11–14.15)**
III	49 (43–54)	—	—	**2.2 (1.64–2.96)**	—	—	**1.65 (1.21–2.26)**
IV	25 (15–35)	—	—	—	—	—	—
Debulking surgery		IDS	—	—	IDS	—	—
PDS	60 (54–65)	**2.12 (1.57–2.88)**	—	—	**1.75 (1.26–2.43)**	—	—
IDS	34 (24–44)	—	—	—	—	—	—
Outcome of PDS		RD ≤1 cm	RD >1 cm	—	RD ≤1 cm	RD >1 cm	—
No macroscopic RD	73 (63–81)	**2.51 (1.49–4.24)**	**7.00 (3.35–14.62)**	—	**2.08 (1.20–3.60)**	**5.47 (2.59–11.54)**	—
RD ≤1 cm	47 (34–60)	—	**2.78 (1.36–5.69)**	—	—	**2.63 (1.28–5.39)**	—
RD >1 cm	22 (5–48)	—	—	—	—	—	—
Outcome of IDS		RD ≤1 cm	RD >1 cm	—	RD ≤1 cm	RD >1 cm	—
No macroscopic RD	51 (33–67)	**1.94 (1.01–3.70)**	**2.96 (1.38–6.34)**	—	1.84 (0.94–3.62)	**2.69 (1.13–6.39)**	—
RD ≤1 cm	13 (3–32)	—	1.53 (0.74–3.16)	—	—	1.46 (0.61–3.51)	—
RD >1 cm	24 (5–51)	—	—	—	—	—	—

Note: Bold values are significant at $p < 0.05$ (reference categories in 1st column).

Abbreviations: CI, confidence interval; EHR, excess hazard ratio. IDS, interval debulking surgery; PDS, primary debulking surgery; RD, residual disease.

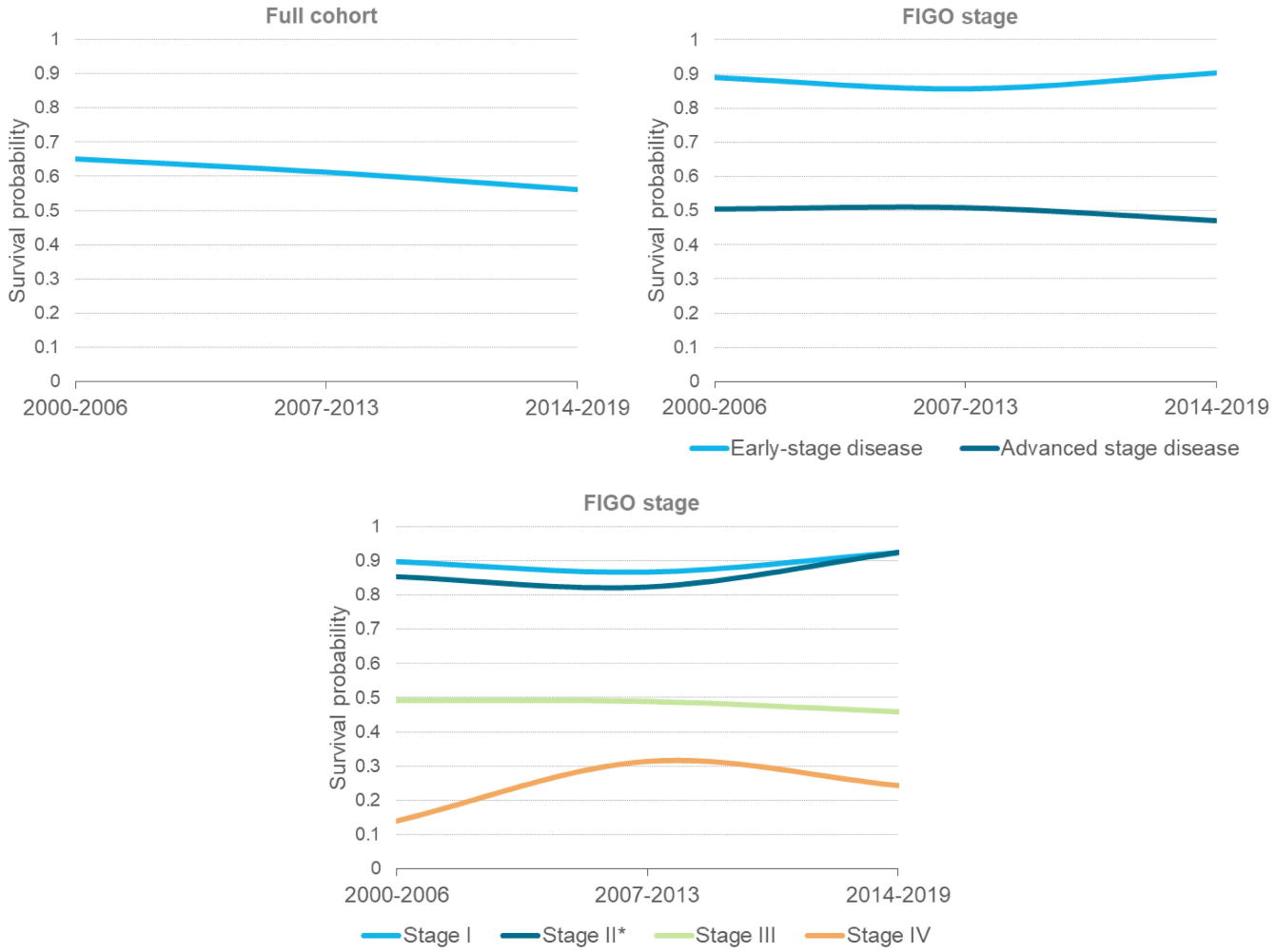

FIGURE 5 Temporal trends in 5-year relative survival of low-grade serous carcinoma patients, shown for the full cohort and stratified by FIGO stage (early-stage vs advanced stage and stage I–IV). *Significant at $p < 0.05$.

performance status) and which we were not able to adjust for in the present study. In our study, we found a considerable increase in the proportion of patients treated with IDS. It is not likely that this can be attributed solely to the abovementioned patients' extent of disease or bad performance status. More likely, this may be explained by the fact that neo-adjuvant chemotherapy and IDS have become more common over the years for ovarian cancer treatment in general.[41,42] However, primary debulking without residual disease should be the standard except for those in whom primary resection is not feasible. This is because it is highly likely that treatment of LGSC with neo-adjuvant chemotherapy yields a low probability of response (4%–11%) and even the risk of progression, as a result of its relative chemoresistance.[12,13]

The present study is subject to the limitations and biases inherent to retrospective studies. Despite having included one of the largest cohorts of LGSC patients so far, an estimated small percentage (<5%) of LGSC patients might not have been included in the study because the Netherlands Cancer Registry does not cover all of the new cancer patients.[19] Besides, patients diagnosed with a grade 2 tumor (Shimizu/Silverberg) were regarded as HGSC and were therefore not included in the study, although they might have been classified as LGSC according to the current two-tier classification in the case of central review of pathology slides. Furthermore, we had to deal with changing definitions on the outcome of debulking surgery at the expense of the number of patients analyzed. Last but not least, we were not able to study the administration of endocrine, molecularly targeted and anti-angiogenic treatment modalities, which might have influenced patient outcomes.

5 | CONCLUSION

We observed that LGSC was diagnosed as FIGO stage III and stage IV disease more often over the years, and IDS was increasingly preferred over PDS in these patients. Survival outcomes were best in patients without residual disease (PDS group) and survival following PDS was superior to survival following IDS. The results of our study support the current recommendations to perform primary debulking surgery aiming for the removal of all macroscopically visible disease, in patients eligible for primary surgery.

AUTHOR CONTRIBUTIONS

Conceptualization: KD, HW, JB, AK. Data curation: KD, HW, AK. Formal analysis: KD, HW. Funding acquisition: not applicable. Investigation: KD, HW. Methodology: all authors. Project administration: KD. Resources: HW, MW. Software: not applicable. Supervision: RK, HN, JB, AK. Validation: RK, HN, AK. Visualization: KD, HW. Roles/Writing—original draft: KD, HW, AK. Writing—review & editing: all authors.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Wentzensen N, Poole EM, Trabert B, et al. Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. *J Clin Oncol*. 2016;34:2888-2898.
2. Köbel M, Kalloger SE, Huntsman DG, et al. Differences in tumor type in low-stage versus high-stage ovarian carcinomas. *Int J Gynecol Pathol*. 2010;29:203-211.
3. Trétarre B, Molinié F, Woronoff A, et al. Ovarian cancer in France: trends in incidence, mortality and survival, 1980–2012. *Gynecol Oncol*. 2015;139:324-329.
4. Bennetsen AKK, Baandrup L, Aalborg GL, Kjaer SK. Non-epithelial ovarian cancer in Denmark - incidence and survival over nearly 40 years. *Gynecol Oncol*. 2020;157:693-699.
5. WHO Classification of Tumours Editorial Board. *WHO Classification of Tumours - Female Genital Tumours*. IARC; 2020.
6. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. *Am J Surg Pathol*. 2004;28:496-504.
7. Matsuo K, Machida H, Matsuzaki S, et al. Evolving population-based statistics for rare epithelial ovarian cancers. *Gynecol Oncol*. 2020;157:3-11.
8. Matsuo K, Machida H, Grubbs BH, Sood AK, Gershenson DM. Trends of low-grade serous ovarian carcinoma in the United States. *J Gynecol Oncol*. 2018;29:e15.
9. Berek JS, Kehoe ST, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*. 2018;143(Suppl 2):59-78.
10. Nickles Fader A, Java J, Ueda S, et al. Survival in women with grade 1 serous ovarian carcinoma. *Obstet Gynecol*. 2013;122:225-232.
11. Plaxe SC. Epidemiology of low-grade serous ovarian cancer. *Am J Obstet Gynecol*. 2008;198:459.e1-459.e9.
12. Colombo N, Sessa C, Bois AD, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. 2019;30:672-705.
13. Management of low-grade, serous carcinomas of the ovary. https://www-uptodate-com.proxy-ub.rug.nl/contents/management-of-low-grade-serous-carcinomas-of-the-ovary
14. Lazurko C, Clark M, Pulman K, et al. Hormone maintenance therapy for women with low-grade serous ovarian cancer in the front-line setting: a systematic review. *Gynecol Oncol*. 2021;163:209-214.
15. Slomovitz B, Gourley C, Carey MS, et al. Low-grade serous ovarian cancer: state of the science. *Gynecol Oncol*. 2020;156:715-725.
16. Pauly N, Ehmann S, Ricciardi E, et al. Low-grade serous tumors: are we making progress? *Curr Oncol Rep*. 2020;22:8.
17. Gershenson DM. Low-grade serous carcinoma of the ovary or peritoneum. *Ann Oncol*. 2016;27(Suppl 1):i45-i49.
18. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in The Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. *Cell Oncol*. 2007;29:19-24.
19. Schouten LJ, Höppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, The Netherlands. *Int J Epidemiol*. 1993;22:369-376.
20. World Health Organization. *International Classification of Diseases for Oncology (ICD-O)*. World Health Organization; 2000.
21. Netherlands Comprehensive Cancer Organisation (IKNL). https://iknl.nl/en/ncr
22. Shimizu Y, Kamoi S, Amada S, Akiyama F, Silverberg SG. Toward the development of a universal grading system for ovarian epithelial carcinoma: testing of a proposed system in a series of 461 patients with uniform treatment and follow-up. *Cancer*. 1998;82:893-901.
23. Prat J. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet*. 2014;124:1-5.
24. TNM-classification, Union for International Cancer Control (UICC). https://www.uicc.org/resources/tnm
25. Waterhouse J, Muir CS, Correa P, Powell J. *Cancer incidence in five continents*. Vol 3. IARC; 1976:456.
26. Dickman PW, Coviello E. Estimating and modeling relative survival. *Stata J*. 2015;15:186-215.
27. Ederer F, Axtell LM, Cutler SJ. The relative survival rate: a statistical methodology. *Natl Cancer Inst Monogr*. 1961;6:101-121.
28. Whitney CW, Spirtos N. *Gynecologic Oncology Group Surgical Procedures Manual*. Gynecologic Oncology Group; 2009.
29. Angarita AM, Stone R, Temkin SM, Levinson K, Fader AN, Tanner EJ. The use of "optimal cytoreduction" nomenclature in ovarian cancer literature: can we move toward a more optimal classification system? *Int J Gynecol Cancer*. 2016;26:1421-1427.
30. Zapardiel I, Morrow CP. New terminology for cytoreduction in advanced ovarian cancer. *Lancet Oncol*. 2011;12:214.
31. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: a gynecologic oncology group study. *Cancer*. 2012;118:3087-3094.
32. Köbel M, Kang EY. The evolution of ovarian carcinoma subclassification. *Cancers (Basel)*. 2022;14:416.
33. Kurman RJ. *International Agency for Research on Cancer. WHO Classification of Tumours of Female Reproductive Organs*. IARC; 2014.
34. Matsuo K, Machida H, Grubbs BH, et al. Diagnosis-shift between low-grade serous ovarian cancer and serous borderline ovarian tumor: a population-based study. *Gynecol Oncol*. 2020;157:21-28.
35. United Nations. Department of Economic and Social Affairs, Population Division. World Population Prospects 2019: Highlights. ST/ESA/SER.A/423. 2019.
36. Vatansever D, Taskiran C, Mutlu Meydanli M, et al. Impact of cytoreductive surgery on survival of patients with low-grade serous ovarian carcinoma: a multicentric study of Turkish Society of Gynecologic Oncology (TRSGO-OvCa-001). *J Surg Oncol*. 2021;123:1801-1810.
37. Grabowski JP, Harter P, Heitz F, et al. Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the AGO study group metadatabase. *Gynecol Oncol*. 2016;140:457-462.
38. Scott SA, Llaurado Fernandez M, Kim H, et al. Low-grade serous carcinoma (LGSC): a Canadian multicenter review of practice patterns and patient outcomes. *Gynecol Oncol*. 2020;157:36-45.

39. Bonsang-Kitzis H, Panchbhaya N, Bats A, et al. Surgical implications of advanced low-grade serous ovarian cancer: analysis of the database of the Tumeurs Malignes Rares Gynécologiques network. *Cancers (Basel)*. 2022;14:2345.
40. Bogani G, Leone Roberti Maggiore U, Paolini B, et al. The detrimental effect of adopting interval debulking surgery in advanced stage low-grade serous ovarian cancer. *J Gynecol Oncol*. 2019;30:e4.
41. Knisely AT, St Clair CM, Hou JY, et al. Trends in primary treatment and median survival among women with advanced-stage epithelial ovarian cancer in the US from 2004 to 2016. *JAMA Netw Open*. 2020;3:e2017517.
42. Patel A, Iyer P, Matsuzaki S, Matsuo K, Sood AK, Fleming ND. Emerging trends in neoadjuvant chemotherapy for ovarian cancer. *Cancers (Basel)*. 2021;13:626.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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