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Ovarian Carcinoma - A Single Centre Case-Series Descriptive Analysis of Surgical Procedures

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Rezumat

Cancerul ovarian: analiza descriptivă a procedurilor chirurgicale într-o serie de cazuri dintr-un singur centru

Context: Cancerul epitelial de suprafață ovarian (OSEC) este o entitate în care, conform datelor de genomică şi de patologie acumulate în ultimele două decenii, sunt agregate mai multe entități nosologice diferite cu etiologii distincte. În cancerul ovarian, chirurgia este pivotul tratamentului, la care se adaugă prin recomandare tratamentul oncologic medical în majoritatea cazurilor.
Material şi Metodă: Acesta este un lot de 263 cazuri cu OSEC dintr-un singur centru de referință operate din ianuarie 2014 până în decembrie 2021 cu o perioadă de urmărire de 28 luni, până la 30 aprilie 2024. Procedurile chirurgicale în OSEC stadiile IIB, III şi IV, pentru a obține R0/citoreducție optimală sunt intervenții complexe, astfel că le-am rezumat şi codificat după cum urmează: 1 = biopsie (a tumorii/peritoneului); 2 = anexectomie bilaterală /unilaterală (AB/AU) ± histerectomie totală (TH) ± omentectomie ± biopsii peritoneale; 3 = (2) cu histerectomie totală cu anexectomie bilaterală (HTAB) ± pe cale extraperitoneală/subperitoneală + peritonectomii (exclusiv diafragmatice) şi electrocauterizarea leziunilor carcinomatoase peritoneale; 4 = (3) cu rezecții viscerale (multiple) ± stomă; 5 = (4) cu peritonectomii diafragmatice/ stripping/rezecție parțială a diafragmului; 6 = chirurgie paliativă.
Rezultate: Operația de debulking (DS) efectuată pentru n=182 paciente obținându-se R0 n=41. Rezultatele pentru pacientele cu țesut tumoral rezidual după DS au înregistrat: <1 cm (49% cazuri), 1,1 până la 2 cm (29%) şi >2 cm (22%). Rezultatele înregistrate pentru carcinomul ovarian endometrial (EC) n=27, în care atât

chirurgia cât şi chimioterapia bazată pe sărurile de platină sunt eficiente, au arătat o probabilitate de supraviețuire fără tumoră la 60 luni de 66%. Pentru carcinomul ovarian cu celulă clară (CCC) n=7 rezultatele înregistrate au arătat o probabilitate de supraviețuire fără tumoră la 60 luni de 14%, cunoscută fiind controversa cu privire la eficiența paclitaxelului in tratamentul CCC. Au fost inregistrate complicații majore la 25 de paciente cu o proporție a fatalității de 5/25.
Concluzii: OSEC este o boală relativ rară şi având în vedere importanța colectării unui număr important de cazuri în funcție de histotip pentru a progresa în cunoaşterea cancerului ovarian este crucial să se stabilească o colaborare a centrelor terțiare cu strategii standardizate şi de control al calității.

Cuvinte cheie: cancer al epiteliului de suprafață ovarian, histo(patological) tip, stadializare TNM, proceduri chirurgicale, debulking surgery / citoreducție, tumoră reziduală

Abstract

Background: Ovarian surface epithelial cancer (OSEC) are an entity in which, according to genomics and pathology data accumulated in the last couple of decades, several different nosological entities with distinct etiologies are aggregated. In ovarian cancer, surgery is the pivot of treatment, to which medical oncological treatment is added by recommendation in most cases.
Materials and Methods: This is a single centre sample of 263 cases with OSEC operated from January 2014 until December 2021 with a 28-month period of follow-up, until 30th April 2024. OSEC surgical procedures in stages IIB to III and IV of the disease are complex interventions in order to have the R0/optimal cytoreduction achieved, so we summarised and coded them as follows: 1 = biopsy (of the tumour/peritoneum); 2 = bilateral/unilateral adnexectomy (BA/UA) ± total hysterectomy (TH) ± omentectomy ± peritoneal biopsies; 3 = (2) with total hysterectomy with bilateral adnexectomy (THBA) ± by extraperitoneal/subperitoneal route+peritonectomies (exclusively diaphragmatic) and electrocauterization of peritoneal carcinomatous lesions; 4 = (3) with visceral (multiple) resections ± stoma; 5 = (4) with diaphragmatic peritonectomies/stripping/partial resection of the diaphragm; 6 = palliative surgery.
Results: Debulking surgery (DS) was carried out for n = 182 patients with no residual tissue = R0 being registered in n = 41. Results for patients with residual tissue (n = 141) after DS recorded the following findings: <1 cm (49% cases), 1.1-2 cm (29%) and >2 cm (22%). Recorded results for endometrial ovarian carcinoma (EC) n = 27 shown a tumour free survival probability estimate (%) at 60 months of 66% as both surgery and platinum based chemotherapy are efficient. For clear cell ovarian carcinoma (CCC) n = 7 recorded results shown a tumour free estimate (%) at 60 months of 14%, being known the controversy as to whether or not paclitaxel is an active drug for CCC. Major complications were recorded in 25 patients with a fatality ratio of 5/25.
Conclusion: Considering OSEC is a relatively rare disease and the importance of collecting substantial numbers of samples by histotypes to further knowledge about ovarian cancer it comes crucial to establish collaborative endeavour of tertiary centers with standardised and quality control strategies.

Key words: ovarian surface epithelium cancer, histo(pathological) type, TNM staging, surgical procedures, debulking surgery / cytoreduction, residual tumour

Introduction

Ovarian cancers are an entity in which are grouped ovarian surface epithelial cancers (OSEC) (over 90% of ovarian cancers) and cancers of the ovary's inherrent tissues - of the sex cord-stroma and germ cells (~5% of ovarian cancers).

In OSEC, according to genomics and pathology data accumulated in the last decades, several different nosological entities with distinct etiologies (1-8) are aggregated, that originate in the epithelia of the various internal genital organs which have a common embryological origin and for which the term "extrauterine Müllerian epithelium" has been proposed (9,10), lesions for which the main common characteristic is dissemination to the ovaries and also frequently to the neighboring genital and pelvic organs (4-6).

The World Health Organization Classification of Tumours: Female Genital Tract Tumours 5th edition (2020) reflects the increased knowledge about the biology of ovarian carcinomas. It recommends immunohistochemistry for the classification of OSEC into histotypes / subtypes of ovarian carcinoma: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), mucinous carcinoma (MC); accumulated data show prognostic differences between histotypes (11,12). It also recommends new criteria for when the primary site is assigned to extrauterine high-grade serous carcinoma / the elder ovarian carcinoma and also, gives criteria for assigning and managing concurrent ovarian and uterine endometrioid carcinomas as synchronous primaries versus metastatic tumours (12).

Among OSEC, high-grade serous carcinomas (HGSC) represent 70%, endometrioid carcinomas (EC) 10%, clear cell carcinomas (CCC) 10% (in populations of Caucasian origin), low-grade serous carcinomas (LGSC) 5%, mucinous carcinomas (MC) 3%, (13,14).

Although OSEC represents 2.5% of cancer cases in women, they cause 5% of deaths (15), with a mortality/incidence ratio >0.6 (16), being the first cause of death among gynaecological cancers (17).

In ovarian cancer, surgery is the pivot of treatment, to which medical oncological treatment is added by recommendation in most cases. Surgeons proceed with a detailed description in the operative report: the extension of the disease in the pelvis, middle abdomen and upper abdomen; sampling of ascites/peritoneal lavage fluid; tissue samples taken for biopsies of any peritoneal lesions suspected of malignancy or, in the absence of lesions, random biopsies are performed from recommended sites; then they write about the exeresis performed and if a complete resection was obtained; in the case of an incomplete resection, the number and size of the lesions (the largest) are described; and last but not least the attitude towards the pelvic and paraaortic lymph nodes is also presented (18-20). In the case of patients with low performance status, comorbidities or with a reduced probability of obtaining an optimal cytoreduction, biopsy followed by neoadjuvant chemotherapy (NACT) and revaluation may lead to subsequent surgical debulking (IDS) (20).

Objectives

To describe the characteristics of an 8-year case series of OSEC presented at a single centre for diagnosis and treatment; to describe the surgical procedures performed and relate to: TNM/FIGO/AJCC staging system for ovarian, fallopian tube, and primary peritoneal cancer, size of tumour, post-surgical residual tissue, neoadjuvant treatment protocols, outcome at 60 months or end of follow-up, e.g. remission or progression of disease; to explore the data according with histological typing; to discuss findings in line with surgical guidelines and protocols; and in line with clinical process redesigns (e.g. debulking surgery).

Material and Methods

This is a single centre sample with data extracted from the centre's electronic database

and from the medical files and the surgical registry for the surgical procedures. Data were extracted for recorded cases from January 2014 until December 2021 with a 28-month period of follow-up, until 30th April 2024. Cases were registered in a single centre of reference - 1st General & Oncologic Surgery Department – Institute of Oncology "Al. Trestioreanu" Bucharest.

Ovarian carcinoma surgical procedures are complex interventions. Stages IIB to III and IV of the disease require peritonectomy and (multiple) visceral resections in order to have the R0 / optimal cytoreduction achieved. For ease of describing and analysis of these procedures we summarised and coded them as follows:

- 1= biopsy (of the tumour or the peritoneum) with Laparoscopic Approach / Laparotomy;
- 2= bilateral / unilateral adnexectomy (BA/UA) ± total hysterectomy (TH) ± omentectomy ± peritoneal biopsies;
- 3= (2) with total hysterectomy with bilateral adnexectomy (THBA) ± by extraperitoneal/subperitoneal route + peritonectomies (exclusively diaphragmatic) and electrocauterization of peritoneal carcinomatous lesions;
- 4= (3) with visceral (multiple) resections ± stoma;
- 5 = (4) with diaphragmatic peritonectomies / stripping / partial resection of the diaphragm;
- 6 = palliative surgery.

When, and if, performed Debulking surgery is described as: Primary Debulking Surgery (PDS) or Interval Debulking Surgery (IDS).

All surgical procedures relate to OSEC staging (21) and to future findings of residual tissue, reported as whether it was cleared or not and if residual tissue was present for any cases this was described with the following groups: under 0.5 cm, 0.5 to 1 cm, 1.1 to 1.5 cm, 1.6 to 2 cm and above 2 cm.

Data were extracted and analyzed for complications of surgery according to Clavien-Dindo classification.

According to WHO (2020) (12) ovarian carcinoma typology classifies as: 1 = HGSC (high-grade serous carcinoma); 2 = LGSC (low-grade serous carcinoma); 3 = CS (carcinosarcoma); 4 = CCC (clear cell carcinoma); 5 = EC (endometrioid carcinoma - where we included endometrioid high-grade and low-grade carcinoma and seromucinous carcinoma); 6 = MC (mucinous carcinoma); 7 = RC (rare carcinoma - where we included undifferentiated carcinoma and mixed carcinoma) and 8 = BLT (borderline tumour).

Data were analysed for staging and histopathology for the whole sample and subsamples. This paper aims at discussing characteristics of OSEC in an 8-year registration period with a 28-month follow-up period and excludes survival, as primary outcome, which has been described elsewhere (Subtirelu et al).

A first line of chemotherapy results in registered outcomes as: complete response (CR), partial response (PR), disease showing stability (SD) and progressive disease (PD). Complete and partial responses allow for tumour free, comparable with literature reporting, survivor probabilities reporting. Other reported results are: partial remission, complete remission, disease showing stability and progressive disease.

The statistical analysis plan (SAP) includes descriptive statistics with t and z-score distributions; quantitative variables have results expressed as mean values and CI 95% for estimates; all other variables are expressed as proportions, to allow for hypotheses formulation in concluding remarks.

Results

The analysed sample is illustrated in *Fig. 1.* PSC cases and BLT cases are completely different cases and similarity in numbers is a coincidence. The 'poor surgical candidate' (PSC) status of n=24 has the following results: 15 out of 24 were stage III (21), and most of cases, 19 out of 24, were histotype 1 (HGSC). One finding, reported elsewhere (Subtirelu et all), shows that there is a significantly lower mean survival time for PSC cases. They have

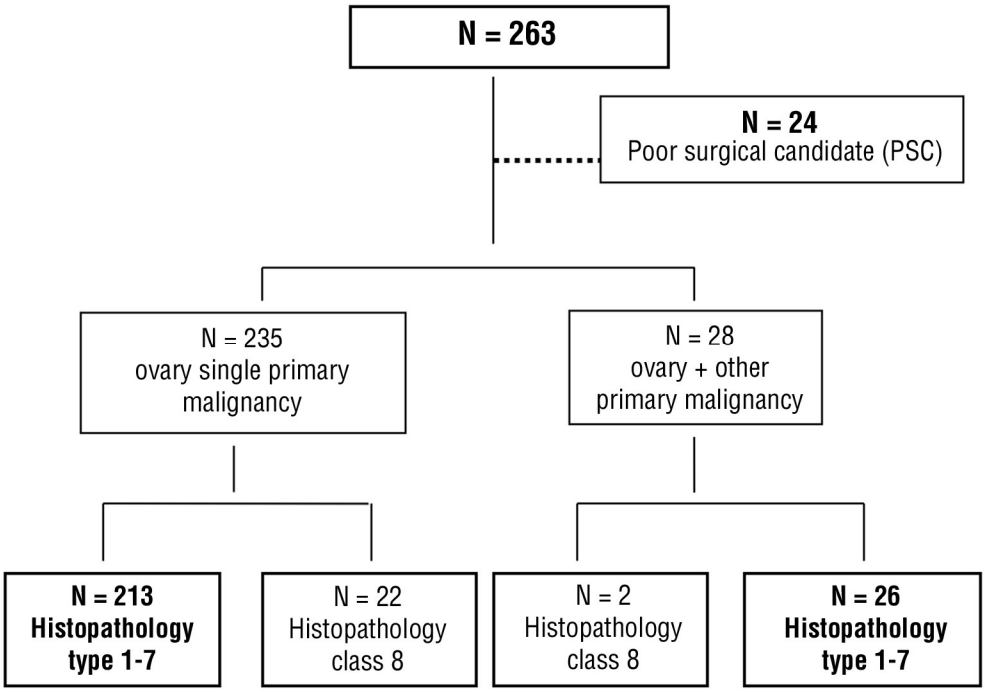

Figure 1. Sample size included in the descriptive analysis (n=263)

a calculated mean survival time of 21 months (CI95% from 12 to 31) compared with 39 months (CI 95% from 33 to 46 months) for the histotype 1 to 7 sub-sample (n=213).

The other major sub-sampling divisions: any histopathological type from 1 to 7 regardless of number of affected sites (one or both ovaries, fallopian tubes, or peritoneum) for n=239 cases; 213 were registered for ovary / fallopian tubes / peritoneum as single primary malignancy and 26 patients with a second primary malignancy synchronous or metachronous.

Histopathological type 8 which consists of borderline tumours (BLT) has the following descriptive results: serous BLT, seromucinous BLT, mucinous BLT.

Fig. 2 shows the structure of the sample by histotype.

Univariate analysis of recorded variables in the database (demographics, tumour dimensions, pleural liquid, duration of surgical intervention, diameter of tumour (ØcT) before read by imagistics tests and after surgical removal and measurement (ØpT)) are summarised in *Table 1*. Results are presented as mean ± sd values and the CI 95% for quantitative variable's estimates for all sample (n=263). Observations are briefly highlighted for pathological findings (e.g. low haemoglobin as well as the presence of liquid

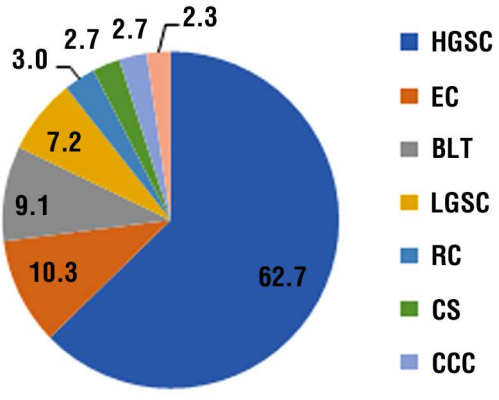

Figure 2. Ovarian carcinoma (OSEC) by histopathology type (n=263)

Table 1. Pre-operative and operative findings by main registered histotype

Variable mean (sd)	Main histotype					All		
	HGSC (n=165)	EC (n=27)	BLT (n=24)	LGSC (n=19)	Other types* (n=28)	Mean (sd)	CI 95% of estimate	
Age (years; sd)	60.3 (10.7)	54.2 (14.9)	49.4 (13.3)	53.7 (13.8)	57.4 (10.7)	57.8 (12.2)	n/a	N=263
ØcT imagistics (cm; sd)	9.8 (4.5)	12.0 (5.3)	16.1 (10.9)	10.5 (4.5)	14.2 (6.8)	11.1 (6.1)	10.3 la 11,8	
ØcT surgical measurement (cm; sd)	9.4 (4.5)	11.4 (4.9)	15.8 (10.0)	10.0 (3.9)	13.2 (6.9)	10.7 (5.8)	9.9 la 11,4	
Difference ØcT (cm)	0.4 (1.7)	0.6 (1.2)	0.3 (3.7)	0.5 (0.84)	1.0 (1.4)	0.44 (1.85)	0.21 la 0,66	
Haemoglobin (g/dl)	11.8 (1.6)	12.5 (1.3)	12.1 (168)	11.7(1.5)	11.4 (1.4)	11.9 (1.6)	11.5 la 12,1	
Duration of surgical intervention (minutes)	192.5 (107)	165.6 (93.2)	140.7 (67.6)	176.8 (101.2)	162.7 (62.1)	180,5 (98.6)	16.,1 la 195,9	N=160
Pleural liquid (ml)	363.6 (318.3)	n/a	n/a	n/a	212.5 ± 103.1	359 (316.8)	256.4 la 461.6	N=39
			N=263					

* four types: RC, CS, CCC, MC

in excess in the pleural cavity). *Table 1* summarises results for characteristics by three main subtypes of tumours as well as the borderline category: 63% HGSC (high-grade serous carcinoma), 10% EC (endometrioid carcinoma), 9% BLT (borderline tumours), 7% LGSC (low-grade serous carcinoma), with other types for 11%.

All patients had haemoglobin values recorded at time of admission. Low haemoglobin readings below the threshold of 11.7 g/dl may diagnose anaemia and these values were recorded for 104 women, prior to surgery, as follows: 37 values < 11.7 g/dl, 49 values of 10 g/dl and 18 values of 8 and 9 g/dl.

Patients suffering from OSEC are not free of other pathology: 45% suffer from raised blood pressure and a similar proportion (40%) from a cardiovascular condition; one in four (26%) suffer from a metabolic disorder: obesity and/or DM type II. Associated pathology and other variables are included in further survival analysis.

The presence of liquid in excess in the pleural cavity was recorded in 15% of cases. Results presented show that 39 women recorded liquid in excess in the pleural cavity, with an average of 360 (sd 317) ml; quantities varied from 100 to 1500 ml; among histotypes: HGSC n=33, RC n=2, CS n=1, CCC n=1, EC n=1 and LGSC n=1.

Of all cases, bilateral lesions were present in n=182 (69%) and unilateral lesions in=81 (31%). Of the bilateral lesions n=134 were HGSC type: n=131 (ovaries only) with three additional cases who presented lesions elsewhere (tube, peritoneum). Bilateral lesions presented also with LGSC (n=13) and EC (n=11) histotypes, with all other types giving the difference in bilateral lesions. Unilateral lesions were: HGSC type 31 cases of which 24 cases had the lesion in the ovary and seven in the tube; this was followed by EC histotype (n=16), BLT (n=15) and with all remaining types (LGSC, CS, CCC, MC and RC) totalling n=19 cases.

Age (*Table 1*) was compared for BLT vs all other types (1 to 7). A mean difference of 9.3 years was observed (with a CI 95% from 3.5 to 15.0; p=0,003) at diagnosis, with the youngest mean value of 49.4 years for the BLT subsample compared with 58.7 years for all other types and this difference is statistically significant. A breakdown by main types (1-7), excluding BLT, shows how mean age varies from 53.7 for LGSC to 60.3 years for HGSC and these differences were tested and are statistically not significant (*Table 1*).

BRCA 1 and 2 were analysed for n=27 cases. Of these n=17 were negative and ten cases were positive, seven of which were positive for BRCA 1, two of which BRCA 2 positive and the remaining one BRCA 1 positive BRCA 2 negative case.

Fig. 3 shows the structure of the sample by surgical procedure 1 to 6.

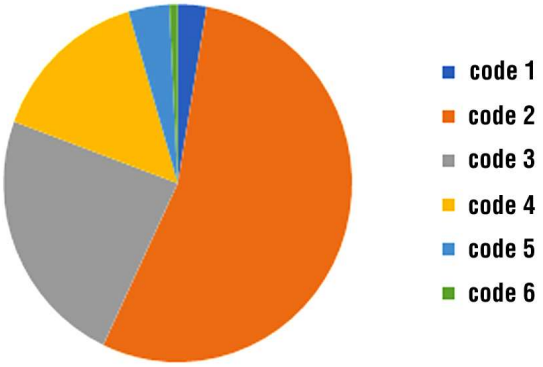

Figure 3. Structure of sample according to surgical procedure (n=263)

All 263 patients underwent at least one surgical procedure (SP). The distribution of the main surgical procedures performed at the optimum clinical status of the patient, by type, is described with the following results:

- 54% underwent a bilateral / unilateral adnexectomy (BA/UA) ± total hysterectomy (TH) ± omentectomy ± peritoneal biopsies;
- 24% underwent THBA by extraperitoneal/subperitoneal route ± omentectomy ± peritoneal biopsies plus + peritonectomies (exclusively diaphragmatic) and electrocauterization of peritoneal carcinomatous lesions;
- 15% underwent THBA by extraperitoneal/subperitoneal route ± omentectomy ± peritoneal biopsies, + peritonectomies (exclusively diaphragmatic) and electrocauterization of peritoneal carcinomatous lesions, plus visceral (multiple) resections ± stoma;
- 3% underwent THBA by extraperitoneal /subperitoneal route ± omentectomy ± peritoneal biopsies + peritonectomies and electrocauterization of peritoneal carcinomatous lesions, plus visceral (multiple) resections ± stoma, with diaphragmatic peritonectomies / stripping / partial resection of the diaphragm.

In addition to these SP in 38 cases were performed node sampling and/or lymphadenectomy for ilio-obturatory ± aortic-caval nodes: HGSC n=25, LGSC n=4, EC n=2, and one each for CS and RC histotypes.

The remaining cases (3%) underwent either biopsies (procedure 1) or palliative surgery (procedure 6). The number of SP per patient ranged between one (in n=162 cases) and n=6 (in one case) with n=2 SP in 78 cases, n=3 SP in 29 cases and n=4 in one case, in 51 patients the first SP was performed in another center.

Fig. 4 shows the distribution of surgical procedures by staging (IIB to IV).

Findings for stages IIB to IV (n=204) that require surgical procedures beyond THBA ± Omentectomy are:

- for stage IIB surgical procedure 2 accounts for n=6, SP 3 accounts for n=13, SP 4 accounts for n=5;
- for stages III which recorded n=161 surgical procedures: SP 1 accounts for n=6, SP 2 accounts for n=73, SP 3 accounts for n=44, SP 4 accounts for n=30, SP 5 accounts for n=6 and SP 6 accounts for n=2;
- for stages IV which recorded n=19 surgical procedures: SP 1 accounts for n=1, SP 2 accounts for n=7, SP 3 accounts for n=3, SP 4 accounts for n=4 and SP 5 accounts for n=4.

Findings by histotype recorded endometrioid carcinomas n=27 with SPs reported by stage:

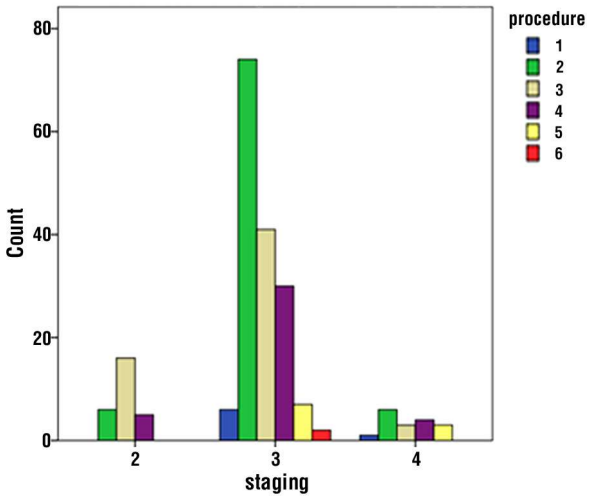

Figure 4. Distribution of surgical procedure by staging (IIB to IV)

- stage I n=8 with n=7 surgical procedure 2 and n=1 SP 3 this one a case with cTNM stage IIB with pathologic report downgrading to pTNM stage IC2;
- stage II n=9 with n=5 SP 2, n=3 SP 3 and n=1 SP 4;
- stage III n=10 with n=4 SP 2, n=3 SP 3, n=2 SP 4 and n=1 SP 5.

Endometrioid carcinomas n=27 recorded n=6 cases with a 2nd primary malignancy of which n=5 endometrial endometrioid carcinoma (all synchronous) and n=1 synchronous squamous cervical carcinoma, both malignancies being operated upon in the same surgery.

Clear cell carcinomas n=7 recorded:

- stage I n=1 with surgical procedure 2;
- stage II n=2 cases with n=1 SP 2 and n=1 SP 3;
- stage III n=4 cases with n=2 SP 3, n=1 SP 4 and n=1 SP 5.

Biopsies for low-likelihood optimal cytoreduction (LLOCR) and / or PSC patients were performed in n=63 cases, with n=19 being performed minimallly invasive of which n=2 were converted to laparotomy. Neoadjuvant chemotherapy (NACT) was administered and IDS performed in n=50 cases with R0 in n=17, optimal cytoreduction (residual tumour < 2 cm) in n=27 and residual tissue >2 cm in n=6.

Four patients underwent for the first procedure an emergency SP for bowel obstruction described as stoma diversion n=2 and resection with anastomosis n=2, which also included biopsies.

A total number of 51 cases had the first procedure in another centre (19%).

Of the procedures carried out, a total of 160 surgical episodes have a recorded time with a mean value of 181 minutes (± 99 minutes). There was no recorded time for PSC cases with respect to the protocol these cases followed (n=24). A further 79 cases have missing values for this variable (30%) and such cases are proposed to be further explored.

Complications were recorded in 25 patients (rate of 9.5%). Major complications were: wound infection with dehiscence n=1, severe diselectrolitemia n=2, fistula/leak n=5, abdominal collection n=1, bleeding / hematoma n=3 (haemoperitoneum n=2, haemopericardium n=1), thrombembolism (profound venous thrombosis, pulmonary thrombembolism) n=5, cardiopulmonary (including myocardial infarction, pneumotorax) n=3, acute renal failure n=3, neurologic n=1, multiple systemic organ failure n=5, death n=5; by Clavien-Dindo scale of surgical complications grade II n=9, grade IIIa n=2, grade IIIb n=3, grade IVa n=2, grade IVb n=4, grade V n=5. As a result the fatality ratio from complications for this case series is 5/25. In this series postoperative mortality rate is 1.9%.

A total of 101 patients (38%) of n=263 in the series registered no post-operatory residual tissue, 60 patients being stage I and IIA, and 41 patients with stage III and IV with DS, 7% had missing values and of the remaining 145 patients (55%), results are: 7% had <0.5 cm, 19% had 0.5 to 1 cm, 5% had 1.1 to 1.5 cm, 11% had 1.6 to 2 cm and 13% had > 2cm. For stages I and IIA this procedure was not registered (n=60), as the surgical procedures for these stages are not defined as DS; in all these patients (n=60) the results were R0=no residual disease.

Debulking surgery (DS) was carried out for n=182 patients (stages IIB to IV), of which n=132 were PDS and n=50 IDS. There were three types of procedures recorded as DS: R0=no residual tumour=41, R2=residual tumour with cut-off at 2 cm (as maximum accepted by published data, with the aim of R2< 1cm (18,19,20)) for optimal cytoreduction=110, beyond 2 cm defining suboptimal cytoreduction=31. DS was not possible in 21 patients because of tumour extension.

Of all cases operated upon (n=263) residual tissue was registered in 62% patients (n=162), with the rest of the patients registering no residual tissue (n=101). Out of 182 with DS residual tissue was registered in 77%, with the rest of the patients registering no residual tissue=R0 (n=41). Results shown for patients with DS with residual tissue (n=141), with variable dimensions (cm), recorded the following findings: under 0.5cm (14% cases), 0.5 to 1 cm (35%), 1.1 to 1.5 cm (9%), 1.6 to 2

cm (20%) and above 2 cm (22%). Of the 24 PSC cases, half recorded residual tissue over 1cm.

This case-series recorded 143 peritoneal and/or retroperitoneal lymph nodes recurrencies in which were recorded n=54 SP, and 56 distant metastasis excluding peritoneal metastases with n=14 SP.

In n=3 cases were recorded entero / colonic fistula/ae with acute peritonitis as complication of antiangiogenetic treatment, which determined emergency SP that resulted in ileo / colonic stoma, all three patients survived. Other two cases recorded complications of ovarian cancer evolution that detetrmined emergency SP, only one patient survived.

Palliative surgery included digestive stomas n=7 and bypass n=1, nephrostoma n=1, ureteral stenting n=1, pleurostomas n=7.

The following outcomes are recorded in the database at the end of the follow-up period for all patients: 74 are tumour free (49 disease free and 25 in complete remission), 20 are not disease free but the disease shows stability under medical maintenance treatment; four have responded only partially to the therapeutic regimen and nine have only presented once to this centre, therefore their status at the end of the follow-up is that of lost to follow-up (8% attrition) in addition to the 156 deaths. Of 107 patients alive at the end of follow-up 23 belong to the BLT sub-sample.

Findings, reported elsewhere (Subtirelu et all), show the following tumour free survival probability estimates (%) at 60 months by stage: stage I – 80%; stage II – 33%; stage III – 18%; stage IV – 16%, and by histotype: HGSC – 16%; LGSC – 62%; CS- 29%; CCC – 14%; EC – 66%; BLT – 94%; MC and RC – 0%.

Discussion

This study describes a single centre case-series of ovarian serous epithelium carcinoma (OSEC) which is a rare disease. The histopathological types of ovarian cancer have known changes in classification in the last 30 years (1-8) with „extrauterine Müllerian epithelium" being proposed as the origin of lesions (9,10) to the ovaries and frequently to organs in the pelvis, middle and upper abdomen (4,6). Cotton (1992) specified that common surface epithelial tumours constitute 70% of primary ovarian neoplasms. The classification used at the time described the tumours as serous, mucinous, endometrioid (typical, clear cell tumours and Müllerian tumour), Brenner - transitional cell tumours and unclassifiable carcinoma (22). The WHO (2020) recommends immunohistochemistry for the classification of OSEC into histotypes / subtypes of ovarian carcinoma as well as new criteria for assigning the primary site in extrauterine high-grade serous carcinoma and also criteria for assigning and managing concurrent ovarian and uterine endometrioid carcinomas as synchronous primaries versus metastatic tumours (12).

Age at diagnosis falls within the range described in the literature with BLTs occuring in women 10 years younger than women with invasive OSECs (23).

All patients had a recorded value for haemoglobin at the time of diagnosis and prior to the surgical intervention. Of these 40% represent abnormal readings indicating anaemia when the threshold is set at 117 g/L. The 104 cases with anaemia have no other related data extracted to allow for a validated diagnostic (e.g. RBC, Hct, MCV, etc.). Of the 104 cases only 13 were classified as PSC.

The difference recorded in the tumour dimensions before and during or after surgery is within expected ranges of 0.2 to 0.6 cm as shown by the CI 95% for the 0.44 cm mean value (less than 5 mm).

Surgical procedures include those described by the literature with procedures 2, 3, 4 and 5 here totalling 254 interventions (or 97%) across all 263 cases.

Procedures 3,4, and 5 which account for 42% include peritonectomies and visceral (multiple) resections were performed in cases with peritoneal carcinomatosis ± involvement of abdominal viscera (stages IIB to IV). Debulking surgery for ovarian cancer, first described by Meigs in 1934 (24) and codified by Griffiths in 1975 (25) nowadays aims to complete resection of all visible diseases, or, if

R0 is not possible, to R2 < 1 cm (19,20,26). Findings in the study regarding post-operative residual tissue reflect a surgical output of 23% R0 and 38% R2 < 1 cm for DS n=182 that are in line with implementation of ultra-radical surgery (26).

Endometrial carcinoma n=27 arise from endometriotic foci on the ovary (11). In the study they account for n=27 with n=5 synchronous endometrial endometrioid carcinoma treated alltoghether. Stages II and III record for n=19 with n=9 SP2 and n=10 SPs 3, 4 and 5 with a tumour free survival probability estimate (%) at 60 months of 66% for this histotype as both surgery and platinum based chemotherapy are efficient (27).

Clear cell ovarian carcinoma is, by histotype, a rare disease and similarly to EC arises from endometriosis meaning that the tissue of origin is not the ovary (11). They are usually positive for ARID1A and PIK3CA mutations, but are usually negative for p53 (28). They record for n=7 cases in the study, with stages II and III accounting for n=6 and SP 3, 4 and 5 for n=5, with a tumour free survival probability estimate (%) at 60 months of 14%, being known the controversy as to whether or not paclitaxel is an active drug for CCC (6).

Recorded outcomes showed that at the conclusion of the follow-up period, among the 107 survivors most were tumour free (69%), and 23% with the disease showing stability or partial remission (SD n=20; PR n=4). Findings reflecting 35% histotypes 1-7 sub-sample survivors are within the range of published data (15).

The first scheme of chemotherapy after surgery included 6 cycles of platinum-based combination chemotherapy with a platinum and a taxane, docetaxel being an alternative option to paclitaxel (29-31), with LLOCR / PSC cases being treated with the same combination of chemotherapy for 3-4 cycles (NACT) prior to reappraisal for IDS (31). Maintenance therapy included chemotherapy, angiogenesis inhibitor, and more recently immune checkpoint inhibitors, of which benefited most patients with a germline or somatic BRCA1 or 2 mutation (31-33), results recorded in this case-series being in line with literature (29-33).

Only 8% of living cases had an uncertain and undefined status due to the fact that they only attended once the centre and were soon lost to follow-up thus affecting measurment of patient-reported outcome (34).

Conclusion

Ovarian carcinoma is a rare disease. Age appears to register a statistically significant lower value for BLT compared with other type of histopathology, especially with HGSC. Descriptively, in this large case-series, the main type of registered histopathology (WHO, 2020) remains the HGSC (63%); followed by EC (10%), BLT (9%) and LGSC (7%) and remaining four types - RC, CS, CCC, MC - account for a proportion of 11% of cases. These four categories require a further in-depth analysis and study. Considering OSCE is a relatively rare disease and the importance of collecting substantial numbers of samples by histotypes to further knowledge about ovarian cancer it comes crucial to establish collaborative endeavour of tertiary centers with standardised and quality controlled strategies (5, 35).

Conflicts of Interests

The authors declared no potential conflict of interests.

Ethical Statement

This 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.

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