Chirurgia (2024) 119: 373-384
No. 4, July - August

http://dx.doi.org/10.21614/chirurgia.3025

Ovarian Carcinoma: A Single-Centre Eight-Year Case-Series Study with Survival Analysis

George Daniel Subtirelu[1]*, Andreea Steriu[2], Eugen Bratucu[1,2]

[1]1st General & Oncologic Surgery Department, Al. Trestioreanu Institute of Oncology, Bucharest, Romania
[2]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania

*Corresponding author:
George Daniel Subtirelu, M.D.
1st General & Oncologic Surgery Department, Al. Trestioreanu Institute of Oncology, Bucharest, Romania
E-mail: gdsubtirelu@yahoo.com

Abbreviations:
OC: ovarian cancers;
OSEC: ovarian surface epithelial cancers;
TFS: tumour free survivor;
SAP: statistical analysis plan;
HGSC: High-Grade Serous Carcinoma;
LGSC: Low-Grade Serous Carcinoma);
CS: Carcinosarcoma);
EC: Endometrioid Carcinoma;
ELGC: Endometrioid Low Grade Carcinoma;
EHGC: Endometrioid High Grade Carcinoma;
MC: Mucinous Carcinoma;
RC: Rare Carcinoma;
BLT: Borderline Tumor;
SBLT: Serous Borderline Tumor;
SMBLT: Seromucinous Borderline Tumor;
MBLT: Mucinous Borderline Tumor;

Received: 19.06.2024
Accepted: 22.08.2024

Rezumat

Carcinoamele ovariene: studiu al unei serii de paciente pe o perioadă de 8 ani cu analiză de supraviețuire

Introducere: Acest studiu descrie o serie de cazuri de carcinom ovarian pe o perioadă de opt ani într-un singur centru de referință în functie de stadializarea chirurgicala (pTNM) şi procedura chirurgicală efectuată, şi explorează caracteristicile cancerelor epiteliului de suprafață ovarian (OSEC) în funcție de tipul histopatologic.
Material şi Metode: obținerea de probabilități globale neajustate a supraviețuirii TFS pentru lotul cu un total de n=263 paciente la 12 luni şi 60 luni. S-au făcut ajustări pentru: stadializare (clasificarea stadiilor pTNM), histotip şi pentru pacientele cu status PSC. Histotipul HGSC a fost cel mai frecvent diagnosticat tip (63%). Pacientele cu status PSC arată un timp mediu de supraviețuire şi probabilități de supraviețuire semnificativ mai mici (la 12 şi la 60 de luni) decât toate celelalte cazuri.
Rezultate: în urma calculelor probabilitățile de supraviețuire la 12 luni pentru fiecare histotip sunt: CCC - 14%; RC - 15%; CS - 29%; HGSC - 46%; LGSC - 74%; CE - 79%; MC - 80% şi BLT - 94%. La 60 de luni rezultatele sunt: RC si MC - 0%; CCC - 14%; HGSC - 16%; CS - 29%; LGSC - 62%; CE - 66%; şi BLT - 94%. Timpul mediu de supraviețuire în funcție de histotipul înregistrat, este după cum urmează: CCC - 13 luni (IC 95% de la 0 la 26); RC - 16 luni (IC 95% de la 7 la 26), CS - 22 luni (IC 95% de la 1 la 42), HGSC - 32 luni (IC 95% de la 26 la 38); MC - 33 luni (IC 95% de la 16 la 50); BLT - 52 luni (IC 95% de la 47 la 56); CE - 71 luni (95% CI 56 până la 86); şi LGSC - 74 luni (IC 95% de la 51 la 97). Durata mediană supraviețuire este de 26 de luni (IC95% 15 până la 37) şi de 20 de luni atunci când BLT este exclus (IC95% CI 15 până la 25).

Concluzii: Aceste rezultate pot ghida cercetări ulterioare pentru patologia OSEC în funcție de histotipuri.

Cuvinte cheie: cancer al epiteliului de suprafață ovarian, histo(patologic) tip, stadializare TNM, proceduri chirurgicale, analiza de supraviețuire

Abstract

Introduction: This research describes an eight-year case-series of ovarian carcinoma by surgical (pTNM) staging and surgical procedure, explores the characteristics of ovarian surface epithelial cell (OSEC) tumours by histopathological type in a single centre of reference.
Material and Methods: survival analysis with overall survivor probabilities for n=263 patients for 12 months and 60-month tumour free survival status (TFS). Results by staging (pTNM stage classification), histotype and for poor surgical candidate (PSC) status are shown. Histotype high grade serous carcinoma (HGSC) was the most frequently diagnosed type (63%).
Results: 12-month survivor probabilities according to histotype, rank as follows: clear cell carcinoma (CCC) - 14%; rare carcinoma (RC) - 15%; carcinosarcoma (CS) - 29%; HGSC - 46%; low grade serous carcinoma (LGSC) - 74%; endometrioid carcinoma (EC) - 79%; mucinous carcinoma (MC) - 80% and borderline tumours (BLT) - 94%. At 60 months results are: RC and MC - 0%; CCC - 14%; HGSC - 16%; CS - 29%; LGSC - 62%; EC - 66%; and BLT - 94%. Overall median survival time is 26 months (CI95% 15 to 37); and 20 months when BLT excluded (CI95% CI 15 to 25).
Conclusions: These results may guide further research for the OSEC pathology and its histotypes.

Key words: ovarian surface epithelium cancer, histo(pathological) type, TNM staging, surgical procedures, survival analysis

Introduction

Primary ovarian cancers (OC) arise from one of the three constituent cell lines of the ovary: germ cells (3% of OC), germ cells and sex cord-stromal (2% of OC) and surface ovarian epithelial cells (ovarian surface epithelial cancers or OSEC, as 90% of OC) (1,2), with the latter type originating from peritoneal serous tissue which also lines the ovary. The surface epithelial tissue is of mesodermal origin (3) and it is separated from the ovarian stroma by the basement membrane under which there is a dense connective layer which is collagen rich - the albuginea. The ovarian surface epithelium evolves to take on much more complex characteristics, allows for complex exchanges with the peritoneal cavity, undergoes changes along with surrounding tissue in the ruptures of the ovarian follicles during the ovulatory cycle as well as in their repair. This last function varies with the reproductive cycle and is hormonal dependant (4).

Ovarian surface epithelial cancers include malignant tumours of a diverse nature (5), given that they have different carcinogenesis processes (6,7), with their primary lesion - the starting point of the pathogenesis - originating in the epithelium of other organs of the female genital tract (8). Whilst some OSEC have a starting point the surface epithelium of the ovary others originated elsewhere including after cells have undergone a number of mutations. These cells then reach the ovary where further growth and multiplication occur (9,10).

Most OSEC tumours have developmental

origins in the paramesonephric Müllerian ducts: fallopian tubes, body of uterus, uterine cervix, vaginal recesses (7). It has been widely accepted that the fallopian tube's epithelium stands at the origin of many OSEC tumours as well as primary peritoneal cancer. The serous intra-epithelial carcinoma originating in the tufted epithelium of the fallopian tube's infundibulum is a known precursor of most high grade serous ovarian and peritoneal carcinoma (HGSC) (8,11).

Ovarian carcinogenesis has undergone substantial knowledge development during the past years. Whilst morphology was central to the pathology's knowledge up until the last decade, this has now been superseded by a new, molecular, disease classification. New pathogenetic models and current histopathological classifications have been described with molecular genetics (6,12). This has allowed histopathological types with their particular molecular characteristics to be associated with specific clinical presentations. Therefore, OSEC tumours were classified in histotypes which allows a better guided therapeutical management (5,13).

Ovarian cancer represents 2,5% of all female cancer cases, with a proportional mortality of 5% and it ranks first among causes of death from a gynecological pathology (14,16). A 2023 report modelled the incidence and mortality of ovarian cancer with: 19 710 newly diagnosed cases and 13 270 medically certified deaths due to this cause of death (MCCD) in the USA (14). This points to a decrease when estimates are compared with 2018 reported figures: 22 240 incident cases and 14 070 deaths from this condition (15). Similarly, the reported 5-year survival rate was 50%. New developments in the oncological field, diagnosis and treatment of ovarian cancer have prompted the current study with the aim to explore the pathology in a single Romanian centre of reference.

Objectives

1) to describe the OSEC sample by surgical (pTNM) staging and surgical procedure; 2) to explore the characteristics of OSEC tumours by histopathological type; 3) to perform a survival analysis: a) unadjusted overall survivor probability and for b) 12-month and 60-month tumor free survival (TFS) adjusted probabilities by: 1) staging (pTNM stage classification), 2) by histopathological histotype and 3) by poor surgical candidate (PSC) status.

Material and Methods

An 8-year (January 2014 - December 2021) registered sample in a single centre of reference - 1st General & Oncologic Surgery Department, Al. Trestioreanu Institute of Oncology Bucharest, with data extracted from the centre's electronic database and from the medical files and the surgical registry for the surgical procedures was used for the survival analysis. Study censoring time was set to 30th April 2024 when also all follow-up ended up. The detailed description of the sample is provided in another manuscript (Subtirelu et al, 2024). Survivor probabilities, 12-month and 60-month tumour free survivor probabilities (TFS), are the primary outcomes of this analysis. The statistical analysis plan (SAP) consists of: TNM staging with proportions for main surgical staging (AJCC/FIGO and pTNM staging); description with frequencies of main surgical procedures, with poor surgical candidate status (PSC) (yes/no); survivor probabilities: overall unadjusted probability and adjusted probabilities by staging and histopathology with estimates and 95% CI for all sample and sub-samples: staging, histotype, PSC status. Statistical methods used were Kaplan-Meier (unadjusted probabilities) and actuarial life tables for 12-month and 60-month (TFS) adjusted probabilities for: surgical (pTNM) staging: I to IV, Histotypes: 1 = HGSC (High-Grade Serous Carcinoma), 2 = LGSC (Low-Grade Serous Carcinoma), 3 = CS (Carcinosarcoma), 4=CCC (Clear Cell Carcinoma), 5=EC (Endometrioid Carcinoma, in which we included Endometrioid Low Grade Carcinoma (ELGC) G1 and G2, Seromucinous Carcinoma G1 and G2 and

Endometrioid High Grade Carcinoma (EHGC), 6 = MC (Mucinous Carcinoma), 7 = RC (Rare Carcinoma in which we included Undifferentiated Carcinoma and Mixed Carcinoma) and 8 = BLT (Borderline Tumor in which we included Serous Borderline Tumor (SBLT), Seromucinous Borderline Tumor (SMBLT), Mucinous Borderline Tumor (MBLT)) (17). Analysis was performed with Excel and IBM SPSS Statistics v23.0. Probabilities, mean (CI 95%) and median survival time were used in reporting. Comparison was done with the logrank test.

Results

A total of 263 patients who had surgical procedures in the 1st Department of General and Oncologic Surgery of the Institute of Oncology „Al. Trestioreanu" Bucharest were registered during an eight-year period (January 2014 to December 2021). Twenty-eight patients had a previous or simultaneous diagnosis of another primary malignancy - prior or at the same time the ovarian carcinoma was diagnosed. Those prior diagnosed had a two to 17 years recorded lead-time. The analysed sample is illustrated in *Fig. 1*. Age range at diagnosis was from 19 to 84 years; with a mean value of 57.8 (sd 12.2 years) and a median of 58 years; PSC patients had a mean age of 67.4 (sd 11.9) years; the mean difference of 10.5 years has a CI95% of 5.5 to 15.5 years.

Bivariate results for surgical procedures and histotype are shown for all cases with six main procedures recorded in the surgical register (*Table I*). As an additional procedure to procedures 2 to 5, some of the cases underwent node sampling and/or lymphadenectomy for ilio-obturatory ± aortic-caval nodes. Lymphadenectomy was recorded in 38 cases: 25 - HGSC, four - LGSC, two - EC and one each for CS and RC hystotypes.

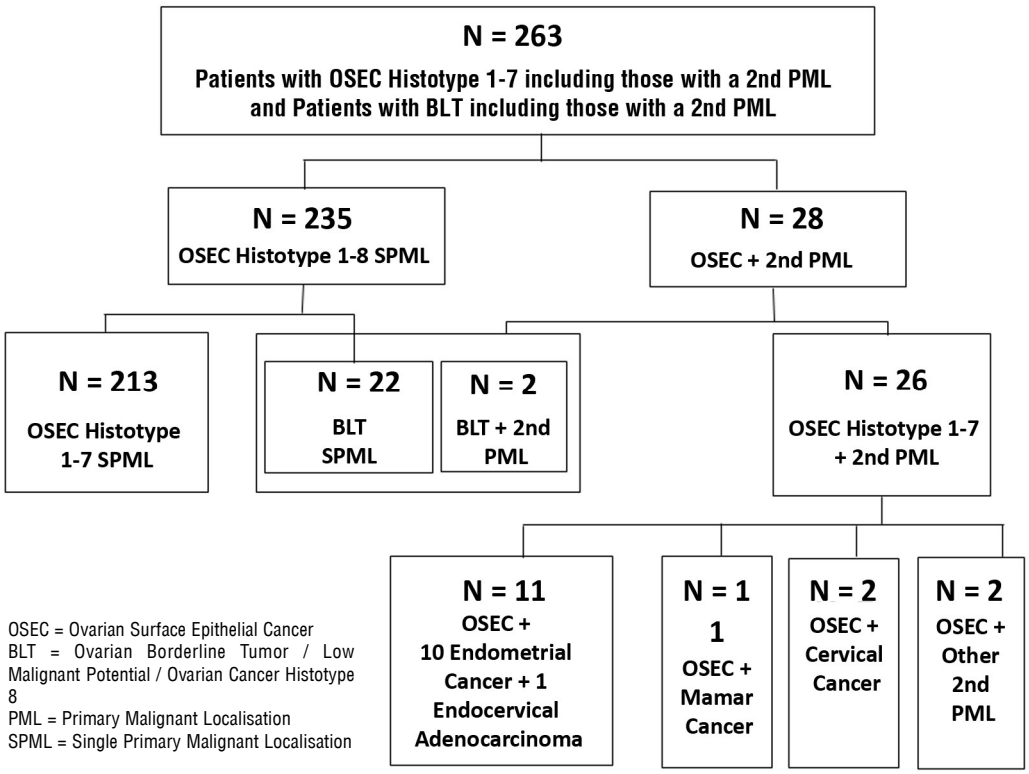

Figure 1. Sample size included in survival analysis (n=263)

Table 1. Bivariate analysis results: main surgical procedure performed at the optimum clinical status and histotype (n=263)

	Surgical procedure (SP)						
	(1)	(2)	(3)	(4)	(5)	(6)	
Histotype	Biopsy (of the tumour or the peritoneum): Laparoscopic Approach / Laparotomy	Bilateral / Unilateral adnexectomy (BA/UA) ± Total hysterectomy (TH) ± Omentectomy ± Peritoneal biopsies	(2) with THBA ± by extraperitoneal/ subperitoneal route + peritonectomies (exclusively diaphragmatic) and electrocauterization of peritoneal carcinomatous lesions	(3) with Visceral (Multiple) Resections ± stoma	(4) with Diaphragmatic Peritonectomies / Stripping / Partial resection of the Diaphragm	Palliative surgery	Total
HGSC	5	84	38	28	8	2	165
LGSC	-	9	6	4	-	-	19
CS	1	2	2	2	-	-	7
CCC	-	2	3	1	1	-	7
EC	-	16	7	3	1	-	27
MC	-	6	-	-	-	-	6
RC	-	4	3	1	-	-	8
BLT	1	21	2	-	-	-	24
Total	7	144	61	39	10	2	263

Surgical Procedures

Tumour dimensions were recorded at two moments: prior to surgery and during surgery. The calculated difference varied little with the mean difference for tumour dimensions at 0.44 cm (CI95% from 0.216 to 0.664 cm).

Surgical Staging

Results show: stage I - 51 cases: with 32 cases in IA, stage II - 32 cases; with 24 cases in stage IIB, stage III - 161 cases; with 115 cases in stage IIIC, stage IV - 19 cases.

Histopathological Types

According to the WHO histotype classification (2020) the structure of the sample is: 62.7% HGSC, 10.3 % EC, 9.1% BLT, 7.2% LGSC and 2.7% for each of the following grades: CS, CCC, RC; and 2.3% MC.

Surgical procedures are described by pTNM stage and HGSC and LGSC histotypes, as in *Figs. 2, 3* and *4*.

The distribution in the case-series of the main surgical procedure performed at the optimum clinical status of the patient is described, by stage, with the following results:

- for stage I n=51: surgical procedure 2 accounts for n=50 (n=19 – BLTs; n=11 - HGSC; n=7 – EC; n=4 – MC; n=6 - LGSC; n=1 – CS; n=1 – CCC; n=1 – RC that also required a surgical procedure for abdominopelvic lymph nodes (LNP)); SP

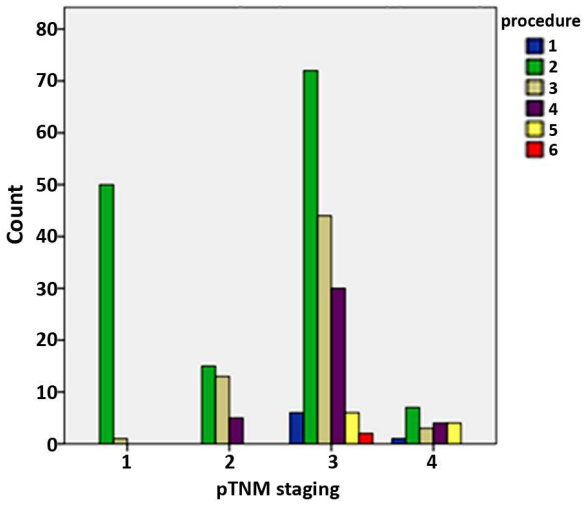

Figure 2. Distribution of surgical procedures by pTNM staging (n=263)

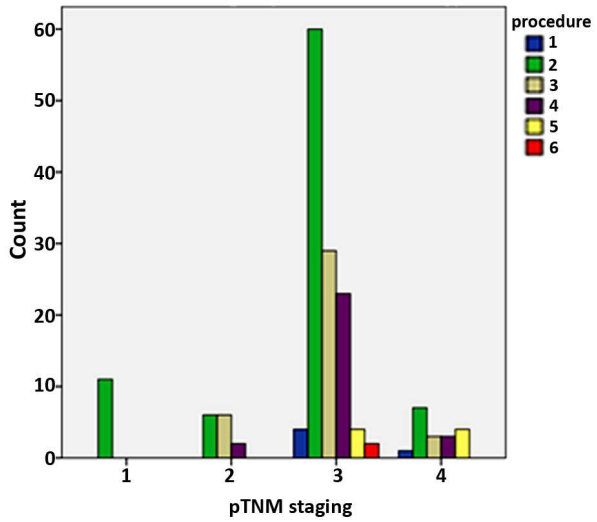

Figure 3. Distribution of surgical procedures for histotype HGSC (n=165)

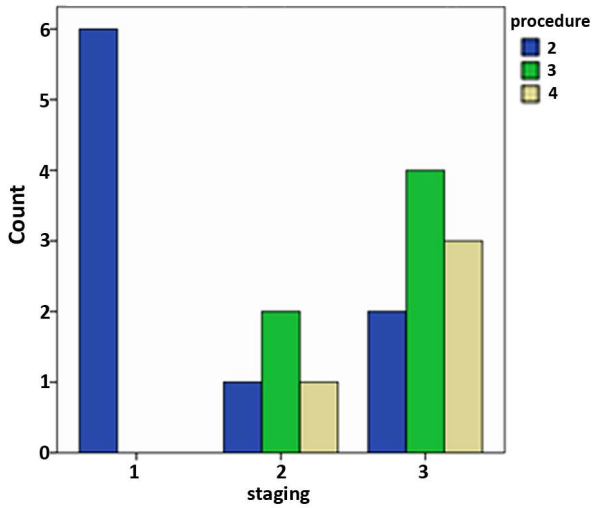

Figure 4. Distribution of surgical procedures for histotype LGSC (n=19)

3 accounts for n=1 – EC downstaging by pathology examination from stage IIB to stage I;

- for stage II n=32: SP 2 accounts for n=14 with n=2 LNPs; SP 3 accounts for n=13 (stage IIB cases) with n=2 LNP; SP 4 accounts for n=5 (stage IIB cases) with n=1 LNP;
- for stage III n=161: SP 1 accounts for n=6 (due to the extension of lesions); SP 2 accounts for n=73 with n=4 LNPs; SP 3 accounts for n=44 with n=14 LNPs; SP 4 accounts for n=30 with n=3 LNPs; SP 5 accounts for n=6 with n=2 LNPs; SP 6 accounts for n=2;
- for stage IV n=19 (n=7 stage IVA; n=12 stage IVB): SP 1 accounts for n=1; SP 2 accounts for n=7; SP 3 accounts for n=3; SP 4 accounts for n=4 with n=2 LNPs; SP 5 accounts for n=4 with n=2 LNPs.

Findings by histotype recorded HGSC n = 165 with surgical procedures reported by stage:

- stage I n=11, of which n=10 stage IA and n=1 stage IB, as a clinical observation n=9 cases alive at 36 to 111 months at the end of study;
- stage II n=14 (n=3 stage IIA and n=11 stage IIB) with n=6 SP 2, n=6 SP 3 and n=2 SP 4;
- stage III n=122 with n=4 SP 1, n=60 SP 2 with n=4 LNPs, n=29 SP 3 with n=10 LNPs, n=23 SP 4 with n=3 LNPs, n=4 SP 5 with n=1 LNP, n=2 SP 6;
- stage IV n=18 with n=1 SP 1, n=7 SP 2, n=3 SP 3, n=3 SP 4 with n=2 LNPs – as a clinical observation n=2 cases alive at 71 respectively 67 months at the end of study, n=4 SP 5 with n=2 LNPs – as a clinical observation n=1 case alive at 28 months at the end of study.

Results by histotype for LGSC recorded n=19 surgical procedures, reported by stage:

- stage I n=6 with n=6 SP 2 with n=2 LNPs;
- stage II n=4 with n=1 SP 2, n=2 SP 3 and n=1 SP 4;
- stage III n=9 with n=2 SP 2, n=4 SP 3 with n=2 LNPs, and n=3 SP 4.

Survival Analysis

Survivor probability values, at 12- and 60-month (TFS), including by staging, major histopathology and PSC status together with mean survival time values (CI95%) are given in *Table 2* and *Figs. 5-8*. A total of 156 deaths were registered during the study period and 107 patients have survived the period.

Table 2. Survival analysis output by all sample (n=263) and by histotypes 1 to 7 single localisation sub-sample (n=213)

	N=263					N=213				
	12- mo probability estimate (%)	60-mo TFS probability estimate (%)	Mean value for survival time (months)	CI95% for mean value for survival time (months)	Median (months)	12- mo probability estimate (%)	60-mo probability estimate (%)	Mean value for survival time (months)	CI95% for mean value for survival time (months)	Median (months)
pTNM staging										
Stage I (n=51)	87	80	87	74 to 101	95	84	73	81	62 to 100	94
Stage II (n=35)	49	30	49	37 to 61	51	78	42	54	40 to 68	56
Stage III (n=160)	32	18	32	26 to 38	19	41	18	32	25 to 38	18
Stage IV (n=17)	22	18	22	11 to 33	15	22	11	19	8 to 29	14
Histotype										
High-Grade Serous Carcinoma (HGSC) (n=165)	46	16	32	26 to 38	19	44	16	31	25 to 37	18
Low-Grade Serous Carcinoma (LGSC) (n=19)	74	62	74	51 to 97		78	66	78	54 to 101	
Carcinosarcoma (CS) (n=7)	29	29	22	1 to 42	5	33	33	23	0 to 47	2
Clear cell carcinoma (CCC) (n=7)	14	14	13	0 to 26	5	17	-	13	0 to 28	2
Endometrioid carcinoma (EC) (27) (n=27)	79	66	71	56 to 86		74	67	69	52 to 87	
Mucinous carcinoma (MC) (n=6)	80	-	33	16 to 50	40	100	-	33	16 to 50	40
Rare carcinoma (RC) (n=8)	15	-	16	7 to 26	15	0	-	12	6 to 19	15
Borderline tumour (BLT) (n=24)	94	94	52	47 to 56		na	na	na	na	
HGSC vs all other										
HGSC (n=165)	46	16	32	26 to 38		44	16	31	25 to 37	
All other (n=98)	63	50	62	51 to 74		56	47	58	44 to 71	
PSC status										
Absent (239)	53	27	42	36 to 48		49	25	39	33 to 46	
Present (n=24)	37	11	24	15 to 33		31	11	21	12 to 31	
Overall			41	35 to 47	26			38	32 to 44	20

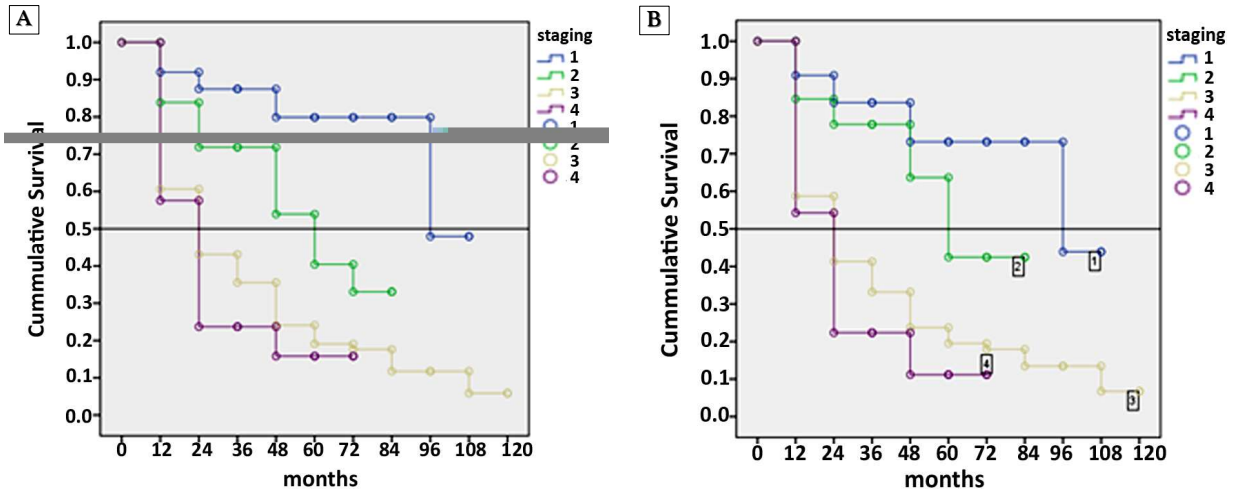

Figure 5. **(A)** Survivor probabilities for ovarian surface epithelial malignant tumours by surgical staging (n=263); **(B)** Survivor probabilities for OSEC by surgical staging, single localisation excluding BLT and second primary localisation (n=213)

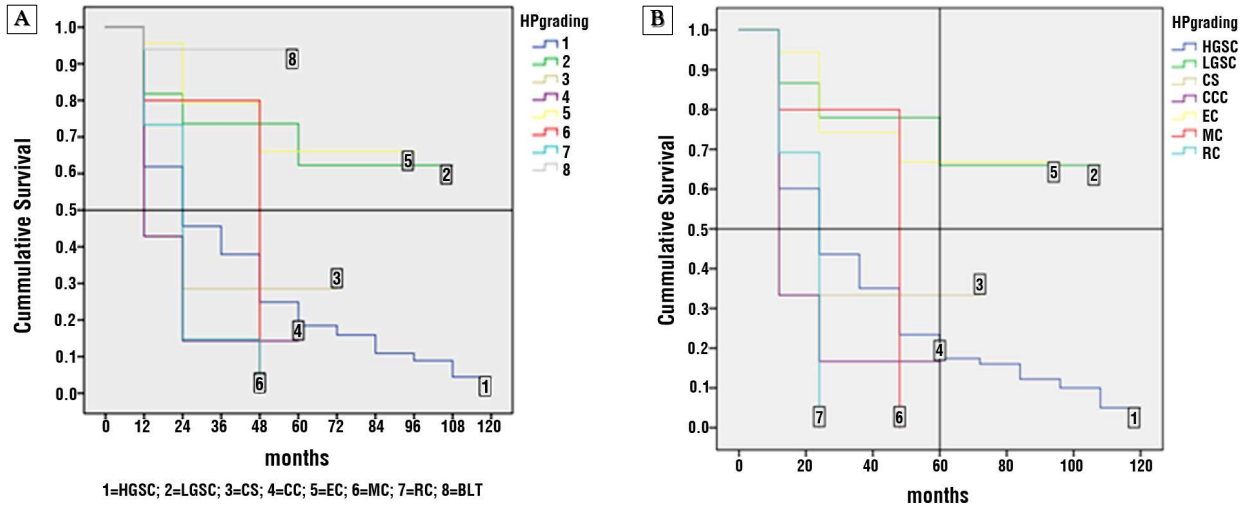

Figure 6. **(A)** Survivor probabilities for OSEC by histotype (n=263); (B) Survivor probabilities for OSEC by histotype, single localisation excluding BLT and second primary localisation (n=213).

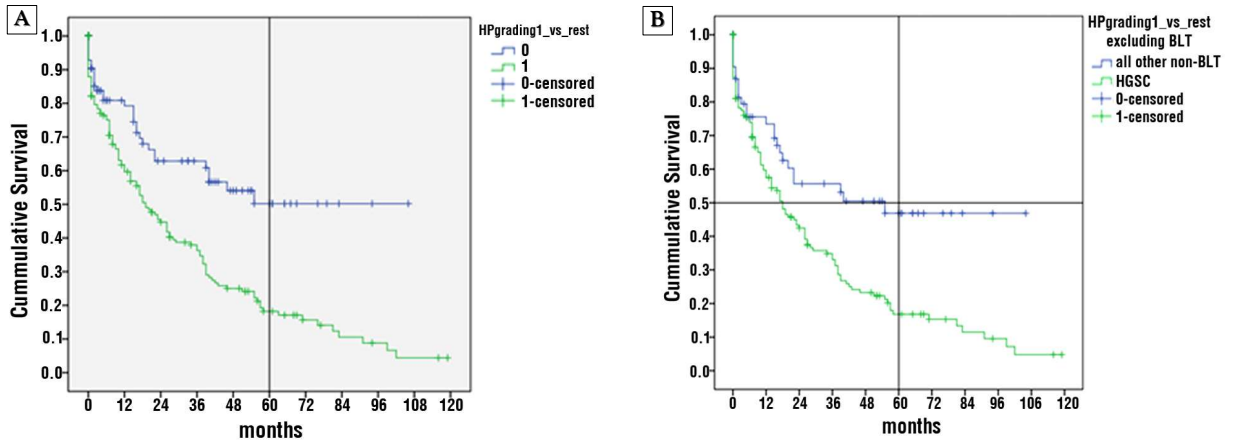

Figure 7. **(A)** Survivor probabilities for OSEC according to dichotomised histotype: HGSC vs all other types including BLT (n=263); **(B)** Survivor probabilities for OSEC according to dichotomised histotype: HGSC vs all other types excluding BLT and 2nd primary localisation (n=213).

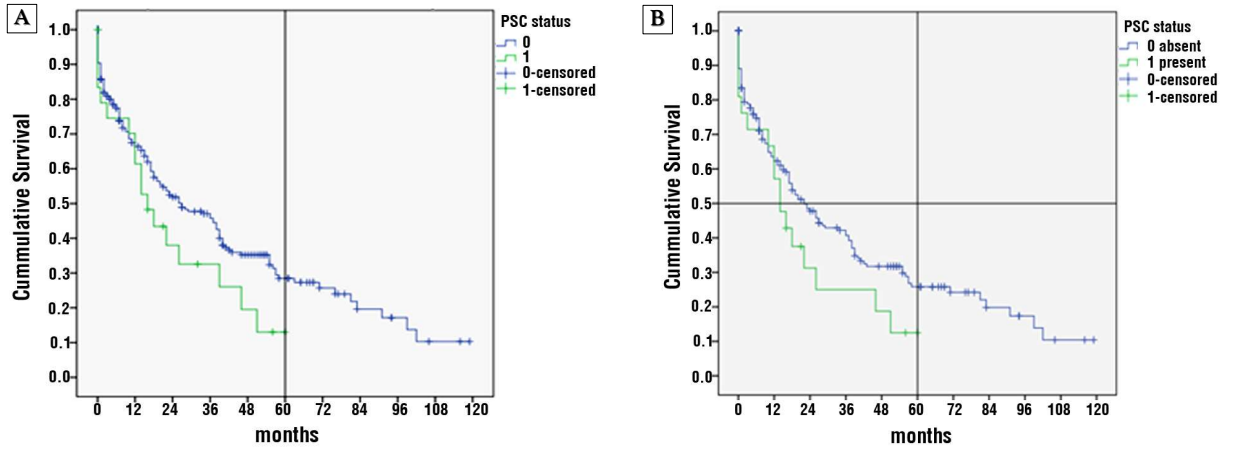

Figure 8. **(A)** Survivor probabilities for OSEC by PSC status (n=263); **(B)** Survivor probabilities for OSEC by PSC status excluding BLT and 2nd primary localisation (n=213).

Probabilities for a 60-month TFS by pTNM staging are: I - 80%, II - 30%, III - 18% and IV - 18%. By histotypes values are: 94% (BLT), 66% (EC), 62% (LGSC), 29% (CS) and 16% (HGSC); with three histotypes - CCC, RC and MC - for which values are 14% (n=7 cases) 0% (n=6 and n=8 cases respectively). Cases with PSC status (n=24) had a 12-month probability of 37% compared with 53% for non-PSC status (n=239); similarly, a 60-month TFS probability was 11% in PSC (n=24), compared with 27% in non-PSC (n=239).

The unadjusted overall mean survival time was 41 months (CI95% from 35 to 47 months) with a statistically significant difference of 18 months between PSC (24 months; CI95% from 15 to 33 months) and non-PSC cases (42 months; CI 95% from 36 to 48 months).

The overall median survival time (n=263) was 26 months (CI 95% from 15 to 37 months). Median time for stages varied from 15 months (stage IV) to 95 months (stage I). By histotype this was calculated with values from 5 to 40 months.

Stages I and II show better survivor probabilities at 12 months when compared to staging III and IV; however, the stage II shows a significant drop for the 60-month probability (*Fig. 5 A,B* and *Table 2*). The exclusion of BLT and OSEC with a second primary malignancy has the biggest impact on stage II survivor probabilities (*Fig. 5B* and *Table 2*).

BLT followed by EC may indicate higher survivor probabilities than those for all other types, especially when compared with HGSC (*Fig. 6A*; and *Table 2*).

PSC cases, although small in number (n=24) have significantly lower survivor probabilities than non-PSC cases, difference which becomes more visible beyond 12 months: 37% vs 53% at 12 months and 11% vs 27% at 60 months (*Fig. 8 A,B*; *Table 2*).

Discussion

Ovarian carcinomas are rare diseases including by histotype. However, by moving from morphopathology exams to molecular genetics in the past years has proven to be an important step in guiding therapeutic management of this serious and fatal disease which has had known only some survival improvement in the past 30 years (18-21).

In this study analysis for surgery shows the most used procedure n=124 for SP 2. Of these n=51 SPs performed in stage I cases and of these n=19 for BLTs as it's common this histotype presents mostly with early stage (22,23). Also n=11 performed for stage I HGSCs of which n=9 cases alive at 36 to 111 months at the end of study; two of these eleven cases connected with BLTs, possibly showing / as a result of another carcinogenetic pathway with a different prognosis (6).

For stages IIB to IV results show a continuous effort for maximal cytoreduction as ESGO and NCCN recommandations request (24-26), with SPs 3, 4 and 5 which account for 42% in the 263 case-series being in line with published data (27).

HGSC and LGSC were viewed as different grades of the same histopathological type of ovarian carcinoma until studies of the groups of Kurman, Crum, Köbel and many others. According to published data HGSC and LGSC are cancers of the "müllerian epithelium" with different carcinogenetic pathways (5-8,13), with LGSC showing lesser response to platinum-taxane chemotherapy but responding to endocrine therapy (28-30). Analysis of surgical procedures by these histotypes showed for HGSC cases stage III and IV n=66 SPs 3, 4 and 5, and for LGSC cases stage III (no stage IV in the case-series) n=7 SPs 3 and 4, aiming to achieve maximal cytoreduction for both histotypes. As LGSC histotype appears to have lesser response to adjuvant therapy it come extremely important comprehensive staging and complete surgical resection of all gross disease (24-26,29,30).

A Cochrane meta-analysis showed a decrease in HGSC cancer mortality among women with risk reducing salpingo-oophorectomy (RRSO versus no RRSO) who were BRCA1 mutation carriers (HR 0.10, 95% CI 0.02 to 0.41; IP = 54%; P = 0.001; 2 studies; very low-certainty evidence), but uncertain for BRCA2 mutation carriers due to low frequency

of HGSC cancer deaths in BRCA2 mutation carriers. RRSO is still an area of debate and it is unclear whether RRSO differs in effectiveness by type of mutation carried (31).

In this research a survival analysis was carried out for a large 8-year case series of ovarian carcinoma. A total of 263 cases were included followed by a sub-sample analysis where BLTs (n=24) and multiple localisation of primary malignant tumours (n=26) were removed resulting in a sub-sample of n=213. By staging, results show that stage III was the most frequently recorded stage, followed by I, II and IV. Four out of five cases, 80% of all cases, account for the following histopathological types: HGSC (63%), EC (10%) and LGSC (7%); BLT account for 9%.

Survivor probabilities and mean survival times (CI95%) show highest value for Stage I as expected and comparable to the literature (19). With BLT grading included (n=263) the 60-month survival probability is 80% and when excluding BLT cases (n=213) this probability is 73%. Additionally, this contrasts, for example, with the probability of its counterpart, the HGSC histotype has a 16% probability at 60-months and results from this study are close to other reported results in the literature (15,19). PSC cases, although small in number (n=24) show similar low probability at 60-month: 11%. It was noted that PSC cases were, also, on average, of an older age than the rest of cases, with a difference of 10.5 years (CI95% of 5.5 to 15.5 years).

According to cancer registers and one particular detailed report we found that the overall survivor probabilities range in the region of 90%, 20% and 6% for stages I, III and IV (18,19), results which are on a par with our findings at 88%, 18% and 11%.

The overall mean survival time was 41 months (CI95% 35 to 47 months) and the median time 26 months (CI 95% 15 to 37 months) for this centre, compared with a value of 20 months (CI95% 15 to 25 months) for histotypes 1 to 7only (n=213). As expected, the longest mean survival time is for Stage I and stands at 87 months (CI95% from 74 to 101), however, almost all BLT cases belong to stage I, where BLT cases make 19 out of 51 cases. When BLTs and OSEC with a second primary malignancy are removed from analysis (n=213) the mean survival time for stage I decreases to 81 months (CI95% from 62 to 100 months) and the mean survival time goes up by 5 months for stage II (*Fig. A,B*; *Table 2*). The 6 month difference, and according with the calculated limits of their two CI95%, is statistically not significant. However, clinical significance must play a role in a conclusion formulation in these situations, such as: based on the current analysis, when a stage I ovarian carcinoma was surgically removed this showed a 6-month lead survivor time based on the all sample analysis (n=263). Therefore, the odd one out is stage II where a higher survivor probability is calculated after BLTs and cases with a second primary malignancy were excluded from analysis. However, both stages, I and II, share not only almost all BLTs (n=19) but also half of cases with a second primary malignancy, or 14 cases out of n=28 (*Fig. 1*). Moreover, a second primary cancer localisation was either previously or simultaneously diagnosed yet treated promptly along with the first. However, when previously diagnosed, a lead time which varied between two and 17 years (seven cases) meant a possible 'therapeutic advantage' for these cases; this is only assumed. Similarly, the 6-month difference for a mean survival time may bear clinical significance in the absence of a statistical one.

Stages III and IV give similar mean survival times and, for example, an overall difference of one or 3 months in these estimates is also statistically not significant when calculated for the complete sample (n=263) along with the calculated estimate in the selected sub-sample (n=213).

Overall, clinical significance is the most important feature, regardless of tumour staging. With histopathological results by type, HGSC was present in 63% of cases and has also the worst 60-month outcome (survivor probability of 16%). Other histopathological types showed even worse outcomes, for example the RC tumour type has a mean survival time of 12 months (CI95% from

6 to 19 months) with a 15% survivor probability, very similar to CCC tumour type which has 14% survivor probability at 12 months. The difference beween the two types being that in the RC type no survivor was observed at the 60-month mark, whilst the CCC type kept the same value. No conclusion can be drawn due to the very small number of cases for these two histotypes and these results must be treated and interpreted with extreme caution due to small numbers (*Table 2*). This is why the median survival times are accounted for and reported from this research. One option in improving on this type of information is by accruing on such number of cases, mainly if refference tertiary centres would join forces through common and collaborative research endeavours (20,32,33).

This survival analysis was performed to allow for further and more detailed analyses which aim to include: residual tumour levels, post-surgical complications, as well as other demographical (age at diagnostic) and with other clinical variables which must be further considered in such adjusted analyses.

Limits of this study show that interrupted descriptive time-series study designs could not allow for, or, cannot establish during a post-registration follow-up, whether: 1) any of the 24 BLT cases have "converted" into either a different cellular tumour type or have led to a TFS (tumour free survival) stage and/or, whether 2) tumour surgical removal ± chemo-therapy were actually therapeutically highly effective, thus resulting in the 94% probability of survival at 60-month. When aiming towards comparing complex treatments' effectiveness it is the study design which plays a highly important role (32). This is where complex reviews, including those with predictive pre-diagnosis modeling assist in therapeutic management (19,33,34). For example, prospective follow-up observational studies may overcome limitations associated with uncertainty of cellular origin (33). Given that BLT have uncertain outcomes and given their proportion of 9% in this sample (almost one in 10 patients), a further analysis will allow for a closer look at this sub-sample, occasionally proving to be an important histotype in the development of a more aggressive OSEC type (35,36,37).

Conclusion

Ovarian cancer is rare and this 8-year case-series has shown that histotype HGSC was the most frequent type of tumour diagnosed (63%) of cases. Poor surgical candidates (PSC) show a significantly lower mean survival time and survivor probabilities (12 and 60-month) than all other cases; the mean age of these cases is significantly older when compared with non-PSC cases. Upon analysis, we found that 12-month survivor probabilities according to histotype are: CCC - 14%; RC - 15%; CS - 29%; HGSC - 46%; LGSC - 74%; EC - 79%; MC - 80% and BLT - 94%. At 60 months results are: RC and MC - 0%; CCC - 14%; HGSC - 16%; CS - 29%; LGSC - 62%; EC - 66%; and BLT - 94%. Mean survival time by registered histotype, according to our findings, is: CCC - 13 months (CI 95% from 0 to 26); RC - 16 months (CI 95% from 7 to 26), CS - 22 months (CI 95% from 1 to 42), HGSC - 32 months (CI 95% from 26 to 38); MC - 33 months (CI 95% from 16 to 50); BLT - 52 months (CI 95% from 47 to 56); EC - 71 months (95% CI 56 to 86); and LGSC - 74 months (CI 95% from 51 to 97). Given the small numbers in sub-samples most results don't have a statistically significant difference; yet clinical significance remains important. Results from this study are close to the findings from other reported results in the literature of the past 30 years and, considering the developments in diagnostic tests, they may guide new research in this ovarian malignant pathology.

Conflicts of Interests

The authors declared no potential conflict of interests.

Ethical Statement

This observational descriptive case-series

study was conducted in accordance with the principles of the Declaration of Helsinki with anonymus data collection, with the permission of Institute of Oncology Alexandru Trestioreanu Bucharest Ethics Committee.

References

1 Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7-33.
2 Jelovac D, Armstrong DK. Recent Progress in the Diagnosis and Treatment of Ovarian Cancer. CA Cancer J Clin. 2011;61:183-203.
3 Sadler TW. Langman's Medical Embriology. 10th ed 2006; ed. in Romanian Bucharest: Callisto; 2008:153.
4 Auersperg N, Wong AST, Choi KC, Kang SK, Leung PCK. Ovarian Surface Epithelium: Biology, Endocrinology, and Pathology Endocrine Reviews 2001;22(2):255-288.
5 Kurman RJ, Ie-Mingh Shih. Pathogenesis of ovarian cancer: Lessons from Morphology and Molecular Biology and their Clinical Implications. Int J Gynecol Pathol 2008;27(2):151-160.
6 Kurman RJ, Ie-Mingh Shih. The dualistic model of ovarian carcinogenesis. Revisited, Revised and Expanded. Am J Pathol. 2016;186(4):733-47.
7 Ie-Mingh Shih, Yeh Wang, Tian-Li Wang. The Origin of Ovarian Cancer Species and Precancerous Landscape. Am J Pathol. 2021;191(1):26-39.
8 Crum CP, Drapkin R, Miron A, Ince TA, Muto M, Kindelberger DW, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol. 2007;19(1):3-9.
9 Beaudet L, Scriver CR, Sly WS, Valle D. A Human Genetics Primer. In: Vogelstein B, Kinzler KW, editors. The Genetic Basis of Human Cancer. New York: McGraw-Hill; 1998. p. 3-31.
10 Fathalla MF. Incessant ovulation and ovarian cancer – a hypothesis re-visited. FVV IN OBGYN. 2013;5(4):292-297.
11 Kuhn E, Kurman RJ, Ie-Mingh Shih. Ovarian Cancer Is an Imported Disease? Curr Obstet Gynecol Rep. 2012;1(1):1-9.
12 The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609-615.
13 Köbel M, Kang EY. The Evolution of Ovarian Carcinoma Subclassification. Cancers 2022;14:416.
14 American Cancer Society, Cancer Facts & Figures 2023.
15 American Cancer Society, Cancer Facts & Figures. Special Edition: Ovarian Cancer, 2018. 2018.
16 Burstein HJ, Krilov L, Aragon-Ching JB, Baxter NN, Chiorean EG, Chow WA, et al. Clinical Cancer Advances 2017: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. J Clin Oncol. 2017; 35(12):1341-1367.
17 Parkash V, Aisagbonhi O, Riddle N, Sidon A, Panse G, Fadare O. Recent Advances in the Classification of Gynecological Tract Tumors. Arch Pathol Lab Med 2023;147:1204-1216.
18 Bell R, Petticrew M, Luengo S, Sheldon TA. Screening for ovarian cancer: a systematic review. Health Technol Assess. 1998;2(2):i-iv, 1-84.
19 Hippisley-Cox J, Coupland C. Identifying women with suspected ovarian cancer in primary care: derivation and validation of algorithm. BMJ. 2011; 344:d8009 .
20 Vaughan S, Coward JI, Bast RC Jr., Berchuck A, Berek JS, Brenton JD, et al. Rethinking Ovarian Cancer: Recommendations for Improving Outcomes. Nat Rev Cancer. 2012;11(10):719-725.
21 Kohn EC, Romano S, Lee JM. Clinical implications of using molecular diagnostics for ovarian cancers. Ann Oncol. 2013;24 Suppl 10(Suppl 10): x22-26.
22 Hauptmann S, Friedrich K, Redline R, Avril S. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. Virchows Arch. 2017;470:125-142.
23 Kipp B, Vidal A, Lenick D, Chritmann-Schmid C. Management of borderline ovarian tumors (BOT): results of a retrospective single center study in Switzerland. J Ovarian Res. 2023;16(1):20.
24 Ovarian Cancer Surgery Guidelines, Advanced Stage v1 (provisional document). Published online October 2016 by European Society of Gynaecological Oncology.
25 Querleu D, Planchamp F, Chiva L, Fotopoulou C, Barton D, Cibula D, et al. European Society of Gynaecological Oncology (ESGO) Guidelines for Ovarian Cancer Surgery. Int J Gynecol Cancer. 2017;27(7):1534-1542.
26 Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakht K, Berchuck A, et al. Ovarian Cancer Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19(2):191-226.
27 Norppa N, Staff S, Helminen M, Auranen A, Saarelainen S. Improved survival after implementation of ultra-radical surgery in advanced epithelial ovarian cancer: Results from a tertiary referral center. Gynecol Oncol. 2022; 165(3):478-485.
28 Vang R, Ie-Mingh Shih, Kurman RJ. Ovarian low-grade and high-grade serous carcinoma: pathogenesis, clinicopathologic and molecular biologic features, and diagnostic problems. Adv Anat Pathol. 2009;16(5):267-282.
29 Grisham RN, Slomovitz BM, Andrews N, Banerjee S, Brown J, Carey MS, et al. Low-grade serous ovarian cancer: expert consensus report on the state of the science. Int J Gynecol Cancer. 2023;0:1-14.
30 Manning-Geist BL, Kahn RM, Nemirovsky D, Girshman J, Laibangyang A, Gordhandas S, et al. Chemotherapy response in low-grade serous ovarian carcinoma at a comprehensive cancer center: readdressing the roles of platinum and cytotoxic therapies. Cancer. 2023; 129:2004-2012.
31 Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO. Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. Cochrane Database Syst Rev. 2018;8(8):CD012464.
32 Leary AF, Quinn M, Fujiwara K, Coleman RL, Kohn E, Sugiyama T, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup (GCIG): clinical trial design for rare ovarian tumours. Annals of Oncology 28:718-726, 2017.
33 van Calster B, Valentin L, Froyman W et al. Validation of models to diagnose ovarian cancer in patients managed surgically or conservatively: multi-centre cohort study. BMJ 2020;370:m2614;
34 Breen J, Ravikumar N, Orsi NM, Allen K, Adusumilli P, Zucker K, et al. Diagnostic artificial intelligence in histopathology of ovarian cancer: a systematic review. PROSPERO 2022 CRD42022334730 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD4202233 4730
35 Morice P, Uzan C, Fauvet R, Gouy S, Duvillard P, Darai E. Bordeline ovarian tumour: pathological diagnostic dilemma and risk factors for invasive or lethal recurrence. Lancet Oncol. 2012;13(3):e103-115.
36 Hannibal CG, Vang R, Junge J, Frederiksen K, Kurman RJ, Kiar SK. A nationwide study of ovarian serous borderline tumors in Denmark 1978-2002. Risk of recurrence, and development of ovarian serous carcinoma. Ginecol Oncol. 2017;144(1):174-180.
37 Peres LC, Cushing-Haugen KL, Köbel M, Harris HR, Berchuck A, Rossing MA, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. JNCI J Natl Cancer Inst. 2019;111(1):60-68.