ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 12, Issue, 01, pp.9603-9610, January, 2020

DOI: https://doi.org/10.24941/ijcr.37830.01.2020

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

TYPES, STAGING, AND MANAGEMENT OF EPITHELIAL OVARIAN CARCINOMA: A REVIEW OF THE LITERATURE

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ARTICLE INFO

Article History:
Received 12th October, 2019
Received in revised form
28th November, 2019
Accepted 09th December, 2019
Published online 30th January, 2020

Key Words:

Epithelial ovarian cancer, EOC, Cytoreduction, Debulking, Neoadjuvant, Chemotherapy.

ABSTRACT

Epithelial ovarian tumors have been reported to mostly come from the simple cuboidal epithelial covering of the ovaries, accounting for 75% of all ovarian tumors and 90-95% of ovarian malignancies. This literature review aims to summarize the evidence of types, staging and management of Epithelial Ovarian Carcinoma. Epithelial ovarian cancer (EOC) is responsible for the highest mortality rate among women secondary to gynecologic malignancy, with a low 5-year relative survival of only 44%. The possible explanations for such low survival rates are the high incidence of resistance towards the chemotherapeutic agents used in the management of EOC and the lack of consideration of the great degree of heterogeneity of epithelial ovarian cancers in the current standards of care. The current literature review highlights the latest perspectives of EOC including the identification of the various subtypes of EOC, the most practical staging system used, and the current therapeutic advancements for EOC.

Citation: ***Maryam Al-Zahrani.*** **2020.** "Types, Staging, and Management of Epithelial Ovarian Carcinoma: A Review of the Literature", *International Journal of Current Research*, 12, (01), 9603-9610.

INTRODUCTION

Ovarian cancer is identified as any malignant tumor that occurs within the ovarian tissues (Ring, Pakish *et al*. 2016). It is perceived as the eighth most frequent type of cancer in the women population worldwide. It is estimated that 225,500 cases have been diagnosed with ovarian cancer in 2008 (Jemal, Bray *et al*. 2011). Even though it has a low incidence rate, ovarian cancer is recognized as the seventh most common cause of cancer-related mortality in women, causing more than 140,000 deaths worldwide per year (Jemal, Bray *et al*. 2011). According to the presumed cells of origin, ovarian cancer can be categorized into epithelial ovarian cancer (EOC), ovarian germ cell tumor, and sex cord-stromal tumor. EOC is believed to derive from the epithelial covering of the outer surface of the ovary, accounting for approximately 95% of all cancers occurring in the ovaries (Quirk and Natarajan 2005). Furthermore, EOC is the most fatal subset among ovarian cancer; it is considered the primary cause of death in patients with gynecological malignancies (Auersperg, Wong *et al*. 2001). As EOC is recognized as the most dangerous and frequent type of ovarian cancer, EOC has been the main focus of most ovarian cancer research and it is the main scope of this current review. Owing to the current advances in the surgical and chemotherapeutic management of EOCs, the overall prognosis of these rare tumors are very favorable today, and the majority of patients tend to survive the disease without being affected by treatment-related adverse outcomes or toxicities, such as loss of fertility (Gershenson 2007). Even in the setting of advanced disease, these cases have a fair chance at being cured (MP 2002). Therefore, we conducted this research to review the recent advancements in the management of EOC.

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Screening Strategies for Epithelial Ovarian Cancer: EOC is characterized by the presentation of non-specific symptoms. The lack of reliable early screening methods makes the diagnosis of EOC at the more curable early stages more difficult. Moreover, it has been suggested in the literature that on average, EOCs have already progressed to a later stage up to 1 year prior to their diagnosis (Brown and Palmer 2009). Hence, based on the inverse correlation between survival and disease staging at the time of diagnosis, the ability to identify and detect early disease, in order to prevent its progression to invasive disease, may offer the most effective and practical method to save those patients. These screening methods should have the ability to identify the precursors of advanced-stage disease with both high levels of sensitivity and specificity, in order to become clinically useful and practical tools for detecting EOCs (Clarke-Pearson 2009). That being said, little is currently known regarding the early natural history of EOC. Therefore, efforts should be made to reach 50% or more sensitivity in identifying EOCs of early stages in normal-risk women. Accordingly, the identification of specific molecular markers of EOCs and the development of tools that can provide the required levels of sensitivity and specificity to

identify this low prevalence disease, pose a great challenge in clinical practice. At the present time, Cancer Antigen (CA-125) measurement, transvaginal ultrasonography, and pelvic examination are used as diagnostic measures for the detection of EOC. However, CA125 is the only recommended test to monitor the patients' response to therapy, as well as post-treatment outcomes in the case of recurrent disease (Sturgeon, Duffy *et al*. 2008). That being said, these proposed diagnostic measures have very limited clinical utility regarding the detection of early diseases, as they are commonly associated with false-positive and false-negative results (Schorge, Modesitt *et al*. 2010). Consequently, the resulting false observations will lead to unnecessary surgical interventions and could even cause serious complications. Meanwhile, the recently published Prostate, Lung, Colorectal, and Ovarian (PLCO) trial concluded that the use of CA123 and TVU as annual screening methods does not minimize ovarian cancer mortality in normal-risk women, but instead these tests result in a rise in unnecessary surgical interventions (Buys, Partridge *et al*. 2011). Based on the above-mentioned observations, one can summarize that the screening for EOC in the general population should not be carried out to minimize the risk of unnecessary interventions and costs. Screening for women at risk of EOC should only be offered in the context of a research study.

A Summary of Frequent and Infrequent Sub-types of Epithelial Ovarian Cancers: There are many histologic subtypes of ovarian cancers, the most frequent of which is serous carcinoma, followed by clear cell carcinoma (CC) and Endometrioid adenocarcinoma (EC), which are reported to have almost the same frequency (Ramalingam 2016). In the study by Seidman *et al*. (Seidman, Elsayed *et al*. 1993), it was noted that among 220 consecutive women with surface epithelial carcinoma, almost 80% of patients presented with intra-abdominal carcinomas of serous histology, especially when peritoneal carcinomas, carcinosarcomas, and mixed carcinomas with serous components were considered. Therefore, it is now well-recognized that serous carcinomas represent a great number of advanced-stage ovarian cancers. The second most-prevalent subtype has been proposed to be variable between CCC and EC (Seidman, Horkayne-Szakaly *et al*. 2004). In another study carried out by Seidman *et al*. (Seidman, Horkayne-Szakaly *et al*. 2004), the authors noted that CCC was the second most common ovarian cancer followed by EC. The overlapping characters and features between the high-grade serous carcinoma (HGSC) and EC could be a possible explanation for such differences.

Previously, primary mucinous carcinomas (MUC) of the ovaries were considered the second most prevalent epithelial ovarian tumors, however, they are now known to be much less frequent, as the majority of these cancers represent metastases (Seidman, Kurman *et al*. 2003). Recognition of the morphologic spectrum of the metastatic cancers in the ovary with the use of immunohistochemistry has resulted in a significant reduction in the reported incidence rates of primary ovarian MUCs (Seidman, Kurman *et al*. 2003 Herein, we will point out the variations between the various histologic subtypes of epithelial tumors of the ovaries as regards their immunophenotypic profiles (Table 1). We will also point out the immunophenotypic features of the MUC of the ovaries (Table 2). Less frequent types of epithelial ovarian cancers include squamous cell carcinoma (SCC), papillary thyroid cancer, sebaceous carcinoma, and carcinoid tumors that are typically correlated with mature cystic teratomas; we will not discuss these types of tumors any further in this review, because they are beyond the scope of our research (Ramalingam 2016).

Differentiation of Epithelial Ovarian Cancer Sub-Types Based on Imaging and Clinical Data: Primary EOCs can be categorized into subtypes of serous, mucinous, clear cell, and endometrioid carcinomas (Kurman, Carcangiu *et al*. 2014). Recently, estimation of the subtypes of ovarian carcinomas based on various clinical data and imaging modalities has been implicated to be of practical value in the differentiation of the various subtypes of EOCs. Tanaka *et al*. (Tanaka, Okada *et al*. 2016) used the clinical and imaging features obtained from the records of 125 consecutive patients with primary ovarian cancer in a multivariate model to differentiate between various types of EOCs. The authors incorporated various clinical and imaging variables in their model, including bilateralism, tumor morphology and diameter, solid portion ratio, relative signal intensity on T2-weighted images (T2WI) and diffusion-weighted images (DWI), contrast ratio, endometriosis on MRI and the calcification, peritoneal dissemination, lymph nodal metastasis, clinical staging, thromboembolism on CT, various tumor markers, and serum calcium levels (Table 3). Serous carcinomas had a significantly strong correlation with bilateral diseases ($p= 0.04$), smaller tumor size ($p= 0.001$), higher signal intensity on DWI, and restricted diffusion ($p= 0.016$), especially when compared with clear cell type. Moreover, they tended to predominantly present as solid masses, however, this finding did not reach statistical significance in the multivariate model (Table 3). In addition, the presentation with hypercalcemia was noted to be observed less frequently in this type of ovarian carcinoma ($p= 0.013$). On the other hand, 12 of the 13 cases with MUC of the ovary presented with multilocular cystic masses, however, this difference was not statistically significant. MUC of the ovary has significantly higher levels of CA19-9 ($p= 0.009$) and a smaller ratio of the solid portion ($p= 0.039$). In the same context, CCC tended to present as a unilateral disease ($p= 0.000$) with larger ratio of the solid portion ($p= 0.031$) in younger women ($p= 0.002$) as well as hypercalcemia ($p= 0.011$). Meanwhile, intraperitoneal dissemination was the only variable that showed a less significant correlation with EC ($p= 0.051$).

Management of Epithelial Ovarian Cancer Based on FIGO Staging Criteria: The staging criteria of EOCs include a standard surgical staging, which is comprised of peritoneal washings, total hysterectomy, and bilateral salpingo-oophorectomy, an inspection of all abdominal organs and peritoneal surfaces, sampling of suspected regions of biopsy, total omentectomy, and para-aortic lymphadenectomy. Following a complete standard surgical staging, the International Federation of Gynecology and Obstetrics (FIGO) staging system for ovarian carcinomas should be applied in order to initiate the most appropriate management approach (Supplementary Table 1) (Mutch and Prat 2014). At the present time, the standard management of EOC involves the correct surgical staging in early stages, while complete tumor cytoreduction followed by platinum and taxane-based chemotherapy is the preferable approach in advanced stages (Romanidis, Nagorni *et al*. 2014). Meanwhile, if primary cytoreduction was is considered appropriate due to extensive disease or poor patient condition, patients would be treated with neoadjuvant chemotherapy followed by interval debulking surgery and adjuvant chemotherapy (Martin-

Camean, Delgado-Sanchez *et al*. 2016). Primary debulking surgery, complete macroscopic tumor excision, includes splenectomy, diaphragmatic and liver resection, resection of the intestines and any other affected abdominal organ if needed to reach complete cytoreduction (Zapardiel, Peiretti *et al*. 2011, Peiretti, Bristow *et al*. 2012). The definition of optimal and suboptimal cytoreduction varies across studies, making the differentiation between them very difficult. Cytoreduction can be categorized into three classes related to patient survival: no macroscopic disease, macroscopic disease up to 1 cm, and macroscopic disease >1 cm. These three categories can be further referred to as complete resection, minimal residual, and gross residual, respectively (Zapardiel and Morrow 2011). There are three proposed types of surgical management of EOCs in the literature. The first is primary cytoreduction, which is approached to remove the higher tumor mass prior to any other interventions. The second is interval surgery, which is attempted in patients who would benefit from neoadjuvant chemotherapy prior to surgical management. The third type is secondary cytoreduction, which is the surgical management of choice in recurrent cases. In the case of standard surgical staging, the laparoscopic approach seems preferable than the laparotomy approach in providing less morbidity and mortality, resulting in fewer adhesions-preferred in cases of fertility preservation, reducing in-hospital stay, and accelerating recovery (Colomer, Jimenez *et al*. 2008). All of these beneficial outcomes allow the patient to initiate chemotherapy treatment earlier.

Proposed Therapeutic Interventions of Epithelial Ovarian Cancer in the Literature

Primary cytoreduction: Primary debulking surgery followed by platinum and taxane chemotherapy is considered the optimum management approach in cases of advanced EOC with the curative intention (Oncoguía 2014).On the other hand, cytoreduction often includes a certain number of surgeries, such as bowel resection, especially the rectosigmoid (which is important in 30% to 50% of patients with advanced EOC), diaphragm stripping, peritoneal resection, splenectomy, partial pancreatic or liver resection, cholecystectomy, hysterectomy, and salpingo-oophorectomy (Zapardiel, Peiretti *et al*. 2011, Peiretti, Bristow *et al*. 2012, Oncoguía 2014, Romanidis, Nagorni *et al*. 2014). The extension of the procedure carried out during the time of primary cytoreduction surgery is often dependent upon the location and extent of the disease, surgeon's expertise, medical setting equipment, and the patient's general health condition, as well as other comorbidities (Oncoguía 2014, Narasimhulu, Khoury-Collado *et al*. 2015). Residual tumor following surgery and sensibility to platinum chemotherapy are considered independent predictive factors of patients' survival (Bristow and Chi 2006, Colomer, Jimenez *et al*. 2008, Narasimhulu, Khoury-Collado *et al*. 2015). Meanwhile, complete resection during primary debulking surgery is perceived as the most critical independent prognostic variable in cases of advanced ovarian cancer (Vergote, Tropé *et al*. 2010, Elattar, Bryant *et al*. 2011, Oncoguía 2014, Romanidis, Nagorni *et al*. 2014, Rutten, van de Vrie *et al*. 2015). Survival is inversely correlated with residual disease following surgery. However, recent reports revealed a rise in survival rates in patients with the residual disease under 1 cm (Vergote, Tropé *et al*. 2010, Elattar, Bryant *et al*. 2011, Oncoguía 2014, Nick, Coleman *et al*. 2015). Multiple clinical trials conducted by the Gynecological Oncologic Group (GOG) indicate that RO, no cancer cell observed microscopically at the resection margin, resection resulted in the longest median overall survival (Nick, Coleman *et al*. 2015). European prospective randomized clinical trials implicate favorable outcomes in patients with complete cytoreduction (99.1 months in R0 resection vs 36.2 months in patients with residual disease < 1cm (Nick, Coleman *et al*. 2015). Debulking surgery offers the removal of poorly-vascularized tumors, which are poorly-accessible by the conventional chemotherapeutic agents. It also helps in the removal of chemo-resistant clones, which are less-responsive to chemotherapy (Narasimhulu, Khoury-Collado *et al*. 2015). The morbidity correlated with debulking surgery does not result in increased mortality. In fact, it improves overall survival rates (Narasimhulu, Khoury-Collado *et al*. 2015). Patients with residual disease, even <1 cm, are reported to have a worse prognosis than R0 patients. Meanwhile, patients with the highest preoperative disease burden have shorter progression-free survival and overall survival, compared with those of moderate or low disease burden (Horowitz, Miller *et al*. 2015). This relationship was maintained in R0 patients.

Going in line with other published research, this analysis revealed significant overall survival and progression-free survival outcomes in favor of R0 over residual disease < 1cm. This finding highlights the need for more aggressive surgery if R0 can be achieved. That being said, even in these cases, the initial disease burden remained a significant prognosticator. R0 can be correlated with wide variations in the outcome depending on the disease burden (Horowitz, Miller *et al*. 2015). In a certain set of patients with advanced EOCs undergo debulking surgery, however, complete cytoreduction could not be achieved. This results in a further increase in morbidity without improvement in the overall survival. Multiple meta-analyses, conducted in the United States, revealed an optimal cytoreduction rate of 42% (Nick, Coleman *et al*. 2015). On the other hand, patients with suboptimal outcomes will not witness an improvement in survival but will suffer higher morbidity (Gomez-Hidalgo, Martinez-Cannon *et al*. 2015, Nick, Coleman *et al*. 2015, Rutten, van de Vrie *et al*. 2015). Some authors proposed various criteria to predict the outcomes of cytoreduction, which are based upon serum biomarker levels, preoperative imaging modalities, and laparoscopic-based scores (Gomez-Hidalgo, Martinez-Cannon *et al*. 2015, Nick, Coleman *et al*. 2015, Rutten, van de Vrie *et al*. 2015). Suidan *et al*. (Suidan, Ramirez *et al*. 2014) identified three clinical and six radiological features correlated with suboptimal cytoreduction. These features included age ≥ 60 years, CA-125 ≥ 500 U/mL, ASA 3-4, retroperitoneal lymph nodes above the renal hilum (including supra-diaphragmatic nodes) > 1cm, diffuse small bowel adhesions or thickening, peri-splenic lesions >1 cm, small bowel mesentery lesion > 1cm, lesions of the root of the superior mesenteric artery > 1cm, and lesser sac lesion > 1cm. Some factors had more predictive capability than others; lesser sac lesions >1 cm revealed a predictive value score of 4, which was significantly higher than other proposed criteria. These findings imply that ovarian carcinomas extensive enough to reach the lesser sac may have already reached other anatomic locations as well. Meanwhile, Fotopoulou *et al*. (Fotopoulou, Richter *et al*. 2010) proposed that patients with primary EOC are more likely to have optimal debulking outcomes if the tumor has not extended beyond four abdominal fields. Moreover, the authors reported that the analysis did not reveal any significant association between CA-125 levels, ascites, or the FIGO staging system with the resectability of the disease.

Table 1. Immunophenotypical profiles of the most common subtypes of Epithelial Cancers of the Ovary

	Histologic Subtypes				
Biomarker	HGSC	LGSC	CCC	EC	MUC
PAX8	Positive	Positive	Positive	Positive	Focal positive
CK7	Positive	Positive	Positive	Positive	Positive
CK20	Negative	Negative	Negative	Negative	Focal positive
ER	Positive	Positive	Negative	Positive	Focal positive/negative
WT1	Positive	Positive	Negative	Negative	Negative
Napsin A	Negative/Positive	Negative	Negative	Negative/Positive	Negative
HNF1 β	Negative/Positive	Negative	Positive	Negative/Positive	Negative
P53	Diffuse strong positivity	Wild-type	Wild-type/Diffuse	Wild-type	Wild-type
CDX2	Negative	Negative	Negative	Positive in Squamous morules	Positive/Negative
P16	Diffusely positive	Patchy positive	Patchy or diffuse	Can be patchy	Patchy
Ki-67	High	Low	N/A	N/A	N/A

CCC: Clear cell carcinoma; CDX2: caudal-type homeobox 2; CK2: cytokeratin 7; CK20: cytokeratin 20; EC: Endometrioid carcinoma; ER: Estrogen receptor; HGSC: High-grade serous carcinoma; LGSC: Low-grade serous carcinoma; HNF1 β: Hepatocyte nuclear factor-1 beta; MUC: Mucinous carcinoma; N/A: Not applicable; PAX8: paired box gene 8; WT1: Wilms tumor gene 1. This Table is adapted from the study of Ramalingam (2016).

Table 2. Immunophenotypical features of MUC of the ovary in comparison to other MUC of other organs

Immunohistochemical Stain	Ovarian MUC	Lower GI tract, including the Appendix	Pancreaticobiliary Tract	Stomach
PAX8	Positive	Negative	Negative	Negative
CK7	Positive	Negative	Positive	Positive
CK20	Negative/Focal positive	Positive	Negative	Negative
ER	Positive/Negative	Negative	Negative	Negative
DPC4	Intact Expression	Intact expression	Loss of expression	Intact expression

CK7: Cytokeratin 7; CK20: Cytokeratin 20; DPC4: Deleted in pancreatic carcinoma locus 4; ER: Estrogen receptor; PAX8: paired box gene 8. Adapted from the study of Ramalingam (2016).

Table 3. Differentiation of EOC subtypes based on the incorporation of various imaging and clinical variables in a Multivariate Model

Ovarian Cancer Subtype	Significant Variables from the Univariate Model	B	P-value	OR	95% CI of OR
Serous adenocarcinoma	Age	.086	.040	1.090	1.004-1.184
	Largest tumor diameter	-.038	.001	.963	.942-.984
	DWI signal ratio	1.544	.016	4.684	1.329-16.510
	Bilateralism	2.952	.001	19.146	3.149-116.424
	Hypercalcemia	-3.804	.013	.022	.001-.452
Mucinous adenocarcinoma	Ratio of the solid portion	-11.603	.039	.000	.000-.562
	Calcification	1.487	.071	4.425	.882-22.195
	CA19-9	.002	.009	1.002	1.00-1.003
Clear cell adenocarcinoma	Age	-.099	.002	.906	.850-965
	Largest solid portion diameter	.021	.031	1.021	1.002-1.040
	Bilateralism	-3.00	.000	.050	.010-.258
	Hypercalcemia	2.709	.011	15.009	1.859-121.174
Endometrioid adenocarcinoma	Dissemination	-.916	.051	.400	.160-1.003

OR: Odd's ratio; DWI: Diffusion-weighted images; CI: Confidence interval. This Table has been adapted from the study of Tanaka *et al*. (2016).

Supplementary Table 1. FIGO 2014 Ovarian Cancer Staging

STAGE I: Tumor confined to the ovaries		
IA	Tumor limited to 1 ovary, capsule intact, no tumor on the surface, negative washings	
IB	Tumor involves both ovaries otherwise like IA	
IC: Tumor limited to 1 or both ovaries		
IC1	Surgical spill	
IC2	Capsule rupture before surgery or tumor on ovarian surface	
IC3	Malignant cells in the ascites or peritoneal washings	
STAGE II: Tumor involves 1 or both ovaries with a pelvic extension (below the pelvic brim) or primary peritoneal cancer		
IIA	Extension and/or implant on the uterus and/or fallopian tubes	
IIB	Extension to other pelvic intraperitoneal tissues	
STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes		
IIIA: Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis		
IIIA	Positive retroperitoneal lymph nodes only	
	IIIA1 (i)	Metastasis ≤ 10mm
	IIIA1 (ii)	Metastasis > 10mm
IIIA2	Microscopic, extra-pelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
IIIB	Macroscopic, extra-pelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to the capsule of liver/spleen	
IIIC	Macroscopic, extra-pelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to the capsule of liver/spleen	
STAGE IV: Distant metastasis excluding peritoneal metastasis		
IVA	Pleural effusion with positive cytology	
IBV	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

Supplementary Table 2. Comparison of the outcomes of primary debulking surgery in comparison with neoadjuvant chemotherapy

	Primary Debulking Surgery	Neoadjuvant Chemotherapy
Number of cases	336	334
Age: Median (range)	62 (25-86)	63 (33-81)
Stage	257 (76.5%)	253 (75.7%)
IIIC	77 (22.9%)	81 (24.3%)
IV	2 (0.6%)	0 (0%)
PFS	12 months	12 months
OS	29 months	30 months

PFS: Progression-free survival; OS: Overall survival. Adapted from the study of Vergote *et al*. (2010).

A set of surgical approaches, to reach complete cytoreduction, have also been described in the literature. Implants ablation, using argon beam coagulator (ABC), has been described as an effective technique when used in conjunction with traditional surgery. Furthermore, this technique has been reported to significantly increase the feasibility of reaching optimal disease status and complete removal of all visible tumors in patients with macroscopic metastatic ovarian carcinomas (Bristow and Montz 2001, Renaud and Sebastianelli 2013). The degree of ABC tissue destruction and hemostasis is proportionate to the amount of power setting as well as the duration of application. This technique, in particular, is of great therapeutic value in removing all visible tumors located in the gastro-colic ligament, lesser sac, bowel mesentery, abdominal peritoneum, and pelvis (Bristow and Montz 2001). In addition, the disease above the diaphragm poses a challenging issue. Diaphragmatic surgery is the major procedure approached in upper abdominal cytoreductive surgery. Thoracoscopy-dependent thoracic exploration includes video-assisted thoracoscopic surgery (VATS) and trans-diaphragmatic thoracoscopy. A recent study conducted by Spirtos *et al*. (Fleury, Kushnir *et al*. 2012) reported data from the Women's Cancer Centre at the European Society of Gynecology Oncology (ESGO) on 57 women who underwent trans-diaphragmatic thoracoscopy at the time of surgery for apparent stage IIIC EOC, but without positive chest radiographs or computed tomography (CT) scans.

Almost half of the patients (40%) were found to have disease reaching the parietal or visceral pleura. All of the patients presenting with the pleural disease showed involvement of the diaphragm peritoneum, while over 90% of those patients had positive retroperitoneal lymph nodes. The majority of masses (88%) found above the level of the diaphragm were small (< 1cm) and could be ablated or resected. Terauchi *et al*. (Terauchi, Kobayashi *et al*. 2009) carried out a prospective study in patients with advanced EOCs with diaphragmatic metastases in order to evaluate trans-diaphragmatic thoracoscopic-assisted pleural biopsy as well as intrathoracic washings. A total of ten women with stage IIIC ovarian cancer with prominent diaphragmatic lesions were identified. Thirty-percent of the patients had metastatic lesions as well as positive cytology within the thoracic cavity, whereas, 20% had positive biopsy results and an additional 20% of patients had positive cytology. Meanwhile, 70% of patients were upstaged to stage IV. On the other hand, Yin *et al*. (Yin, Jiang *et al*. 2015) investigated the feasibility of trans-diaphragmatic thoracic exploration (TDTE) without the use of thoracoscopy. TDTE is indicated in patients with untapped pleural effusion, full-depth diaphragmatic invasion and positive pleural disease on computed tomography.

Neoadjuvant chemotherapy and interval surgery: Even though cytoreduction is considered the best approach for the management of advanced EOC, there are certain factors that make it hard to reach complete cytoreduction in a particular subset of patients. Therefore, patients with poor performance status and difficult-to-resect disease are appropriate candidates for neoadjuvant chemotherapeutic approach. That being said, there is no validated uniformed selection criterion for immediate referral to the neoadjuvant chemotherapeutic approach (Bristow and Chi 2006, Narasimhulu, Khoury-Collado *et al*. 2015). This has been noted in the study of Aletti *et al*. (Aletti, Eisenhauer *et al*. 2011) who identified a set of patients in whom the benefits of aggressive debulking surgery did not outweigh the risks. This very high-risk population can be detected based on the presence of three criteria: high tumor dissemination or stage IV, poor performance status (ASA ≥3), poor nutritional status (preoperative albumin level <3.0 g/dL) or age ≥ 75 years. In that group of patients, the resulting morbidity was too high to justify aggressive surgical efforts, where the median overall survival in this set of patients was only 17 months. In this study, the neoadjuvant chemotherapeutic approached was proposed to be the most appropriate option for this small set of patients. The role of neoadjuvant chemotherapy is to result in better perioperative morbidity as well as to shrink the tumor to achieve optimal outcomes (Oza, Cook *et al*. 2015). Furthermore, it allows for the selection of platinum-resistant cases (Bristow and Chi 2006). However, the potential limiting factor in this approach is the formation of fibrosis, which might make the surgical approach more difficult (Vergote, Tropé *et al*. 2010). Contradictory reports regarding the superiority of the neoadjuvant approach to primary cytoreduction are observed in the literature. A meta-analysis including 835 patients revealed that the use of the neoadjuvant approach was associated with inferior overall survival compared to initial surgery. It was noted that each 10% increase in cytoreduction was correlated with an increase in median survival by 1.9 months (Bristow and Chi 2006). Administration of neoadjuvant chemotherapy is not reported in the literature as primary cytoreduction. There are two randomized, controlled, clinical trials conducted by the European Organization for Research and Treatment of Cancer Research (EORTC) and the Medical Research Council (MRC) Clinical Trials Unit; both trials showed no significant differences in overall survival between the studies groups of primary cytoreduction surgery and the neoadjuvant chemotherapy arm prior to surgery. However, cases with complete resection during primary cytoreduction had an improvement in overall survival (Nick, Coleman *et al*. 2015). On the other hand, Vergote *et al*. (Vergote, Tropé *et al*. 2010) noted no differences in mortality between the studied groups that underwent incomplete primary cytoreductive surgery and the arm that was administered neoadjuvant chemotherapy prior to surgery. The median overall survival was 29 and 30 months, respectively. Meanwhile, the median progression-free survival was 12 months for both groups (Supplementary Table 2). The decision whether a case with advanced EOC (stage IIIC or IV) better receive debulking surgery or neoadjuvant chemotherapy followed by interval surgery is thought to be made based on

patients' characteristics, surgeon's experience, CT and serum biomarkers levels, and laparoscopy (Gomez-Hidalgo, Martinez-Cannon *et al*. 2015, Nick, Coleman *et al*. 2015, Rutten, van de Vrie *et al*. 2015). Based on the aforementioned observations, it is believed that upfront maximal cytoreduction is still considered the standard management approach, even though further research should be focused on proposing selection criteria of the most appropriate management approach in every single case in order to receive the optimal outcomes, as well as how to determine if the patient can benefit from the neoadjuvant chemotherapeutic approach and not the cytoreductive approach.

Secondary cytoreduction

Approximately, 60% of cases with epithelial ovarian cancer will have a recurrence. Life expectancy in cases of EOC is thought to lie between 12 and 18 months (Fagotti, Fanfani *et al*. 2010), however, it varies depending upon the characteristics of the disease (Vargas-Hernandez, Moreno-Eutimio *et al*. 2014). Based upon the time of recurrence, patients can be categorized into four different types: cases that progress during the chemotherapy treatment period, known as platinum-refractory cases; cases that progress during the 1st six months after initiating chemotherapy, known as platinum-resistant women; cases that progress after 1 year of treatment, the platinum-sensitive women; cases that progress between 6-12 months, with intermediate sensibility towards platinum (Oncoguía 2014). A predicting system, known as the ROVAR scoring system, for the recurrence of EOC after primary treatment with surgical cytoreduction and platinum-based chemotherapy has been proposed in the literature Rizzuto, Stavraka *et al*. 2015). It includes four variables, such as tumor staging and grade at diagnosis, CA-125 serum levels, and the presence of residual disease n CT scan following chemotherapy. The ROVAR score has a proposed sensitivity and specificity of 94% and 61%, respectively. However, this scoring system has not been yet validated by other researchers. The theoretical values of secondary cytoreduction aim at minimizing the number of tumor cells so that chemotherapy would be more likely to be beneficial, removal of poorly-vascularized tumors, and eliminating pharmacologic sanctuaries (Hauspy and Covens 2007). It has been noted that the response rate to 2nd line chemotherapeutic regimens after recurrence for platinum-sensitive patients is 30% or more, while in the case of platinum-resistant cases, the response rate was noted to be lower (10-25%) (Vargas-Hernandez, Moreno-Eutimio *et al*. 2014).

Conservative treatment and fertility preservation: It's reported that 3-17% of all EOCs occur in women under the age of 40 (47). As a consequence, there are many cases in their reproductive age with EOC who have not fulfilled their reproductive needs. In an attempt to give a solution to this issue, fertility-sparing regimens have been successfully attempted in a certain set of patients with early EOC. However, to date, there are no proposed criteria for the selection of patients for conservative surgery. Based on the ESGO guidelines, patients should fulfill certain criteria: < 40 years of age, referral to a tertiary healthcare center, compliance with a close follow-up during and after treatment to be able to detect contralateral ovarian recurrence or uterine malignancy, and undergoing appropriate staging and pathological testing, which must be performed by a designated gynecologic pathologist (Terauchi, Kobayashi *et al*. 2009).

Meanwhile, patients with grade 3 EOC should not be considered for conservative surgery. The proposed fertility-sparing surgery includes unilateral salpingo-oophorectomy on the side of the EOC with complete standard surgical staging, including peritoneal sampling, pelvic and para-aortic lymph node removal, and omentectomy (Zapardiel, Diestro *et al*. 2014). In these cases, the laparoscopic approach offers better results in terms of fewer adhesions. It is recognized that the chemotherapeutic approach compromises the function of the ovaries. Carboplatin and paclitaxel are reported to be less toxic to the ovaries than other cytostatic drugs (Zapardiel, Diestro *et al*. 2014). Various reports reveal many positive outcomes related to the use of fertility-sparing surgeries with a conception rate from 60% - 100%, while abortion was noted in less than 30% of cases (Colomer, Jimenez *et al*. 2008, Zapardiel, Diestro *et al*. 2014). According to the aforementioned observations, conservative treatment of an early EOC offers a practical opportunity for women in their reproductive age to fulfill their reproductive needs.

Intraperitoneal chemotherapy: Intraperitoneal chemotherapy (IP) is considered a step in the treatment plan of patients with advanced EOC, who underwent complete cytoreduction. This therapy aims at exposing the peritoneal cavity, the main site of the disease in EOC, to a sustained, high concentration of chemotherapeutics, while normal tissues are relatively spared. IP chemotherapy offers a maximal drug delivery to the tumor site without increasing the systemic adverse effects of the used agents (Armstrong, Bundy *et al*. 2006). Armstrong *et al*. (Armstrong, Bundy *et al*. 2006) investigated two sets of patients with stage-III ovarian cancer following optimal debulking surgery. The first group was given intravenous paclitaxel and cisplatin, while the other group received intravenous paclitaxel as well as intraperitoneal cisplatin and paclitaxel. The authors noted that the intraperitoneal study arm had a significantly higher mean duration of progression-free survival and overall survival. However, grades 3 and 4 pain and fatigue, as well as several hematological, gastrointestinal, metabolic, and neurologic toxic effects, were also more prevalent in this study arm. Moreover, patients in the IP chemotherapy arm had an overall worse quality of life (QOL) prior to completing four cycles of treatment and 3-6 weeks after treatment. In the same context, Tewari *et al*. (Tewari, Java *et al*. 2015) examined patients with stage-III EOC or peritoneal cancer without residual disease > 1cm following surgery. The authors noted a significantly higher median progression-free survival in patients treated with intravenous (IV) carboplatin and paclitaxel followed by IP cisplatin in comparison with patients treated with IV paclitaxel and cisplatin alone (25 vs 20 months; P =0.019), respectively.

The overall survival was also significantly higher in the IP chemotherapy arm with a median of 61.8 months in comparison with a median OS of 51.4 months in the IV group (P =0.042). Moreover, the IP study arm was associated with a 21% reduction in the risk of progression and a 23% reduction in the risk of death. In cases with stage-III EOC who underwent suboptimal cytoreduction surgery followed by IP paclitaxel/platinum chemotherapy; they had a median progression-free survival of 24.9 months in comparison to 20.2 months in patients who were treated with IV chemotherapy. The median OS in patients in the IP chemotherapy arm was 61.8 months compared to 50.9 months in the IV chemotherapy arm (Ziebarth, Landen *et al*. 2012). It was also noted that the residual disease following surgery was an independent

predictor of progression-free survival, where the progression-free survival and OS in patients with residual disease (0.6 – 1.0 cm) were reduced. Furthermore, the literature highlights the superiority of IP chemotherapy compared to IP chemotherapy under hyperthermic conditions (HIPEC). In conclusion, the aforementioned observations highlight the considerable efforts that are being applied collectively in order to improve the therapeutic strategies directed against epithelial ovarian cancer. More research is warranted in the clinical setting to confirm the reported findings as well as to give a clearer understanding of how patients are selected to receive each of the proposed therapeutic approaches and regimens.

Acknowledgments: None

Funding: None

Conflict of Interest: The authors declare no conflict of interest

Key Points

- Epithelial ovarian tumors account for 90-95% of ovarian malignancies.
- Epithelial ovarian cancer (EOC) has a low 5-year relative survival of only 44%.
- Chemotherapy resistance and absence of tailored strategies explain mortality rates.

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