

## Original Research Article

### **Does hormonal status affect outcome of aromatase inhibitor maintenance post-adjuvant chemotherapy in high grade serous ovarian cancer (HGSOC)? Single center experience**

#### **Abstract**

**Background:** Epithelial ovarian cancer (EOC) is a hormone-related malignancy where receptor status serves as a prognostic factor. While the role of molecular targets, including estrogen receptor (ER) and progesterone receptor (PgR), in predicting tumor response is debated, studies suggest hormonal therapy may benefit advanced EOC patients. However, its efficacy based on tumor characteristics and specific agents remains unclear. We hypothesized that endocrine therapy could serve as maintenance treatment for ER/PgR-positive FIGO stage III/IV high-grade serous ovarian cancer (HGSOC) after debulking surgery and adjuvant chemotherapy, particularly in resource-limited settings where other maintenance options are inaccessible. **Methods:** This prospective, phase II randomized clinical study evaluated the safety and efficacy of maintenance endocrine therapy using aromatase inhibitors (AIs), letrozole (2.5 mg daily) administered off-label. Patients received treatment for up to five years or until experiencing adverse effects, symptomatic recurrence, or requiring further chemotherapy. Correlations with ER and PgR immunohistochemistry were assessed. **Results:** A total of 84 HGSOC patients underwent debulking surgery (53 with prior neoadjuvant chemotherapy) followed by adjuvant platinum-based chemotherapy. Participants were randomized (2:1) to either AI maintenance (n=56, 66.7%) or observation. Median treatment duration was 13 months (range: 2–26), with no adverse events necessitating discontinuation. No significant differences were observed in relapse rates or disease-free survival between the two groups. **Conclusions:** Maintenance endocrine therapy after debulking surgery and chemotherapy in HGSOC, regardless of receptor status, does not provide significant benefit despite its low cost and manageable toxicity profile in resource-limited settings. **Keywords:** HGSOC, aromatase inhibitor, ER, PgR, ovarian cancer, endocrine therapy.

#### **Introduction**

Epithelial ovarian cancer (EOC) ranks as the seventh most prevalent cancer and the eighth leading cause of cancer-related deaths among women globally. According to the World Health Organization, approximately 60% of ovarian cancer cases are diagnosed at advanced stages (1). Despite advancements in treatment, a recent meta-analysis revealed that the five-year overall survival rate for ovarian cancer has remained relatively unchanged since 1980, with the Surveillance, Epidemiology, and End Results (SEER) database reporting a survival rate of 47.4% for the period 2008–2014 (2).

Innovative treatments, including anti-angiogenesis agents and PARP inhibitors, have demonstrated significant promise in primary and recurrent ovarian cancer management. Bevacizumab, a VEGF-targeting antibody, has shown efficacy in improving progression-free survival (PFS) and overall survival (OS) in high-risk cases, albeit at high costs (3,4). Similarly, PARP inhibitors like olaparib, rucaparib, and niraparib have been approved for use in BRCA-

mutated ovarian cancer in various clinical settings (5). However, the need for cost-effective and well-tolerated maintenance therapies remains pressing (6).

Hormonal pathways, particularly those involving estrogen and progesterone receptors (ER and PgR), play a crucial role in ovarian cancer progression. Estrogen signaling influences VEGF production and tumor-endothelial cell migration, while PgR activity has been linked to apoptosis and cell cycle arrest in ovarian cancer cells (7,8). Research has shown that high PgR expression correlates with improved survival in high-grade serous ovarian cancer (HGSOC), making endocrine therapy a potential maintenance option (9).

Although studies have demonstrated the efficacy of hormonal treatments like letrozole and tamoxifen in specific ovarian cancer subtypes, the role of ER and PgR as predictive markers for endocrine therapy remains debated (10,11). Data from a prospective study in HGSOC suggested that letrozole maintenance therapy significantly improved recurrence-free survival (RFS) compared to observation, particularly when initiated within three months post-adjuvant chemotherapy (12,13). Despite these findings, prospective trials investigating endocrine therapy as a maintenance strategy in ER/PgR-positive HGSOC are scarce.

We hypothesize that endocrine therapy could serve as an effective and affordable maintenance option for ER/PgR-positive HGSOC, particularly in resource-limited settings where alternatives like bevacizumab and PARP inhibitors may be unavailable. This study aims to evaluate the impact of hormonal status on the outcomes of aromatase inhibitor maintenance therapy post-adjuvant chemotherapy in HGSOC.

### **Patients and methods:**

This prospective, phase II randomized open-label clinical trial was conducted to evaluate the efficacy and safety of maintenance endocrine therapy compared to observation in patients with ER/PR-positive FIGO stage III/IV high-grade serous ovarian cancer (HGSOC). Participants were randomized to receive either maintenance aromatase inhibitors (AIs) post-debulking surgery and adjuvant chemotherapy or no additional treatment. Outcomes were correlated with ER/PR expression assessed via immunohistochemistry (IHC). The study was approved from ethical committee and informed consent was taken from all participants after full explanation about the study and their right to withdraw at any time if they wish. **Inclusion Criteria:** Women aged 18–80 years with histologically confirmed FIGO stage III/IV HGSOC, ER/PR-positive status ( $\geq 1\%$  nuclear staining on IHC), ECOG performance status  $\leq 2$  and completion of at least 4 cycles of platinum-based chemotherapy. **Exclusion Criteria:** Age  $> 80$  years, poor performance status, comorbidities, active infections, pregnancy, or lactation, Previous use of tamoxifen or AIs or contraindications to endocrine therapy. All patients underwent the following procedures: comprehensive history collection, standard physical examination, and routine baseline laboratory tests, including tumor markers such as CEA and CA 125, which were retested when necessary. A radiological assessment was performed, including baseline computed tomography (CT) scans of the chest, abdomen, and pelvis after the conclusion of adjuvant chemotherapy and prior to the initiation of adjuvant aromatase inhibitor (AI) treatment, with additional scans as needed. For pathological evaluation, paraffin blocks from selected cases were obtained from the oncology center's pathology department archive at Mansoura University. Tissue sections, sliced to a

thickness of 4  $\mu\text{m}$ , were stained using the ROCH automatic immunohistochemistry instrument (VENTANA BenchMark GX), employing monoclonal antibodies for estrogen receptor (ER) and progesterone receptor (PR) (Rabbit monoclonal Primary Antibody REF 790-4324 for ER and REF 790-2223 for PR). In immunohistochemical evaluation, ER and PR were deemed positive if at least 1% of tumor cell nuclei exhibited nuclear positivity, which included weak, moderate, and strong staining. The histoscore (H-score) was calculated by multiplying the staining intensity (ranging from 0 for absent to 3 for intense) by the percentage of cells showing each staining level, resulting in a maximum total score of 300 for both ER and PR IHC assessments across all cases. Newly diagnosed patients with high-grade serous ovarian cancer (HGSOC) at FIGO stages III and IV, who have estrogen receptor (ER) and progesterone receptor (PgR) positive tumors, were randomized into two groups. One group received off-label maintenance therapy with aromatase inhibitors (AIs) as Letrozole at 2.5 mg daily - following debulking surgery and adjuvant platinum-based chemotherapy. Patients continued this treatment until they experienced significant side effects or symptomatic recurrence that necessitated further chemotherapy. The alternative group consisted of patients opting for only monitoring without any maintenance therapy. The AI group was compared to those in the non-AI group, who chose solely observation without maintenance treatment. Patient evaluations included CT imaging and CA 125 measurements, conducted only when clinically warranted. Monitoring for side effects during anti-hormonal therapy using AIs was carried out with particular attention to potential bone density loss. This was aligned with protocols commonly applied in breast cancer cases, involving regular DEXA scans and the addition of Vitamin D, calcium supplements, or bisphosphonates when necessary. **Primary Objective:** Disease-free survival (DFS) and relapse rate (RR). **Secondary Objective:** Toxicity and tolerability of AIs. This trial seeks to provide insight into the role of endocrine maintenance therapy in improving outcomes for patients with advanced ER/PR-positive HGSOC, potentially informing future treatment guidelines. DFS was defined as the time from randomization to recurrence of tumor or death, and it is typically used in the adjuvant treatment setting. Relapse free survival (RFS) was defined as the length of time after finishing primary adjuvant chemotherapy until relapse defined by progression on a CT scan.

#### Statistical analysis:

Data were analyzed on a personal computer running IBM SPSS© for windows (Statistical Package for Social Scientists) Release 20. A two-tailed p value  $< 0.05$  was considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. For descriptive statistics of quantitative variables, the mean, and standard deviation or the median and range were used to describe central tendency and dispersion. Association between categorical variables were tested by the Chi Square Test. For parametric analysis, The independent-samples t-test was used to compare the means between two groups. For non-parametric analysis, Mann-Whitney U test was used. Survival analyses was calculated by the Kaplan-Meier Product-Limit Estimator. Comparison of the survival was performed by the Log-Rank Test Exploring variables for their independent prognostic effect on survival was carried out using the multivariate stepwise Cox's proportional regression hazard model.

#### Results:

A total of 84 patients with high grade serous ovarian carcinoma underwent surgical debulking (neoadjuvant chemotherapy in 53 patients) and followed by adjuvant chemotherapy were randomly assigned (2:1 ratio) to undergo either maintenance non-steroidal AI (with zoledronic acid 4mg / 6months with calcium and vitamin D support) or follow up. **Table 1:** The study presents a detailed overview of patient characteristics, pathological findings, and treatment details crucial for understanding the patient population and their clinical outcomes. Demographically, a significant portion of patients (70.2%) were aged  $\geq 50$  years, with peri/postmenopausal women comprising 66.7%, which is consistent with typical ovarian malignancy profiles. The average BMI was notably high ( $33 \pm 6.5$ ), indicating a predominantly overweight/obese group, potentially affecting disease progression and therapeutic responses. Clinically, 91.7% of patients presented with abdominal or pelvic pain and 63.1% experienced abdominal enlargement due to ascites, suggesting many were at an advanced disease stage. Radiologically, most displayed bilateral adnexal masses (67.9%) and significant omental/peritoneal involvement (81%), indicative of considerable tumor burden typical of advanced disease. The staging distribution showed a striking 86.9% in FIGO III/IV, underscoring the need for effective neo-adjuvant and debulking treatments. Impressively, the response rate to neo-adjuvant chemotherapy was 98.1%, with 64.2% achieving normalized CA125 levels, though only 15.1% attained a pathological complete response. Post-treatment, 66.7% of patients underwent non-steroidal aromatase inhibitor maintenance for a median duration of 13 months, which is vital for ongoing disease management. Additionally, monitoring bone health through DXA scans and administering zoledronic acid highlighted a robust clinical approach to mitigating treatment-related risks. **Table 2:** Relapse patterns indicated that a significant majority of relapses (58.8%) involved both local and distant metastases, demonstrating aggressive disease progression in relapsed patients. While patients undergoing maintenance therapy with aromatase inhibitors (AI) exhibited a lower relapse rate of 28%, this difference was not statistically significant ( $P = 0.21$ ). Additionally, higher relapse rates were observed in patients with FIGO stage III/IV (91.2%) and those with omental/peritoneal infiltration (88.2%), reinforcing the established link between advanced-stage disease and poor prognosis. Furthermore, the absence of significant correlations between normalized post-neoadjuvant CA125 levels or complete pathological response (pCR) and relapse underscores the urgent need for new predictive biomarkers. **Table 3:** In this study, we observed that while patients aged 50 and above exhibited marginally better outcomes, this difference was not statistically significant. Additionally, neither obesity nor menopausal status significantly influenced relapse rates, indicating that other factors may be more crucial in disease progression. For patients with Stage III/IV cancer, 95% displayed a trend toward higher relapse rates, and those with ascites also showed a notable tendency for relapse at 65%, which aligns with Table 2's findings. Lastly, a trend suggesting improved outcomes with normalized CA125 levels was noted, yet it did not achieve statistical significance. **Table 4:** In the analysis of ER H scores, it was observed that a significant majority of patients, both in no-relapse (65.7%) and relapse (64.7%) groups, exhibited moderate to strong ER positivity, suggesting that this level of positivity does not significantly influence relapse risk ( $P = 0.9$ ), indicating limited prognostic value for ER strength in predicting relapse. Furthermore, among patients with positive ER H scores, 80% were in the no-relapse group compared to only 20% with negative scores; however,

this association was not statistically significant ( $P = 0.46$ ), likely due to small sample size. In the context of PR H scores among ER-positive patients receiving maintenance aromatase inhibitors (AI), 85.7% of no-relapse patients had negative PR scores compared to 66.7% of relapsed patients, hinting that PR negativity may correlate with a diminished response to AI, though this was not statistically significant ( $P = 0.236$ ). Conversely, a higher percentage of relapsed patients (33.3%) had positive PR H scores compared to just 14.3% in the no-relapse group, indicating a potential association between PR positivity and increased relapse rates in this cohort that could require further exploration.

There was no significant statistical difference in DFS as regard the maintenance AI vs. follow up,  $p = 0.15$  (number of events was 20, 13 respectively) (**fig; 1**). Also, evaluation of DFS among patients who received the maintenance AI showed no significant statistical difference as regard different variables include age ( $p = 0.69$ , number of events was 8 and 12, for less than 50y and  $\geq 50y$  respectively), and obesity ( $p = 0.38$ , number of events was 7 and 13, for non-obese and obese BMI  $\geq 30$ , respectively) (**fig; 2,3**). DFS was evaluated in certain subgroups; age less than 50y, obese patients, advanced stage (III – IV); DFS was significantly worse in young patients who are less than 50y who received maintenance AI ( $p = 0.037$ , number of events was 8 and 4, for maintenance AI and follow up, respectively) (**fig; 4**, however it was subgroup analysis with small number of patients).

Overall Interpretation: **ER Positivity:** Although a higher percentage of ER-positive patients avoided relapse, the differences were not statistically significant. This highlights the need for additional markers or larger sample sizes to confirm ER H score's predictive value. **PR Positivity:** The trend toward increased relapse in PR-positive ER-positive patients receiving maintenance AI suggests that PR status could serve as an additional prognostic indicator. **Clinical Relevance:** These findings suggest that hormonal receptor profiles, especially the combination of ER and PR status, may have nuanced implications for relapse risk, particularly in the context of AI therapy. Tailored treatment strategies based on receptor profiles could improve outcomes.

## Discussion

The prognosis for ovarian cancer, particularly high-grade serous ovarian carcinoma (HGSOC), remains unfavorable despite advancements in treatment. With a five-year relapse rate of 75%, outcomes have improved only marginally over the past decades (14). Maintenance therapies have emerged as a promising strategy to extend progression-free survival (PFS) following primary treatment. Currently, the standard of care includes anti-angiogenic agents such as bevacizumab and PARP inhibitors for FIGO stage III-IV HGSOC. However, their limitations, including high costs, significant toxicity, and quality-of-life impairments, restrict their broader applicability (15,16).

Currently, endocrine therapies such as tamoxifen or aromatase inhibitors (AIs) are only considered standard for recurrent HGSOC cases. However, even in this setting, trial results have

been underwhelming due to the inconsistent use of estrogen receptor (ER) and progesterone receptor (PR) expression as predictive biomarkers (17).

The Phase II PARAGON basket trial, which investigated endocrine therapy in ER-positive gynecological cancers after the first relapse, demonstrated a clinical benefit rate (CBR) of 44% and an improvement in the quality of life. These findings, along with data from large breast cancer studies, suggest that maintenance endocrine therapy may offer more advantages than disadvantages for ovarian cancer patients (18).

Despite these findings, data on maintenance therapy for HGSOc following primary surgery and adjuvant chemotherapy remain scarce. There are no definitive recommendations for its use in this setting due to inconsistent prognostic and predictive effects reported in the literature. Currently, approved maintenance therapies include antiangiogenic agents such as bevacizumab and PARP inhibitors. However, their use is limited by high costs, toxicity, and negative impacts on quality of life (19).

A single-center prospective observational study in FIGO stage III/IV HGSOc patients found that letrozole maintenance therapy significantly prolonged recurrence-free survival (RFS). After 24 months, 60% of patients receiving letrozole were recurrence-free compared to 38.5% in the control group ( $p = 0.035$ ), with RFS reaching a median of 50 months in one subject versus 13.2 months in the control group. Additionally, among patients who received bevacizumab, 87.5% of those treated with letrozole in combination with bevacizumab were recurrence-free at 12 months compared to only 20.8% of patients treated with bevacizumab alone ( $p = 0.026$ ). Notably, starting letrozole maintenance therapy within three months of completing adjuvant chemotherapy significantly improved progression-free survival (PFS). The median age of patients receiving letrozole maintenance was 71 years, all were advanced-stage cases, and 91.3% completed six cycles of platinum-based chemotherapy. Importantly, no major side effects or treatment interruptions were observed (13).

In our study, 84 patients with HGSOc underwent surgical debulking (53 receiving neoadjuvant chemotherapy) followed by adjuvant chemotherapy. Patients were randomized (2:1) to either non-steroidal AI maintenance therapy or follow-up. The mean age was 55 years, and the majority of patients (56) were peri- or postmenopausal. Obesity ( $BMI \geq 30$ ) was reported in 57 patients. Common presentations included abdominal or pelvic pain and ascites, seen in 77 (91.7%) and 53 (63.1%) patients, respectively. The mean baseline CA-125 level was 1081.5, and bilateral adnexal masses were present in 67.9% of patients. Advanced FIGO stages (III-IV) were predominant (73 patients). Neoadjuvant chemotherapy (paclitaxel/carboplatin) was administered to 53 patients, with a range of 3–8 cycles.

Of the 84 patients, 56 (66.7%) received non-steroidal AI maintenance therapy for a median duration of 13 months (range: 2–26). These patients also received zoledronic acid (4 mg every six months) with calcium and vitamin D supplementation. Importantly, no adverse events necessitating treatment interruptions were reported.

Relapse was observed in 34 patients (40.5%), with no statistically significant differences in RR between those receiving maintenance AI and those in the follow-up group. Similarly, no

significant differences in relapse rates were observed across different variables or among subgroups based on ER or PR positivity. Disease-free survival (DFS) analysis revealed no overall significant difference between groups. However, younger patients (<50 years) on maintenance AI experienced significantly worse DFS ( $p = 0.037$ ), with eight events in the maintenance group versus four in the follow-up group.

### **Comparison of Findings**

Endocrine therapy has long been established in breast cancer management, with aromatase inhibitors (AIs) like letrozole being extensively utilized in hormone receptor-positive cases. However, its role in ovarian cancer, particularly in the maintenance setting, remains controversial. Although the PARAGON trial demonstrated a 44% clinical benefit rate (CBR) and improved quality of life with endocrine therapy in estrogen receptor (ER)-positive gynecological cancers after relapse (20,21), data supporting its use in HGSOC maintenance therapy are limited.

A recent prospective observational study evaluated letrozole as a maintenance therapy in FIGO stage III-IV HGSOC patients. This study reported a significant improvement in recurrence-free survival (RFS) among patients treated with letrozole compared to controls (60% vs. 38.5% recurrence-free at 24 months;  $p = 0.035$ ) (13). Additionally, the combination of letrozole with bevacizumab showed a superior recurrence-free rate at 12 months compared to bevacizumab alone (87.5% vs. 20.8%;  $p = 0.026$ ). These findings align with breast cancer studies, which have consistently demonstrated the efficacy and favorable safety profile of AIs (22-24).

In contrast, our study, which randomized 84 patients with advanced-stage HGSOC to receive maintenance AI therapy or follow-up, found no significant difference in relapse rates (RR) or disease-free survival (DFS) between the two groups. Interestingly, a subgroup analysis revealed worse DFS in younger patients (<50 years) receiving maintenance AI therapy, a finding that warrants further investigation. Additionally, no significant association was observed between hormonal receptor status (ER/PR positivity) and treatment response, highlighting the need for more precise predictive biomarkers.

### **Interpretation of Results**

The discrepancy between our findings and those of previous studies could be attributed to differences in patient populations, study designs, and treatment regimens. For instance, the observational study that demonstrated the benefit of letrozole maintenance included older patients (median age 71 years), whereas our cohort had a mean age of 55 years. Furthermore, the initiation of maintenance therapy within three months of completing adjuvant chemotherapy was a critical factor for improved outcomes in the observational study (13). In our trial, the median duration of maintenance therapy was 13 months, but the timing of initiation varied.

The absence of a significant benefit in our study may also reflect the heterogeneity of HGSOC. While a high proportion of epithelial ovarian cancers express ER, the prognostic and predictive value of ER expression remains inconsistent in the literature (25,26). Additionally, the limited sample size and lack of stratification by molecular subtypes in our study may have influenced the results.

## Clinical Implications and Future Directions

While endocrine maintenance therapy offers a low-cost and well-tolerated alternative to anti-angiogenic agents and PARP inhibitors, our findings suggest it may not be an effective strategy for HGSOC in its current form. The lack of significant improvements in RR and DFS, regardless of hormonal receptor status, underscores the need for further research.

Large-scale, randomized controlled trials, such as the ongoing MATAO trial, are crucial to elucidate the role of AIs in the maintenance setting for ovarian cancer. These studies should incorporate comprehensive biomarker analyses to identify subgroups of patients most likely to benefit from endocrine therapy. Until more robust evidence is available, the use of AIs in the maintenance setting for HGSOC should be approached with caution.

## Conclusion

In summary, while endocrine therapy with AIs has demonstrated efficacy in breast cancer and select ovarian cancer settings, our study does not support its routine use as maintenance therapy in HGSOC. The low cost and favorable safety profile of AIs make them an appealing option, but their lack of significant benefit in improving RR or DFS in our cohort highlights the need for more targeted and personalized treatment approaches.

## Strengths of the Study

- **Innovative Research Focus:** The study explores the under-researched area of maintenance endocrine therapy in advanced hormone receptor-positive high-grade serous ovarian cancer (HGSOC), a significant contribution to the field.
- **Prospective Randomized Design:** The prospective, randomized, open-label clinical trial design ensures a systematic comparison between maintenance therapy with aromatase inhibitors (AIs) and observation, improving the reliability of results.
- **Comprehensive Patient Selection:** Inclusion of well-defined criteria (ER/PR positivity, FIGO stage III/IV, performance status  $\leq 2$ ) and exclusion of confounding factors (e.g., prior endocrine therapy use) strengthen the study's focus on a specific population.
- **Detailed Biomarker Analysis:** Immunohistochemistry (IHC) for ER/PR positivity with H-score quantification provides robust data on receptor status, which is crucial for interpreting the hormonal impact.
- **Monitoring for Side Effects:** Systematic evaluation of AI-related side effects, including bone health assessment, adds a layer of safety monitoring often overlooked in such studies.
- **Comparison with Observation:** The inclusion of a control group (observation-only) enhances the ability to assess the true impact of maintenance therapy.
- **Real-World Relevance:** The study includes routine clinical assessments (CT scans, CA-125 levels), making its findings applicable in real-world settings.

## Limitations of the Study

- **Small Sample Size:** With only 84 participants, the study may lack the statistical power to detect subtle differences, particularly in subgroup analyses.

- **Heterogeneity of Population:** Variability in age, timing of AI initiation, and hormonal receptor expression (ER/PR levels) introduces confounding factors that may dilute observed effects.
- **Open-Label Design:** Lack of blinding may introduce bias in reporting outcomes or assessing relapse rates.
- **Limited Follow-Up Duration:** The median duration of maintenance therapy (13 months) and overall follow-up may not be sufficient to capture long-term outcomes such as overall survival.
- **Focus on Single-Center Data:** Being a single-center study limits the generalizability of the findings to broader populations.
- **Non-Significant Primary Outcomes:** The lack of statistically significant differences in disease-free survival (DFS) and relapse rates reduces the strength of the conclusions.
- **Potential Underestimation of Predictive Markers:** The study relies solely on ER/PR status without incorporating other molecular or genetic markers that could influence endocrine therapy response.
- **Unaddressed Cost-Effectiveness:** While endocrine therapy is low-cost, the study does not explicitly evaluate the economic impact compared to standard maintenance therapies like PARP inhibitors or bevacizumab.
- **Subgroup Analysis with Limited Numbers:** Significant findings in subgroups (e.g., worse DFS in younger patients) are based on small event numbers, reducing their reliability and interpretability.
- **Lack of Molecular Stratification:** The study does not differentiate between molecular subtypes of HGSOC, which may respond differently to hormonal therapies.
- **Absence of Quality-of-Life Metrics:** The study focuses on clinical outcomes without assessing quality of life, an important consideration for maintenance therapies.

### **Recommendations for Future Studies**

- Increase sample size and include multicenter trials to improve generalizability.
- Incorporate molecular subtyping and additional biomarkers to refine patient selection.
- Extend follow-up duration to assess long-term outcomes, including overall survival.
- Evaluate quality of life and cost-effectiveness to provide a comprehensive view of the therapy's impact.

### **Ethics approval and consent to participate.**

#### **Ethics Approval:**

The study received approval from the Institutional Review Board of the Medical Research Ethics Committee at Mansoura Faculty of Medicine, Mansoura University (Code Number: R.20.06.916.R1), as well as from the managers of the hospital where it was conducted. All patients were informed about the study and provided consent for their enrollment, ensuring that their confidentiality was maintained and that they had the right to refuse participation or withdraw at any time. Confidentiality and personal privacy were respected throughout all phases of the study, and the data collected was exclusively for research purposes and not utilized for any other activities.

#### **Consent to Participate:**

Informed consent was obtained from all participants included in the study. Participants were provided with detailed information about the study objectives, procedures, potential risks and benefits, confidentiality measures, and their right to withdraw at any time without consequences. Written consent was obtained from each participant before their inclusion in the study. Additionally, participants' confidentiality was strictly maintained throughout the research process, and all data were anonymized to ensure privacy.

### **consent for publication.**

My manuscript does not contain any individual person's data in any form ((including any individual details, images, or videos).

### **availability of data and materials**

All the clinical , radiological and pathological data used in this manuscript is available on Mansoura University medical system (Ibn Sina Hospital management System)

<https://srv137.mans.edu.eg/mus/newSystem/>

### **References**

- 1-Santucci C, Carioli G, Bertuccio P, Malvezzi M, Pastorino U, Boffetta P, Negri E, Bosetti C, La Vecchia C. Progress in cancer mortality, incidence, and survival: a global overview. *European Journal of Cancer Prevention*. 2020 Sep 1;29(5):367-81.
- 2-Vaughan S, Coward JI, Bast Jr RC, Berchuck A, Berek JS, Brenton JD, Coukos G, Crum CC, Drapkin R, Etemadmoghadam D, Friedlander M. Rethinking ovarian cancer: recommendations for improving outcomes. *Nature Reviews Cancer*. 2011 Oct;11(10):719-25.
- 3-Perren TJ, Swart AM, Pfisterer J, Ledermann JA, Pujade-Lauraine E, Kristensen G, et al. A phase 3 trial of bevacizumab in ovarian cancer. *The New England journal of medicine*. 2011;365(26):2484-96.
- 4-Oza AM, Cook AD, Pfisterer J, Embleton A, Ledermann JA, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *The Lancet Oncology*. 2015;16(8):928-36.
- 5-Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *The Lancet Oncology*. 2017;18(1):75-87.
- 6-Langdon SP, Gourley C, Gabra H, Stanley B. Endocrine therapy in epithelial ovarian cancer. *Expert review of anticancer therapy*. 2017;17(2):109-17.
- 7-Matsuo K, Sheridan TB, Mabuchi S, Yoshino K, Hasegawa K, Studeman KD, Im DD, Rosenshein NB, Roman LD, Sood AK. Estrogen receptor expression and increased risk of lymphovascular space invasion in high-grade serous ovarian carcinoma. *Gynecologic oncology*. 2014 Jun 1;133(3):473-9.

- 8- Takahashi A, Kato K, Kuboyama A, Inoue T, Tanaka Y, Kuhara A, Kinoshita K, Takeda S, Wake N. Induction of senescence by progesterone receptor-B activation in response to cAMP in ovarian cancer cells. *Gynecologic oncology*. 2009 May 1;113(2):270-6.
- 9- van Kruchten M, van der Marel P, de Munck L, Hollema H, Arts H, Timmer-Bosscha H, de Vries E, Hospers G, Reyners A. Hormone receptors as a marker of poor survival in epithelial ovarian cancer. *Gynecologic oncology*. 2015 Sep 1;138(3):634-9.
- 10-Borella F, Fucina S, Mangherini L, Cosma S, Carosso AR, Cusato J, Cassoni P, Bertero L, Katsaros D, Benedetto C. Hormone receptors and epithelial ovarian cancer: recent advances in biology and treatment options. *Biomedicines*. 2023 Aug 1;11(8):2157.
- 11- Langdon SP, Herrington CS, Hollis RL, Gourley C. Estrogen signaling and its potential as a target for therapy in ovarian cancer. *Cancers*. 2020 Jun 22;12(6):1647.
- 12- McLaughlin PM, Klar M, Zwimpfer TA, Dutilh G, Vetter M, Marth C, du Bois A, Schade-Brittinger C, Reuss A, Bommer C, Kurzeder C. Maintenance Therapy with Aromatase Inhibitor in epithelial Ovarian Cancer (MATAO): study protocol of a randomized double-blinded placebo-controlled multi-center phase III Trial. *BMC cancer*. 2022 May 6;22(1):508.
- 13- Heinzelmann-Schwarz V, Mészáros AK, Stadlmann S, Jacob F, Schoetzau A, Russell K, Friedlander M, Singer G, Vetter M. Letrozole may be a valuable maintenance treatment in high-grade serous ovarian cancer patients. *Gynecologic oncology*. 2018 Jan 1;148(1):79-85.
- 14-Hoppenot C, Eckert MA, Tienda SM, Lengyel E. Who are the long-term survivors of high grade serous ovarian cancer?. *Gynecologic oncology*. 2018 Jan 1;148(1):204-12.
- 15-Nag S, Aggarwal S, Rauthan A, Warriar N. Maintenance therapy for newly diagnosed epithelial ovarian cancer—a review. *Journal of ovarian research*. 2022 Jul 28;15(1):88.
- 16-Simion L, Rotaru V, Cirimbei C, Stefan DC, Gherghe M, Ionescu S, Tanase BC, Luca DC, Gales LN, Chitoran E. Analysis of Efficacy-To-Safety Ratio of Angiogenesis-Inhibitors Based Therapies in Ovarian Cancer: A Systematic Review and Meta-Analysis. *Diagnostics*. 2023 Mar 9;13(6):1040.
- 17- Sieh W, Köbel M, Longacre TA, Bowtell DD, DeFazio A, Goodman MT, Høgdall E, Deen S, Wentzensen N, Moysich KB, Brenton JD. Hormone-receptor expression and ovarian cancer survival: an Ovarian Tumor Tissue Analysis consortium study. *The lancet oncology*. 2013 Aug 1;14(9):853-62.
- 18-Kok PS, Beale P, O'Connell RL, Grant P, Bonaventura T, Scurry J, Antill Y, Goh J, Sjoquist K, DeFazio A, Mapagu C. PARAGON (ANZGOG-0903): a phase 2 study of anastrozole in asymptomatic patients with estrogen and progesterone receptor-positive recurrent ovarian cancer and CA125 progression. *Journal of gynecologic oncology*. 2019 Sep 1;30(5).

19-Madariaga A, Rustin GJ, Buckanovich RJ, Trent JC, Oza AM. Wanna get away? Maintenance treatments and chemotherapy holidays in gynecologic cancers. American Society of Clinical Oncology Educational Book. 2019 May 17;39:e152-66.

20- Mileskin, Linda R., Richard J. Edmondson, Rachel O'Connell, Katrin Marie Sjoquist, David Cannan, Rema Jyothirmayi, Philip James Beale et al. "Phase II study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial—ANZGOG 0903." (2016): 5520-5520.

21-Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. The Lancet. 2015 Oct 3;386(10001):1341-52.

22- Meszaros AK, Schwarz VH, Vetter M. Endocrine therapy in epithelial ovarian cancer (EOC) New insights in an old target: A mini review. J Cancer Clin Trials. 2018;3(144):2577-0535.

23- Dickler MN, Barry WT, Cirrincione CT, Ellis MJ, Moynahan ME, Innocenti F, Hurria A, Rugo HS, Lake DE, Hahn O, Schneider BP. Phase III trial evaluating letrozole as first-line endocrine therapy with or without bevacizumab for the treatment of postmenopausal women with hormone receptor–positive advanced-stage breast cancer: CALGB 40503 (Alliance). Journal of Clinical Oncology. 2016 Aug 1;34(22):2602-9.

24- Plummer R, Verheul HM, De Vos FY, Leunen K, Molife LR, Rolfo C, Grundtvig-Sørensen P, De Grève J, Rottey S, Jerusalem G, Italiano A. Pharmacokinetic effects and safety of olaparib administered with endocrine therapy: a phase I study in patients with advanced solid tumours. Advances in therapy. 2018 Nov;35:1945-64.

25- Zhao X, Rødland EA, Sørli T, Vollan HK, Russnes HG, Kristensen VN, Lingjærde OC, Børresen-Dale AL. Systematic assessment of prognostic gene signatures for breast cancer shows distinct influence of time and ER status. BMC cancer. 2014 Dec;14:1-2.

26- Cao H, You D, Lan Z, Ye H, Hou M, Xi M. Prognostic value of serum and tissue HE4 expression in ovarian cancer: a systematic review with meta-analysis of 90 studies. Expert review of molecular diagnostics. 2018 Apr 3;18(4):371-83.

**Table 1: a comprehensive overview of the study's clinical, pathological, and treatment-related aspects.**

Parameter	Details
<b>Age</b>	Mean: 55 years (range: 29–81)
	<50 years: 25 (29.8%)
	≥50 years: 59 (70.2%)
<b>Menopausal Status</b>	Premenopausal: 28 (33.3%)
	Peri/Postmenopausal: 56 (66.7%)
<b>BMI</b>	Mean: 33 ± 6.5
	Overweight/Obese: 77 (91.7%)

	Obese (BMI $\geq$ 30): 57 (67.9%)
<b>Clinical Presentation</b>	Abdominal/Pelvic Pain: 77 (91.7%)
	Abdominal Enlargement (Ascites): 53 (63.1%)
	Constipation: 13 (15.5%)
	Bleeding per Vagina: 6 (7.1%)
	Urinary Symptoms: 3 (3.6%)
	Discharge: 2 (2.4%)
<b>Denovo Metastatic Disease</b>	Pleural Effusion: 6 (7.1%)
	Non-regional Lymph Nodes: 11 (13.1%)
<b>Baseline CA125</b>	Median: 482 (range: 9–6540)
<b>Baseline Radiological Evaluation</b>	Adnexal Mass: Bilateral: 57 (67.9%), Left: 18 (21.4%), Right: 6 (7.1%), No Mass: 3 (3.6%)
	Uterine Infiltration: 14 (16.7%)
	Rectal Infiltration: 15 (17.9%)
	Omental/Peritoneal Involvement: 68 (81%)
<b>Pathological Characteristics</b>	
<b>FIGO Staging</b>	Stage I/II: 11 (13.1%)
	Stage III/IV: 73 (86.9%)
<b>Neo-adjuvant Chemotherapy</b>	Carboplatin/Paclitaxel: 53 (63.1%)
	Number of Cycles: Median: 3 (range: 3–8); 3 cycles: 27 (50.9%)
<b>Post-neo-adjuvant CA125</b>	Median: 25 (range: 2–850)
	Normalized: 34 (64.2%)
	Non-normalized: 19 (35.8%)
<b>Response to Neo-adjuvant Chemotherapy</b>	Responsive (CR/PR): 52 (98.1%)
	SD: 1 (1.9%)
<b>Pathological Complete Response (CR)</b>	Post-Neo-adjuvant: 8 (15.1%)
<b>Treatment Characteristics (AI Maintenance)</b>	
<b>Non-steroidal AI Maintenance</b>	56 (66.7%)
<b>Duration of Maintenance Therapy</b>	Median: 13 months
<b>Precautions</b>	Zoledronic Acid: 4 mg/6 months; DXA Scan Lowest T-score: Mean: $-1.78 \pm 0.7$
<b>Adverse Events</b>	No reported events requiring treatment interruption

**Table 2: Relapse Rates According to Different Variables (N = 84)**

Variable	No Relapse (n = 50)	Relapsed Disease (n = 34)	P-value
Relapse Type	-	Local: 7 (20.6%) Distant Metastases: 7 (20.6%)	-

		Both: 20 (58.8%)	
<b>Follow-up and Maintenance AI</b>	Maintenance AI: 36 (72%) Follow-up: 14 (28%)	Maintenance AI: 20 (58.8%) Follow-up: 14 (41.2%)	0.21
<b>Age</b>	<50y: 13 (26%) ≥50y: 37 (74%)	<50y: 12 (35.3%) ≥50y: 22 (64.7%)	0.36
<b>Menopausal Status</b>	Premenopausal: 16 (32%) Peri/Post: 34 (68%)	Premenopausal: 12 (35.3%) Peri/Post: 22 (64.7%)	0.75
<b>Obesity (BMI ≥30)</b>	Non-obese: 16 (32%) Obese: 34 (68%)	Non-obese: 11 (32.4%) Obese: 23 (67.6%)	0.97
<b>FIGO Staging</b>	Stage I/II: 8 (16%) Stage III/IV: 42 (84%)	Stage I/II: 3 (8.8%) Stage III/IV: 31 (91.2%)	0.34
<b>Omental/Peritoneal Infiltration</b>	No infiltration: 12 (24%) Infiltration: 38 (76%)	No infiltration: 4 (11.8%) Infiltration: 30 (88.2%)	0.16
<b>Ascites</b>	No ascites: 21 (42%) Ascites: 29 (58%)	No ascites: 10 (29.4%) Ascites: 24 (70.6%)	0.24
<b>Neoadjuvant Chemotherapy</b>	No: 21 (42%) Yes: 29 (58%)	No: 10 (29.4%) Yes: 24 (70.6%)	0.24
<b>Post-Neoadjuvant CA125 (53 patients)</b>	Non-normalized: 9 (31%) Normalized: 20 (69%)	Non-normalized: 10 (41.7%) Normalized: 14 (58.3%)	0.42
<b>Pathological Complete Response (pCR)</b>	No: 24 (82.8%) Yes: 5 (17.2%)	No: 21 (87.5%) Yes: 3 (12.5%)	0.71*

\*Fisher exact test was used where applicable.

**Table 3: Relapse Rates in Patients Receiving Maintenance AI (N = 56)**

<b>Variable</b>	<b>No Relapse (n = 36)</b>	<b>Relapsed Disease (n = 20)</b>	<b>P-value</b>
<b>Age</b>	<50y: 11 (30.6%) ≥50y: 25 (69.4%)	<50y: 8 (40%) ≥50y: 12 (60%)	0.47
<b>Menopausal Status</b>	Premenopausal: 14 (38.9%) Peri/Post: 22 (61.1%)	Premenopausal: 7 (35%) Peri/Post: 13 (65%)	0.77
<b>Obesity (BMI ≥30)</b>	Non-obese: 13 (36.1%) Obese: 23 (63.9%)	Non-obese: 7 (35%) Obese: 13 (65%)	0.93
<b>FIGO Staging</b>	Stage I/II: 7 (19.4%) Stage III/IV: 29 (80.6%)	Stage I/II: 1 (5%) Stage III/IV: 19 (95%)	0.14
<b>Ascites</b>	No ascites: 17 (47.2%) Ascites: 19 (52.8%)	No ascites: 7 (35%) Ascites: 13 (65%)	0.37

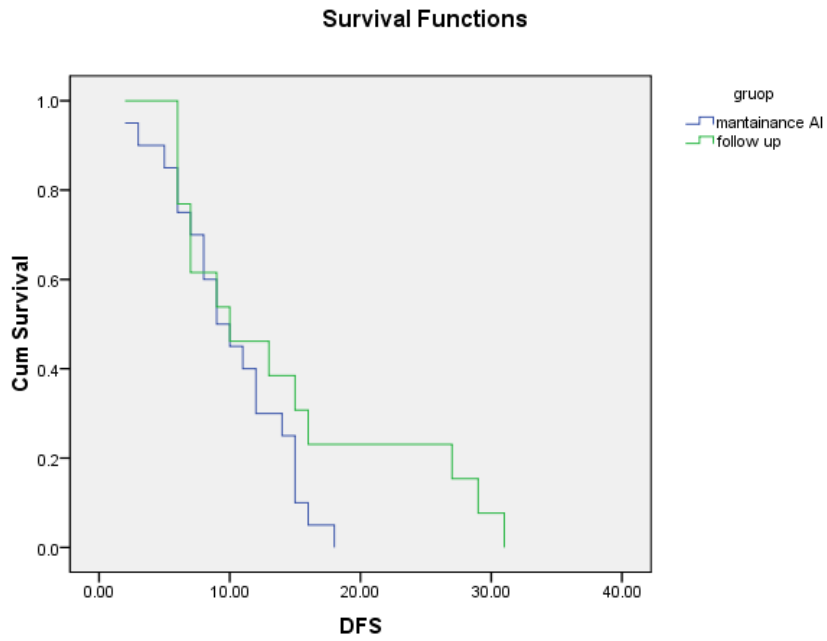
<b>Neoadjuvant Chemotherapy</b>	No: 16 (44.4%) Yes: 20 (55.6%)	No: 7 (35%) Yes: 13 (65%)	0.49
<b>Post-Neoadjuvant CA125 (33 patients)</b>	Non-normalized: 3 (15%) Normalized: 17 (85%)	Non-normalized: 4 (30.8%) Normalized: 9 (69.2%)	0.39*
<b>Pathological Complete Response (pCR)</b>	No: 16 (80%) Yes: 4 (20%)	No: 10 (76.9%) Yes: 3 (23.1%)	1.0*

\*Fisher exact test was used where applicable.

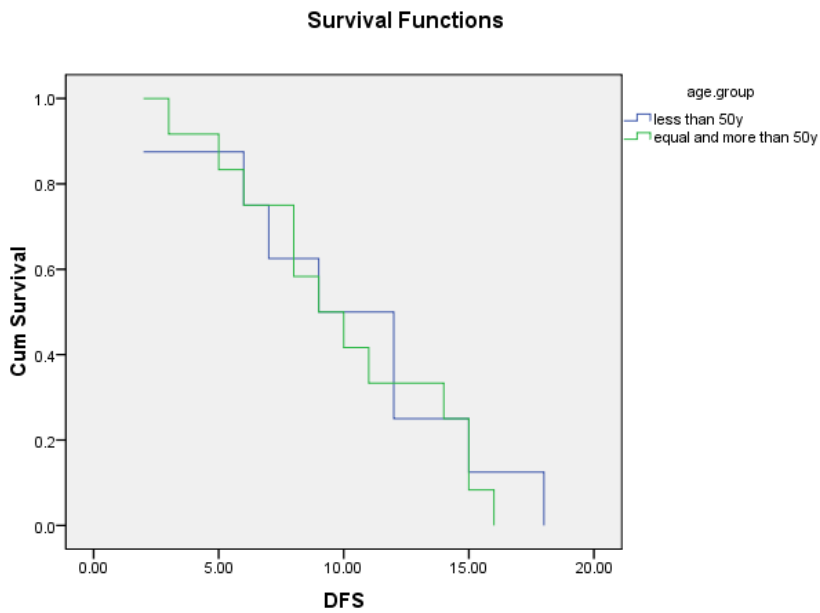
**Table 4: Relapse According to Hormonal Receptor H Score**

Variable	No Relapse (n)	Relapse (n)	Total (n)	P-value
<b>ER H Score: Negative and Mild Positive</b>	12 (34.3%)	6 (35.3%)	18	0.9
<b>ER H Score: Moderate and Strong Positive</b>	23 (65.7%)	11 (64.7%)	34	0.9
<b>ER H Score: Negative</b>	7 (20%)	2 (11.8%)	9	0.46
<b>ER H Score: Positive</b>	28 (80%)	15 (88.2%)	43	0.46
<b>PR H Score in ER Positive Patients on AI: Negative</b>	18 (85.7%)	10 (66.7%)	28	0.236*
<b>PR H Score in ER Positive Patients on AI: Positive</b>	3 (14.3%)	5 (33.3%)	8	0.236*

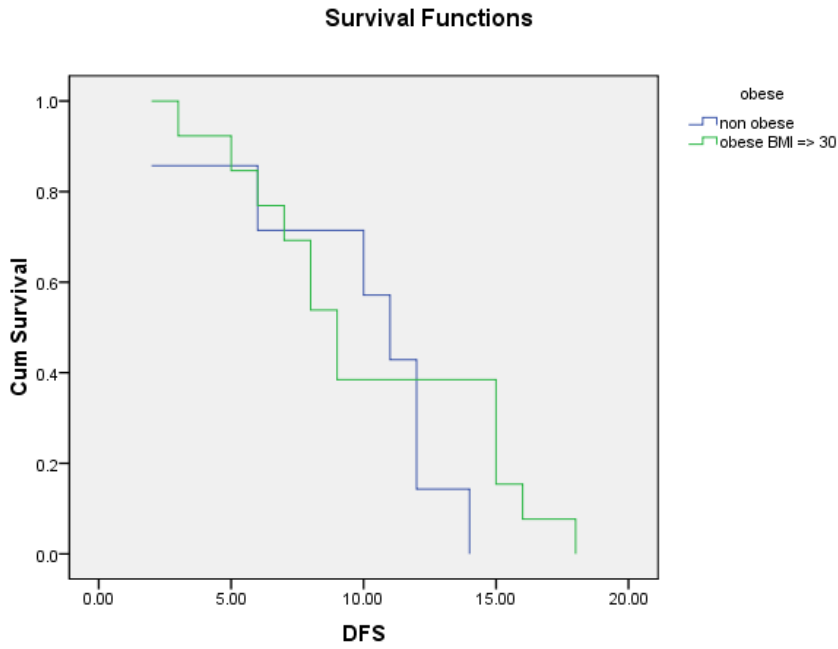
\* Fisher exact test was used where applicable.



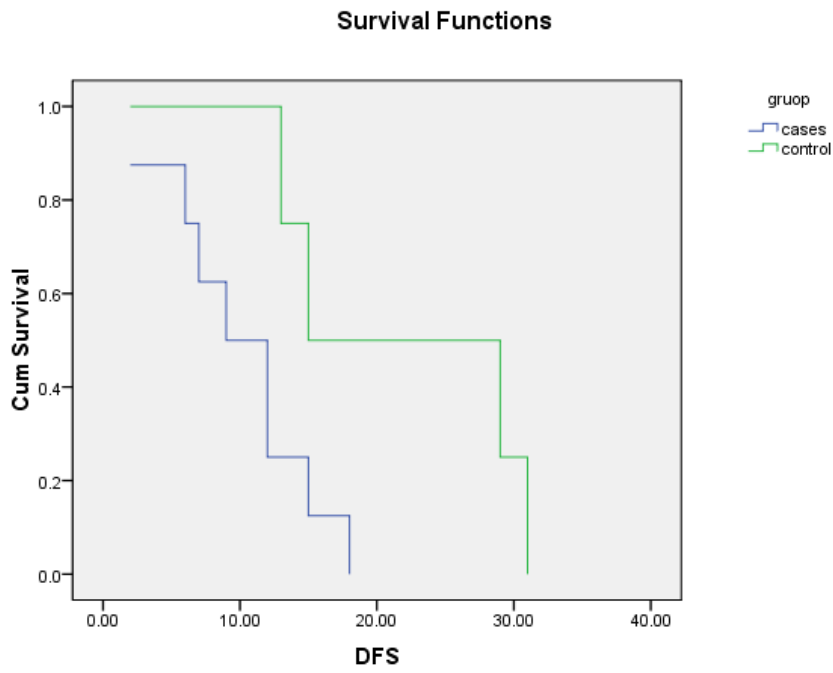
**Fig (1); DFS as regard maintenance AI vs. follow up (p 0.15).**



**Fig (2); DFS as regard age among patients who received maintenance AI (p 0.69).**



**Fig (3); DFS as regard obesity among patients who received maintenance AI (p 0.38).**



**Fig (4); DFS in patients who are less than 50 (p 0.037)**

UNDER PEER REVIEW