CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

FIELD OF MEDICINE

SURGICAL STAGE IN OVARIAN SURFACE EPITHELIAL CARCINOMAS. CRITICAL STUDY

SUMMARY OF THE DOCTORAL THESIS

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ANUL

2024

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Introduction

In ovarian cancer, surgery is the pivot of treatment, to which medical oncological treatment is added by recommendation in most cases [1,2,3].

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).

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% [4,5].

Although OSEC represents 2.5% of cancer cases in women, they cause 5% of deaths [6], with a mortality/incidence ratio >0.6 [7], being the first cause of death among gynaecological cancers [8].

In OSEC, according to genomics and pathology data accumulated in the last decades, several different nosological entities with distinct etiologies [9-16] 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 [17,18], lesions for which the main common characteristic is dissemination to the ovaries and also frequently to the neighboring genital and pelvic organs [12-14].

It is generally accepted that the fallopian tube is the origin of many OSEC and primary peritoneal cancers and that serous intraepithelial carcinoma of the fallopian tube is a precursor to most high-grade ovarian and peritoneal serous carcinomas [10,12].

The World Health Organization (WHO) Classification - Tumors of the Female Genital Tract 5th edition (2020) reflects current knowledge on the biology of ovarian carcinomas. Considering that the use of immunohistochemistry has increased the reproducibility of the classification of ovarian carcinomas [19], and that accumulated data show prognostic differences between histotypes [20,21], it is recommended to use it in the classification of OSEC in histotypes/subtypes of ovarian carcinomas: serous carcinomas of high-grade (HGSC), low-grade serous carcinomas (LGSC), endometrioid carcinomas (EC), clear cell carcinomas (CCC), mucinous carcinomas (MC) [21].

In recent years the understanding of ovarian carcinogenesis which until recently was based on morphology is increasingly taking into account molecular classification, so that new pathogenic models and current histopathological classification integrate molecular genetic findings [15,22] correlating clinical behaviors with histopathological phenotypes and molecular characteristics, with OSEC being classified into histotypes and determining the appropriateness of OSEC treatment [9,20].

We approached this topic, starting from the current histopathological classification, to evaluate the results of surgical treatment and its association with (neo)adjuvant medical treatment both in the context of the current molecular characterization and the proposed histotypes for OSEC.

For this study we set the following objectives:

• To describe and analyze the characteristics of a case-series, from a reference oncology center, with cancers of the ovarian surface epithelium, carcinomas of the fallopian tubes and primary peritoneal carcinomas for which the treatment is the same as that of HGSC;

• To describe and analyze the surgical procedures performed in ovarian cancers against TNM / FIGO / AJCC staging;

• To describe and analyze the characteristics of the case-series with ovarian surface epithelial cancer according to the recorded histotypes and to discuss the surgical treatment of ovarian surface epithelial cancer taking into account the current molecular characterizations and the proposed pathogenic models;

• To analyze the survival probabilities, the average and median survival time of the case-series, with sub-objectives: survival analysis with the Kaplan Meier method; survival analysis with actuarial table; Cox regression.

At the end of this study, its limits and the ways to overcome them are evaluated and specified.

I. General aspects

1. Cancer of the ovarian surface epithelium

1.1. Nosological classification. Carcinogenesis

Ovarian cancer is a heterogeneous disease with several tumor types with different clinical characteristics and behaviors, which makes the elucidation of its carcinogenesis a major problem.

Studies published beginning in the 2000s by the group of Kurman, Shih, Vang, Kuhn, et al., at The Johns Hopkins Medical Institutions, Departments of Pathology, Gynecology/Obstetrics and Oncology, based on morphological and molecular genetic studies proposed a model which classifies the different types of ovarian surface epithelial carcinomas into type I and type II, with obvious differences in their molecular genetic features [9,12,15,16,36].

1.2. Epidemiology

In reports and epidemiological studies published in the *Global Cancer Observatory by the International Agency for Research on Cancer and by the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI)* in the United States, ovarian cancers are reported and analyzed as a single entity [43,44].

1.2.1. Incidence

According to GLOBOCAN, 1786 new cases of ovarian cancer were reported in Romania in 2022, which represented 1.7% of the total of 104661 new cancer cases, placing ovarian cancer in 17th place among new cancer cases in 2022; the cumulative risk for ovarian cancer was 1.1 [43].

1.2.2. Ovarian cancer specific mortality. Survival

In 2022, GLOBOCAN reported for Romania 1195 deaths with a medical cause registered by ovarian cancer, placing it in 12th place among cancer deaths, with a proportional mortality of 2.1% for ovarian cancer deaths [43].

1.2.3. Rare disease. Definition and applicability

Rare diseases according to the European Commission - Directorate C Public Health and Risk Assessment are defined as those diseases that *"including those of genetic origin, are life-threatening or chronic debilitating conditions with such a low prevalence that combined societal efforts are necessary , special, to address them. As a guideline for their frequency, the prevalence is defined around the value of 5 cases per 10,000 inhabitants"* [45].

According to the GLOBOCAN report for the year 2022 in Europe, the incidence of ovarian cancer was 69,472 cases, the prevalence was 208,930 cases, placing this disease on the periphery of rare diseases [43].

1.3. Etiopathogeny

If progress has been made in the study of ovarian carcinogenesis, the etiological factors still remain poorly understood.

Studies have identified several risk factors associated with epithelial ovarian cancers with the mention that they have been observed to vary according to histotypes [47] and although there are known to be differences in their natural course, morphology and genomic/molecular however in epidemiological studies ovarian cancers are frequently analyzed as a single condition [48].

1.4. Screening

There are currently no recommended screening tests for ovarian cancer. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial that evaluated the use of transvaginal ultrasound and the CA125 marker found no benefit on ovarian cancer mortality for up to 19 years of follow-up [47,52] .

1.5. Pathology. Classification

The World Health Organization Classification of Tumors - Tumors of the Female Genital Tract 5th edition (2020) takes into account the current knowledge on the biology of ovarian carcinomas [21].

1.6. Positive diagnosis

The diagnosis of ovarian cancers is established following the histopathological examination, which most of the time requires surgical intervention.

The evaluation of the clinical and biological status correlated with the nutritional status of the patient is important for establishing the status of good surgical candidate vs poor surgical candidate and influences the treatment indication [3].

1.7. Staging. Prognostic factors

According to the Manual for Staging of Cancer 2nd ed. (1977) “Cancer staging is not an exact science. As new information about etiology and new methods of diagnosis and treatment become available, the classification and staging of cancer will change.” [57].

Prognosis in ovarian cancer is determined both by loco-regional and distant anatomic spread of the cancer, as well as by molecular biology and genomic features, such as the six molecular subtypes of ovarian serous and endometrioid carcinomas identified in Tothill's group study, as and their response to treatment [13,59].

1.8. Treatment

In the treatment of cancers of the ovarian surface epithelium, surgery is the essential element, alongside which medical treatment is recommended in stages II - IV, but also in some of the stages I.

1.8.1. Surgical treatment

In ovarian epithelial cancer, only 10% of patients are diagnosed in early stages [60]. According to the studies published by Bristow's (2015) and Querleu's (2017) groups, the most appropriate and well-performed treatment for each patient is conditioned by a high-volume center where the surgical and medical team is qualified and experienced, so the patient has a better chance that the treatments provided are consistent with the recommendations in the treatment guidelines. Standardized operative protocols provide much more complete and valuable data for evaluations than non-standardized operative protocols [1,61,62].

1.8.1.1 Early stage

In the early stages of ovarian epithelial cancers, comprehensive staging is essential and the standard recommended excision is total hysterectomy with bilateral adnexectomy and infracolic omentectomy, these through a median laparotomy, and the minimally invasive approach can be considered [1,63].

1.8.1.2 Advanced stages

In advanced stages, the goal of surgical treatment is complete resection of all macroscopic carcinomatous lesions by debulking surgery.

To achieve this goal, depending on the extent of the lesions, for *Primary Debulking Surgery (PDS)* extensive peritonectomies, visceral resections, diaphragmatic resections, retroperitoneal lymphadenectomy including celiac lymphadenectomy may be necessary, the intention of the surgical treatment being R0 (no macroscopic residual tumor) [1, 64].

1.8.2 Medical treatment

In OSEC, related to surgery, medical treatment when recommended can be posterior to surgery – *adjuvant treatment* or precede surgery – *neoadjuvant treatment* [70-72].

1.8.3 Radiotherapy

Recent studies, that of Brown's group and that of Fields & McGuire's group, show that radiotherapy has a role in the treatment of loco-regional recurrences of ovarian cancer [78,79].

1.9 Locoregional recurrences. Secondary cytoreduction

Secondary cytoreduction for loco-regional recurrences is surgical treatment performed at a time after debulking and cytostatic therapy. From published data it appears that, in particular, patients with a disease-free interval longer than 12 - 24 months and with at most 1 - 2 abdominal or pelvic tumour recurrences benefit from secondary cytoreduction [60,72,80,81].

II. Personal contributions

2. Working hypothesis and general objectives

2.1 Working hypothesis

The working hypothesis and the main purpose of this study, starting from the current histopathological classification, is to analyze and evaluate in detail the surgical procedures performed and the results that were obtained, knowing the extent and difficulty of radical surgery in advanced stages, compared to the new pathogenic models and proposed nosological entities based on molecular genetics studies and to observe new prognostic groups considering the outlined nosological entities and at the same time to identify possible guiding criteria for the adequacy and improvement of treatment. The secondary aim is to identify the limitations of this study.

2.2 General objectives

(1) To describe and analyze the characteristics of a case-series, from a reference oncology center, with ovarian surface epithelial cancers, fallopian tube carcinomas and primary peritoneal carcinomas for which the treatment is the same as that of HGSC.

(2) To describe and analyze surgical procedures performed in ovarian cancers against TNM / FIGO / AJCC staging.

(3) To describe and analyze the characteristics of the case-series with ovarian surface epithelial cancer according to the recorded histotypes and to discuss the surgical treatment of ovarian surface epithelial cancer taking into account the current molecular characterizations and the proposed pathogenic models.

(4) To analyze the survival probabilities, mean duration and median survival of the case-series.

3. General research methodology: Material and method

The studies are retrospective observational, performed on a series of 263 patients registered over a period of 8 years between January 2014 and December 2021 in a single reference center - Department 1 General Surgery and Oncology - Oncological Institute "Al. Trestioreanu" Bucharest with a follow-up period of 28 months, until April 30, 2024. The data were extracted from the center's electronic database, from medical records and operating registers for surgical procedures and from histopathological analysis reports. The criterion for inclusion in the study is the diagnosis of ovarian cancer/carcinoma, of the fallopian tubes and primary peritoneal, being excluded from the research patients with ovarian cancer of the germ cells or of the sexual cords-stroma. The follow-up time until April 30, 2024 was set as the cut-off date.

The database was created in the Microsoft Office Excel 2021 program in which the variables were loaded, grouped and described, quantitative, qualitative (demographic, medical, surgical).

Cases were analyzed by TNM/AJCC/FIGO stages and histopathological subtypes/histotypes – *WHO Classification* for the entire case series and subgroups.

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).

The recorded complications were graded according to the Clavien-Dindo system.

A first line of chemotherapy results in registered outcomes as: complete response (CR), partial response (PR), disease showing stability (SD) and progressive disease (PD).

Local and distant recurrences, time to diagnosis and their treatment were recorded and analyzed.

The statistical analysis plan (SAP) includes descriptive statistics with t and z-score distributions; results for quantitative variables are expressed as mean values and 95% CI for estimates; all other variables are expressed as proportions to allow for the formulation of hypotheses in the final observations and consist of: TNM staging with staging grouping for primary surgery (AJCC/FIGO and pTNM staging); description of the main surgical procedures and their frequency; poor surgical candidate (PSC) status (yes/no); survival probabilities: unadjusted overall probability and probabilities adjusted by staging and histopathology with estimates and 95% CIs for the entire series and subgroups: staging, histotype, PSC status. Statistical methods used were Kaplan-Meier (unadjusted probabilities) and actuarial life tables for adjusted probabilities at 12 months and 60 months (TFS) for: surgical TNM staging: I to IV, Histotypes: 1=HGSC, 2=LGSC, 3= Carcinosarcoma CS, 4= Clear cell carcinoma CCC, 5= Endometrioid carcinoma EC, 6= Mucinous carcinoma MC, 7= Rare carcinoma RC and 8= Border-line tumors BLT. Mean survival time with 95% CI and median survival time were used in reporting. Comparison was made with the logrank test.

Cox regression analysis was performed to identify predictors of survival times at: 12 months, 24 months and 60 months.

Analysis was performed with Microsoft Office Excel 2021 and IBM SPSS v23.0.

Study 1: Description and analysis of case-series characteristics of ovarian surface epithelial cancer, fallopian tube carcinoma and primary peritoneal carcinoma

4.1. Introduction

Cancers of the ovarian surface epithelium are conditions with different clinical, histological, immunohistochemical characteristics, almost 50% of cases being diagnosed in patients aged between 55 and 74 years [15,16,20,44].

The aim of this study is to describe and analyze the characteristics of a case-series, from a reference oncology center, with cancer of the ovarian surface epithelium, carcinoma of the fallopian tubes and primary peritoneal carcinoma.

4.2. Material and method

In the study, carcinomas of the ovarian surface epithelium are defined as those attributed as origin to the ovarian covering epithelium of mesodermal origin, malignant tumours of the germ cell and those of the sex cord-stromal being excluded from the study.

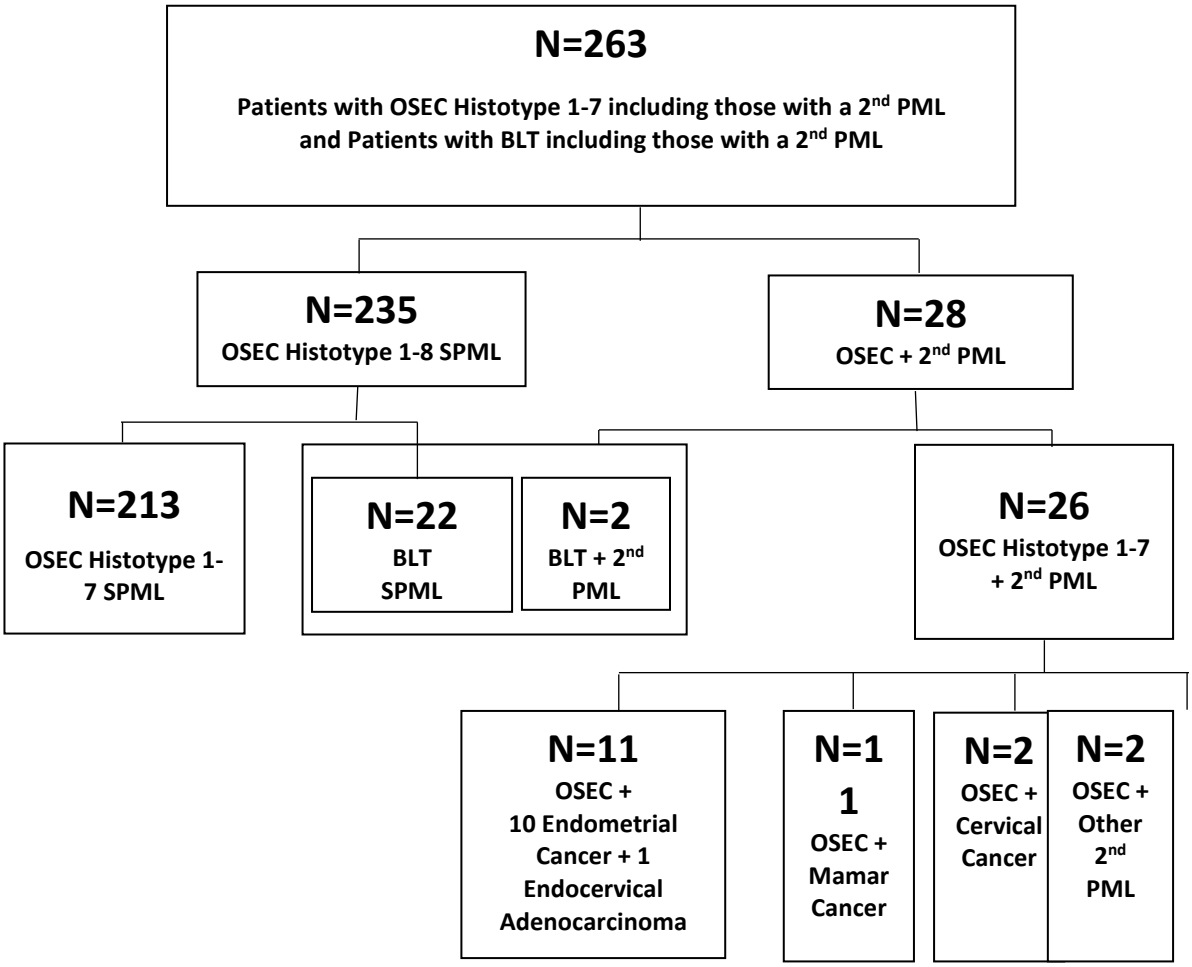
4.3. Results

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). The analysed sample is illustrated in Figure 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.

Age 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 sub-sample 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.

The size of the primary tumor, surgical staging, histopathological types, pleural fluid, duration of the surgical intervention, personal pathological history, uni / bilaterality of the lesions are described and analyzed.



OSEC = Ovarian Surface Epithelial Cancer

BLT =Ovarian Borderline Tumor / Low Malignant Potential / Ovarian Cancer Histotype 8

PML = Primary Malignant Localisation

SPML = Single Primary Malignant Localisation

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

4.4 Discussion

Cases with Poor Surgical Candidate (PSC) status, are in small number (n=24) but their probability of survival is significantly lower than in non-PSC cases, a difference that becomes more visible after 12 months: 37% face of 53% at 12 months and 11% versus 27% at 60 months (Table II) (detailed results are presented in Chapter 7 – Study 4).

4.5. Conclusions

Given that OSEC is a relatively rare disease and that it is important to collect a substantial amount of histotype-classified data to advance the knowledge of ovarian cancer, it is crucial to establish a collaborative endeavour of tertiary centers [13,60].

Study 2: Description and analysis of surgical procedures performed in ovarian cancer against TNM / AJCC staging

5.1 Introduction

In the treatment of cancers of the ovarian surface epithelium, surgery is the pivot, medical oncological treatment being recommended in stages II - IV and for selected cases in stage I [72].

The main aim of this study is to describe and analyze surgical procedures performed according to therapeutic guidelines according to TNM / FIGO / AJCC staging of ovarian, fallopian tube and primary peritoneal cancers, and their outcomes.

5.2 Material and method

For ease of description and analysis of surgical procedures, we have summarized and codified them as presented in *Chapter 3 – General Research Methodology*, where TNM / AJCC / FIGO staging, criteria for cytoreductive surgery and residual tumor tissue reporting are also shown, of the complications of surgical treatment, and of reporting the results of medical oncological treatment.

5.3 Results

All 263 patients underwent at least one surgical procedure. The distribution of the main surgical procedures performed in the optimal clinical condition of the patients, by type, is described with the following results: 55% underwent a bilateral/unilateral adnexectomy +/- total hysterectomy +/- omentectomy +/- peritoneal biopsies; 23% underwent HTAB +/- extraperitoneal/subperitoneal +/- omentectomy +/- peritoneal biopsies plus + peritonectomies (diaphragmatic only) and electrocautery of peritoneal carcinomatous lesions; 15% underwent HTAB +/- extraperitoneal/subperitoneal +/- omentectomy +/- peritoneal biopsies + peritonectomies (diaphragmatic only) and electrocautery peritoneal carcinomatous lesions, plus visceral resections (multiple) +/- stomas; 3% underwent HTAB +/- extraperitoneal/subperitoneal +/- omentectomy +/- peritoneal biopsies + peritonectomies

and electrocautery of peritoneal carcinomatous lesions, +/- visceral resections (multiple) +/- stomas, with peritonectomies/diaphragmatic stripping /partial diaphragm resection.

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.

For stages IIB to IV (Figure 2), the results show a continued effort for maximal cytoreduction, as mandated by ESGO and NCCN recommendations (24-26), with surgical procedures 3, 4, and 5 representing 42% in this series of 263 cases, being close to the data published in the literature [64].

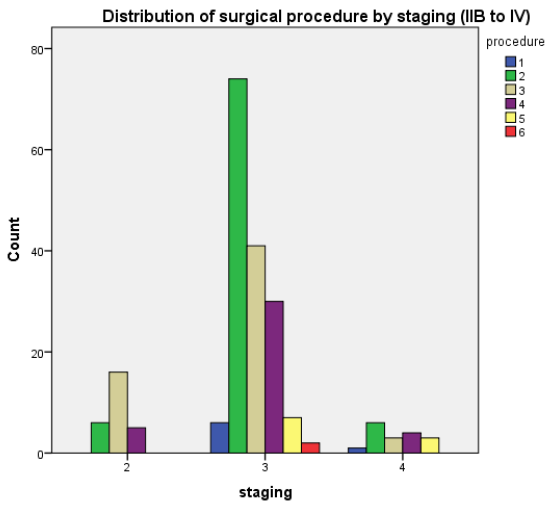


Figure 2 Distribution of surgical procedures by stages IIB - IV

Complications were recorded in 25 patients (rate of 9.5%), according to the 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.

A total of 101 patients (38%) of n=263 in this series had no postoperative residual tissue, 60 patients being stage I and IIA.

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 ([1,2,3]) for optimal cytoreduction=110, beyond 2 cm defining suboptimal cytoreduction=31. DS was not possible in 21 patients because of tumour extension.

The results presented for debulking surgery patients with residual tumour tissue (n=141), with variable sizes (cm), recorded the following findings: below 0.5 cm (14% of cases), 0.5 to 1 cm (35%), 1.1 to 1.5 cm (9%), 1.6 to 2 cm (20%), and over 2 cm (22%). Of the 24 PSC cases, half had residual tissue greater than 1 cm.

In this series of cases there were 143 peritoneal and/or retroperitoneal lymph node recurrences in which n=54 surgical procedures were recorded, and 56 distant metastases excluding peritoneal metastases with n=14 surgical procedures recorded.

5.4. Discussion

The results showing a 35% survival in the subset of histotypes 1-7 are within the range of published data [6].

5.5. Conclusions

Ovarian cancer is rare and this 8-year case series showed that HGSC histotype was the most common type of tumor diagnosed (63%) of the cases. Following the analysis, we found for n=213 the average survival time (months): stage I-81; stage II-54; stage III-32; stage IV-19, and the probabilities of survival at 60 months are: stage I-73%; stage II-42%; stage III-18%; stage IV- 11%.

Study 3: Description and analysis of ovarian surface epithelial cancer and surgical procedures performed by histotype

6.1 Introduction

This study describes and analyzes the surgical procedures performed on a series of OSEC cases from a single referral center by *WHO (2020) Classification* histotypes, proposed in accordance with genomic and molecular studies and immunohistochemical characterization.

6.2 Material and method

Study lot, histotypes and coding of surgical procedures are as described in *Chapter 3-General Methodology* and *Chapter 4-Study 1*.

6.3. Results

Results of bivariate analysis for surgical procedures and histotype are shown for all cases with six main procedures recorded in operative protocols (Table I).

HGSC, LGSC, CS, CCC, EC, MC, RC, BLT are described and analyzed.

6.4. Discussions

Ovarian carcinomas are a malignancy bordering on rare diseases, and if analyzed separately according to histotypes they fall under rare diseases. However, the shift from morphopathology examinations to molecular genetics in recent years has proven to be an important step in guiding the therapeutic management of this serious and fatal disease, which has seen only a slight improvement in survival over the past 30 years [13 ,14,30,90].

Age at diagnosis falls within the range described in the literature, BLT occurring in women 10 years younger than women with invasive OSEC [83].

HGSC and ***LGSC*** were regarded as different grades of the same histopathological type of ovarian carcinoma until studies by the groups of Kurman, Crum, Köbel and many others. LGSC have a reduced response to platinum-taxane combination chemotherapy, but respond to endocrine therapy [75-77]. Analysis of surgical procedures for these histotypes showed for cases of HGSC stages III and IV n=66 surgical procedures 3, 4 and 5, and for cases of LGSC stage III (no stage IV cases were recorded in this series) n=7 surgical procedures 3 and 4, achieving maximum cytoreduction being the aim for both histotypes. Because the LGSC histotype appears to have a poorer response to adjuvant therapy, complete staging and complete surgical resection of all gross lesions is extremely important [1–3,76,77] .

EC n=27 arises from foci of endometriosis on the ovary [20]. In this study they represent n=27, with n=5 synchronous endometrioid endometrial carcinomas treated at the same time, with an estimated probability of tumor-free survival (%) at 60 months of 66% for this histotype given that both surgery, as well as platinum-based chemotherapy are effective [73].

Clear cell ovarian carcinoma is, as a histotype, a rare disease and, similarly to endometrioid carcinoma, arises from endometriosis, meaning that the tissue of origin is not the ovary [20]. The study enrolled n=7 cases with stages II and III representing n=6 and surgical procedures

Table I 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

3, 4 and 5 for n=5, with an estimated tumor-free survival probability (%) at 60 months of 14 %, the controversy being known whether or not paclitaxel is an active drug for CCC [14].

6.5 Conclusions

Ovarian cancer is rare and this 8-year case series showed that HGSC histotype was the most common type of tumor diagnosed (63%) of the cases. Given the small number of patients in the subgroups, most of the results of the survival analysis did not have a statistically significant difference; however, the clinical significance remains important and, given the developments in the diagnosis and treatment of OSEC, may guide new research in this pathology.

Study 4: Analysis of survival probabilities, mean duration and median survival in the case series

7.1 Introduction

Survival analysis is part of the objectives of medical research through which a primary outcome of surgical and medical interventions and treatment is explored, that of adding years to life.

7.2 Material and method

The addressed sub-objectives are: (1) Survival analysis with the Kaplan-Meier method; (2) Survival analysis with actuarial table; (3) Cox regression to identify predictors of survival times.

The statistical methods used were Kaplan-Meier (unadjusted probabilities) and the actuarial table to obtain the adjusted probabilities at 12 and 60 months (tumour-free survival), with adjustment made for: pTNM staging from I to IV, histotypes (Study 3): 1= HGSC, 2=LGSC, 3= CS, 4=CCC, 5=EC, 6=MC, 7=RC, 8=BLT.

Analysis plan

For survival analysis data processing and graphing were performed with MS Excel and IBM SPSS Statistics v23.0. Probabilities, mean and median survival with 95% confidence intervals (95% CI) were calculated. The comparison of the results was done with the logrank test. The results of the survival analysis are presented in Section 7.3.

The analysis was done on all cases but survival probabilities were also calculated for subsets of cases, for example whether the primary tumor was single or not, excluding a certain histotype, according to surgical staging, histotype classification and inoperable cases (Poor Surgical Candidate cases or PSC).

Representative results are presented in Section 7.3. Also part of the results of this Study were published in the article entitled: *"Ovarian Carcinoma: A Single Center Eight-Year Case-Series Study with Survival Analysis". Surgery. 2024; 119(4):379-390.*

7.3 Results

A total of 263 cases were described in Studies 1, 2, and 3, who underwent 364 surgical procedures.

Survival analysis

Survival probabilities and mean duration (95% CI), including median, are shown in Table II.

In the database, at the time of study censoring, 156 deaths were recorded, of which 80 occurred in the first 12 months, 30 deaths in the period up to 24 months, followed by 38 deaths up to 60 months throughout the duration of the study . The remaining 107 patients are survivors of the same period.

Cox regression results show that survival at 60 months is influenced by age only in model 1 and 2; residual tumour is important for survival at 60 months (5 years) regardless of its size; also histotypes 3 (CS), 4 (CCC) and 7 (RC) play an important role for this 60-month survival time.

7.4 Discussions

Stage III and IV cases have similar median survival times, with an overall difference of one or 3 months in these estimates also not statistically significant when calculated for the entire cohort (n=263) together with the estimate calculated in the non-BLT single location subgroup (n=213).

At 24 months, the CCC histotype shows a high value of ln HR = 12, with statistical significance (95% CI 1.32 to 111), where the confidence interval shows the small number of cases for this histotype. The other two histotypes, CS and RC, although they show high values of the beta coefficient (ln HR=8 and ln HR=6) these are accompanied by wide

Table II 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

confidence intervals, which contain the value 1 so that the values have no statistical significance and cannot be included in the regression equation.

Model 3 allows for the development of the discussion on its complexity, a model that contains independent variables related to: patient (age, APP), surgical procedure (tumour residue and complications) and actual diagnosis (tumor histotype).

7.5 Conclusions

Age is a variable that showed consistency across the three models in terms of adjustment across the three periods except model 3 for 12-month survival.

For the survival duration of 60 months almost all histotypes play a substantial and statistically significant role for this survival duration, especially histotypes 3,4 and 7 which show this influence by values of the beta coefficient of: ln HR=11 (CI95% from 1.2 to 100) for histotype 3 (CS); a coefficient ln HR=13 (CI95% from 1.5 to 115) for histotype 4 (CCC); and ln HR =12 (95% CI from 1.4 to 98) for histotype 7 (RC). These confidence intervals are very wide because the number of these histotypes is small. All models should be validated by prospective approach.

8. Research limits

As with any descriptive study, other types of studies of malignant pathology, there are numerous limitations in all the main phases of a research. It is important that these limits are recognized and highlighted so that they can be taken into account in further research [96].

9. Conclusions

The current immunohistochemical and molecular characterizations lead to the observation that several distinct nosological entities are aggregated in ovarian cancer and have determined the proposal of new pathogenic models.

We consider the introduction of immunohistochemical investigations into the diagnostic standards and, in selected cases, of molecular genomics to obtain a personalized profile.

We appreciate that under these conditions it is desirable to consider the evaluation of ovarian cancer treatments according to both the TNM / FIGO / AJCC staging and the subtypes characterized immunohistochemically and molecularly since 2005 - 2010.

With histopathological results according to histotype, HGSC was present in 63% of cases and has the worst outcome at 60 months (survival probability of 16%).

For other histopathological types that have shown even more unfavorable results, for example the tumour types RC *(Rare Carcinoma)* and CCC *(Clear Cell Carcinoma)*, the evaluation of the results of treatments with the aim of improving them is limited by the small number of cases, the results often being reported as clinical observations.

Ovarian cancer is a relatively rare disease and therefore it is important to collect a substantial amount of data classified according to histotype to advance the knowledge of this disease, being decisive the establishment of a collaborative effort of tertiary centers with standardized strategies and quality control of medical procedures.

A similar assessment of post-surgical survival for patients operated on in Romania would be necessary, this being possible only in the presence of a National Cancer Registry that would mention the course of the patients' malignancy and the results of the treatment.

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