Alma Mater Studiorum Università di Bologna
Archivio istituzionale della ricerca

Hysterectomy or not for borderline ovarian tumor in menopause?

Hysterectomy or not for borderline ovarian tumor in menopause?

Diego Raimondo [a], Antonio Raffone [b,c,]*, Manuela Maletta [a,b,]**, Stefano Restaino [d,e], Martina Arcieri [d], Lorenza Driul [d,f], Antonio Travaglino [g], Anna Myriam Perrone [h], Anna Fagotti [i,j], Floriana Mascilini [i], Mario Malzoni [k], Francesca Falcone [k], Giorgio Bogani [l], Stefano Ferla [a,b], Fabio Landoni [m], Roberto Berretta [n], Marcello Ceccaroni [o], Stefania Cicogna [p], Francesco Pantano [q], Giuseppe Trojano [r], Sami Kilzie [s], Cassani Chiara [t,ae], Vito Chiantera [u], Carlo Alboni [v], Eugenio Solima [w], Giovanna Scarfone [x], Ruby Martinello [y], Paolo Manna [z], Basilio Pecorino [aa], Maria Giovanna Vastarella [c], Davide Calandra [ab], Alexandro Paccapelo [ac], Jacopo Lenzi [ad], Luigi Cobellis [c], Giovanni Scambia [i,j], Giuseppe Vizzielli [d,f,1], Renato Seracchioli [a,b,1]

[a] Division of Gynaecology and Human Reproduction Physiopathology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[b] Department of Medical and Surgical Sciences, DIMEC, University of Bologna, Bologna, Italy
[c] Department of Woman, Child, and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", 80138 Naples, Italy
[d] Clinic of Obstetrics and Gynecology, "Santa Maria della Misericordia" University Hospital – Azienda Sanitaria Universitaria Friuli Centrale, Udine, Italy
[e] School in Biomedical Sciences, Gender Medicine, Child and Women Health, University of Sassari, Sassari, Italy
[f] Department of Medicine, University of Udine, Udine, Italy
[g] Pathology Unit, Department of Medicine and Technological Innovation, University of Insubria, Varese, Italy
[h] Division of Oncologic Gynecology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
[i] Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[j] Dipartimento Scienze della Vita e Sanità Pubblica, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Rome, Italy
[k] Endoscopica Malzoni, Centre for Advanced Pelvic Surgery, Avellino, Italy
[l] Gynecological Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy
[m] Gynecologic Clinic Milano Bicocca University, Ospedale San Gerardo, Monza, Italy
[n] Obstetrics and Gynaecology Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy
[o] Department of Obstetrics and Gynecology, Gynecologic Oncology and Minimally Invasive Pelvic Surgery, International School of Surgical Anatomy, IRCCS "Sacro Cuore - Don Calabria" Hospital, Negrar di Valpolicella, Verona, Italy
[p] Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Italy
[q] Ginecologia oncologica Ospedale Civile di Legnano ASST Ovest Milanese, Italy
[r] Department of Maternal and Child Health "Madonna delle Grazie" Hospital ASM Matera, Italy
[s] Ospedale Ca' Foncello – Treviso, Italy
[t] Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy
[u] Istituto Nazionale Tumori IRCS- Fondazione G. Pascale, Napoli, Italy
[v] Minimally Invasive and Robotic Gynecologic Surgery Unit, Policlinico Modena, University of Modena and Reggio Emilia, Modena, Italy
[w] Asst Fatebenefratelli-sacco, ospedale Macedonio Melloni Milano, Italy
[x] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy
[y] Institute of Obstetrics and Gynecology, Department of Medical Sciences, University of Ferrara, Italy
[z] Department of Clinical and Experimental Medicine, Obstetrics and Gynecology Unit, "Magna Graecia" University, Catanzaro, Italy
[aa] Obstetrics and Gynecological Unit, Cannizzaro Hospital Department of Medicine and Surgery, University of Enna "Kore", 94100 Enna, Italy
[ab] Ginecologia ed ostetricia AULSS7 Pedemontana-Ospedale di Santorso, Università degli Studi "G.D'Annunzio" di Chieti e Pescara, Italy
[ac] Epidemiology and Statistics, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[ad] Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum - University of Bologna, Bologna, Italy
[ae] Unit of Obstetrics and Gynecology, IRCCS San Matteo Foundation, Pavia, Italy

* Correspondence to: A. Raffone (antonio.raffone@unicampania.it), Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy.
** Correspondence to: M. Maletta (manuela.maletta@studio.unibo.it), Division of Gynaecology and Human Reproduction Physiopathology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.
[1] Equally contributed as last author.

HIGHLIGHTS

- This study aims to assess the impact of hysterectomy on survival outcomes in postmenopausal women with BOT.

- Hysterectomy reduces recurrence risk in postmenopausal BOT patients (HR = 0.253, p = 0.003).

- 5-year DFS higher in hysterectomy group (98.5 %) than no-hysterectomy group (92.4 %, p = 0.007).

- However, hysterectomy did not significantly affect the risk of death of any cause and the risk of death due to the disease.

- This study enriches the literature with new data on a large cohort of postmenopausal BOT women.

ABSTRACT

Background. The role of hysterectomy for borderline ovarian tumor (BOT) among postmenopausal women is still unclear.

Objective(s). To assess the impact of hysterectomy on survival outcomes in postmenopausal women with BOT.

Study design. This study was a national, multicenter, observational, retrospective, cohort study including all consecutive eligible postmenopausal patients who underwent primary surgery for BOT in 20 Italian centers from January 2005 to December 2017. Patients were divided into two groups: hysterectomy group vs no- hysterectomy group. Primary outcome was disease-free survival (DFS) at 5 years of follow-up; secondary out- comes were overall survival (OS) and disease-specific survival (DSS) at 5 years of follow-up, hazard ratio (HR) for recurrence, death of any cause and death due to BOT, peri-operative complications rates.

Results. 483 patients were included, 144 (29.8 %) women in the no-hysterectomy group and 339 (70.2 %) in the hysterectomy group. Recurrences were significantly more common in the no-hysterectomy group compared to hysterectomy one (8.3 % vs 2.7 %; p = 0.012). The 5-year DFS rate was lower in the no-hysterectomy group than that in the hysterectomy one [92.4 % vs 98.5 %; p = 0.007]. At univariate analyses, women who underwent hysterectomy showed HR of 0.312 (95 %CI:0.131–0.740; p = 0.008) for recurrence. At multivariate analysis, hysterectomy was found to be an independent protective factor for recurrence (HR: 0.253, 95 %CI:0.103–0.618, p < 0.003).

Conclusions. In postmenopausal women with BOT, hysterectomy is associated with a decreased risk of recurrence, while it does not affect the risk of death from any cause or death due to the disease. Based on these findings, hysterectomy should be routinely integrated into the surgical staging of BOT in postmenopausal women.

1. INTRODUCTION

Borderline ovarian tumors (BOTs) are rare epithelial ovarian tumors, characterized by malignant cytological features in absence of frank invasion [1]. Due to the lack of invasiveness, BOTs show an indolent clinical course and most patients have an excellent prognosis with 10-year survival rate up to 95 % [2]. Surgery is the primary treatment for BOT and its radicality varies according to women's age, fertility desire, International Federation of Gynecology and Obstetrics (FIGO) stage and histotype [1]. For postmenopausal women with BOT, although international guidelines uniformly recommend bilateral salpingo-oophorectomy (BSO) and resection of macroscopic disease, they differ for the indication to hysterectomy [1,3].

A recent systematic review and meta-analysis [4] reported a significantly decreased risk of recurrence among women who underwent hysterectomy compared to those who preserved the uterus. However, such an advantage in the risk of recurrence among women who preserved the uterus might be overestimated because of ovarian preservation, a known risk factor for BOT recurrence. In fact, most included studies in this systematic review and meta-analysis assessed women undergoing fertility-sparing surgery (i.e., preservation of at least one ovary) [2]. Accordingly, in a multicenter retrospective study assessing the impact of hysterectomy alone among postmenopausal BOT women not preserving ovaries, hysterectomy did not appear to decrease the risk of recurrence compared to uterine-sparing surgery [5]. Nevertheless, despite the multicenter design, this study was limited by small sample size and numbers of events.

Therefore, the impact of hysterectomy on survival outcomes in postmenopausal BOT women should be still clarified. In this study, we aimed to investigate the impact of hysterectomy on oncological outcomes in a large population of postmenopausal women with BOT.

2. MATERIALS AND METHODS

2.1. Study protocol and patients selection criteria

This was a national, multicenter, observational, retrospective, cohort study following an a priori

defined study protocol. The whole study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement and checklist [6].

Medical records and electronic clinical databases were searched for all consecutive postmenopausal patients who underwent surgical treatment for BOT including removal of both adnexa or only one (if unilateral adnexectomy was performed before for reasons other than BOT) in 20 Italian centers from January 2005 to December 2017. Patients with previous hysterectomy, other coexistent gynecologic cancers, BOT at FIGO stage IV, invasive BOT implants [7] and/or patients referred for recurrence of BOT or completion surgery were excluded from the study.

For the purpose of the study, women undergoing surgery for BOT were divided into two groups based on removal (hysterectomy group) or preservation of uterus (no-hysterectomy group).

Medical reports were searched for extraction of the following patients data: age at diagnosis, body mass index (BMI), parity, American Society of Anesthesiologists (ASA) score [8]), previous abdominal surgery, any preoperative increased levels of CA-125 (>35 U/ml) and CA 19–9 (> 37 U/ml), preoperative suspicion of BOT (based on the ultrasonographic and/or radiological characteristics and/or increased CA-125/CA 19–9), surgical approach, surgical staging, laterality and tumor size (the largest tumor diameter in case of bilateral lesions), presence and site of BOT implants, intraoperative and postoperative complications, follow-up data.

Cases previous to the use of the 2014 FIGO staging system [9] were retrospectively restaged according to this system based on retrieved surgical and pathologic findings. In case of incomplete surgical staging unexplored abdominal areas were considered free from BOT implants. In detail, incomplete surgical staging was defined as the omission of one or more of the following surgical steps: complete exploration of the abdominal cavity (including visualization of diaphragmatic domes, gastric serosa, liver surface, omentum, accessible ileal loops and mesentery, colon, appendix, peritoneum), peritoneal biopsies, peritoneal washing, omental removal.

Intraoperative and postoperative complications were reported according to the Clavien-Dindo (CD) classification [10]; in particular, we defined severe postoperative complications those with a CD

grade > II.

Pathological reports were searched for extraction of the following pathological data: tumor size, histotype, stromal microinvasion, micropapillary pattern and intraepithelial carcinoma, peritoneal cytology. Since World Health Organization (WHO) nomenclature for BOT histotype have changed over the last twenty years, all included cases were reported according to the last WHO edition [7].

2.2. Study outcomes

The primary study outcome was disease-free survival (DFS) at 5 years follow-up, defined as time from surgery until diagnosis of recurrence.

Secondary study outcomes were:

- overall survival (OS) at 5 years follow-up, defined as time from surgery until death from any cause;

- disease-specific survival (DSS) at 5 years follow-up, defined as time from surgery until death due to BOT;

- hazard ratio (HR) for recurrence in women who underwent hysterectomy compared to women who preserved the uterus;

- HR for death of any cause in women who underwent hysterectomy compared to women who preserved the uterus;

- HR for death due to BOT in women who underwent hysterectomy compared to women who preserved the uterus;

- intra- and post-operative complications rates.

2.3. Statistical analysis

Patient demographic and clinical characteristics were reported as frequencies and percentages for categorical variables, and as mean ± standard deviation or median and absolute range for continuous variables. Differences in baseline characteristics between the two study groups were assessed with the chi-squared test, Fisher's exact test, Student's t-test and Mann–Whitney test, where appropriate. Differences in OS, DSS and DFS were analyzed and illustrated with the Kaplan–Meier method and log-rank test, using the date of surgery as the time origin and right-censoring patients lost to follow-

up at the time of the status last known. The 5-year survival status was compared with the asymptotic z test for proportions. The Cox proportional hazards model was used to adjust for potential confounders, enabling an evaluation of the independent effect of hysterectomy on survival outcomes while simultaneously accounting for all relevant variables. In particular, we performed a multivariate analysis considering all the relevant variables using a backward stepwise approach. The prognostic power of covariates was expressed by HR with 95 % confidence intervals (CI). The proportional-hazards assumption was confirmed after checking for nonzero slope of scaled Schoenfeld residuals on time. The median follow-up was calculated with the reverse Kaplan-Meier method. Significance was set at $p < 0.05$. All analyses were carried out using IBM SPSS Statistics for Windows software, Version 28.0 (Armonk, NY: IBM Corp).

2.3.1. Sample size analysis

We assumed an 11 % increase (from 87 % to 98 %, with an HR of 0.15) in the 5-year DFS rate of the hysterectomy group compared to the DFS of the non-hysterectomy group [5]. Considering a two-sided log-rank test with $\alpha = 0.05$ and a power of 80 %, we planned to recruit at least 148 subjects (74 per group) in order to observe at least 11 events (relapses).

3. RESULTS

3.1. Study population

During the study period, 545 postmenopausal women underwent surgical treatment for BOT in the 20 participating centers. Sixty-two (11.4 %) patients not meeting the selection criteria were excluded. Thus, 483 patients were included in the study: 144 (29.8 %) women in the no-hysterectomy group and 339 (70.2 %) in the hysterectomy group.

Of the 144 women who did not undergo hysterectomy, data about the reason for choosing to preserve the uterus were available for 103 (71.5 %) women. In particular, the reason was absence of BOT suspicion during the preoperative assessment of the adnexal masses in 63 (61.2 %) women, women choice in 15 (14.6 %), and decrease of surgical risk based on comorbidities in 25 (24.3 %).

Demographic and clinical characteristics of the whole study population and per study groups were shown in Table 1. Mean age ± SD of patients was 63.0 ± 13.0 years in the no-hysterectomy group and 69.3 ± 10.9 years in the hysterectomy group, with a significant difference (p < 0.001). No statistically significant difference between the two groups was found in terms of BMI, parity, ASA score and previous abdominal surgery. CA 125 levels were significantly increased in patients undergoing hysterectomy (p < 0.001), while no difference between the two groups was recorded for CA 19–9 levels. In the no-hysterectomy group, 73 patients (50.7 %) presented with a preoperative suspicion of BOT, compared to 220 patients (64.9 %) in the hysterectomy group.

Surgical data at index surgery of the whole study population and per study groups were shown in Table 2. Women undergoing hysterectomy had a significantly higher rate of bilateral lesion (p = 0.003), laparotomic approach (p < 0.001), peritoneal biopsies (p = 0.009), peritoneal washing (p < 0.001) and omentectomy (p < 0.001). No-hysterectomy group had a significant higher rate of incomplete staging (p < 0.001). At index surgery, 91.9 % of the entire study population underwent bilateral salpingo-oophorectomy, while 8.1 % had a history of previous unilateral salpingo-oophorectomy and removed only the remaining adnexa. Hysterectomy group patients had a significant higher rate of bilateral adnexectomy at index surgery (p = 0.002). The hysterectomy group showed a significantly longer operative time (p < 0.001), higher intraoperative estimated blood loss (p = 0.001) and longer hospitalization (p < 0.001) compared to the no-hysterectomy one. In all cases, complete cytoreduction of the disease was achieved.

Pathological data of the whole population and per study group were expressed in Table 3. Most of BOT had FIGO stage IA (66.0 %), without difference in terms of FIGO stage between the two study groups. Among patients who underwent hysterectomy with FIGO stage IIB, three microscopic lesions out of 21 cases (14.3 %) were found. Of the 23 patients with FIGO stage III, BOT implants involved the abdominal peritoneum in 20 (87 %), the bowel in 18 (78.3 %), and the omentum in 1 (4 %) of cases, respectively. No diaphragmatic lesion was reported.

Mean tumor size was significantly higher in the hysterectomy group compared to that of the no-

hysterectomy group (p < 0.001). Stromal microinvasion (p = 0.027), positive peritoneal cytology (p = 0.038) and extrapelvic peritoneal implants (p = 0.001) were significantly more frequent among women undergoing hysterectomy. No other significant difference in terms of pathological findings was reported between the groups.

Oncological outcomes of the whole study population and per study groups were shown in Table 4. Median follow-up time was 79.3 months (range, 17.8–236.0 months) in the hysterectomy group and 86.0 months (range, 60.0–209.1 months) in the no-hysterectomy group (p = 0.158).

Twenty-one recurrences (4.3 %) were observed during the follow-up period. Recurrences were significantly more common in the no-hysterectomy group compared to hysterectomy one (12/144, 8.3 % vs. 9/339, 2.7 %; *p* = 0.012). No significant difference was reported regarding the site of the recurrence between the two groups (Supplementary Table 1). Specifically, in the no-hysterectomy group, no uterine recurrence was found during the follow-up period.

Twenty-one (4.4 %) deaths from any cause were reported: 15 (4.4 %) in the hysterectomy group and 6 (4.2 %) in the no-hysterectomy group, without significant difference (*p* = 1.000).

Four (1.2 %) deaths due to BOT occurred in the hysterectomy group and only one (0.7 %) in the no-hysterectomy group, without significant difference (p = 1.000). Only one death related to BOT recurrence and progression was reported during the 5-year follow-up period.

3.2 Study outcomes

3.2.1. Survival analyses

The 5-year DFS rate was lower in the no-hysterectomy group than that in the hysterectomy one [92.4 % (95 %CI: 86.6 %–95.7 %) vs 98.5 % (95 %CI: 96.5 %–99.4 %); p = 0.007]. The 5-year OS and DSS rate did not significantly differ between the no-hysterectomy and the hysterectomy groups [100.0 % vs 99.7 % (95 %CI: 97.9 %–99.9 %); p = 0.315]. Kaplan-Meier curves of DFS, OS, DSS according to the presence of hysterectomy in the surgical treatment were reported in Fig. 1, Supplementary Fig. 1, Supplementary Fig. 2, respectively.

Results of Cox proportional hazards models used to study the association between clinic pathological

variables [hysterectomy, age, CA 125 > 35 U/ml, ASA score ≥ III, advanced FIGO stage (IIIA1, IIIA2, IIIB), tumor size ≥100 mm, histotype, intraepithelial carcinoma, micropapillary pattern, stromal microinvasion, surgical approach, omentectomy, incomplete staging] and DFS, OS and DSS were reported in Tables 5, 6 and 7, respectively.

At univariate analyses, women who underwent hysterectomy showed a HR of 0.312 (95 %CI: 0.131–0.740; p = 0.008) for recurrence (Table 5) 1.177 (95 %CI: 0.456–3.037; p = 0.736) for death of any cause (Supplementary Table 2), 1.932 (95 %CI: 0.215–17.346; p = 0.557) for death due to BOT (Supplementary Table 3).

At multivariate analysis, hysterectomy was found to be an independent protective factor for recurrence (HR = 0.253, 95 %CI:0.103–0.618, p = 0.003, Table 5).

3.2.2. Perioperative complications

Of the entire study population, 13 patients (2.7 %) experienced intraoperative complications, while 33 patients (6.8 %) experienced postoperative complications.

However, the two study groups did not significantly differ in terms of intraoperative complications [4/144 (2.8 %) in the no-hysterectomy group vs. 9/339 (2.7 %) in the hysterectomy group; p = 1.000], and postoperative complications [7/144 (4.9 %) in the no-hysterectomy group vs. 26/339 (7.7 %); p = 0.327). Yet, regarding severe postoperative complications, 8 (1.6 %) cases were reported in the entire population, without significant difference between the two study groups: 2 (1.4 %) in the no -hysterectomy group vs. 6 (1.8 %) in the hysterectomy group (p = 1.000).

4. DISCUSSION

4.1. Principal findings

This study showed that postmenopausal women undergoing hysterectomy for BOT had a significant lower risk of recurrence compared to women not undergoing hysterectomy, although no significant difference in terms of death from any cause, death due to BOT and perioperative complications was reported among the two groups.

4.2. Results in the context of what is known

BOTs account for 15 % of all ovarian epithelial tumors [5] and, differently from invasive ovarian carcinomas, are characterized by a favorable prognosis [1]. In particular, death due to BOT is a rare event with 10-year survival rate reaching 97 % for all combined stages [4], while recurrence is not uncommon (ranging from 5 to 34 %) [2,11–15]. The recurrence rates after surgery for BOT vary according to the presence of one or more recognized risk factors, such as FIGO stage and fertility-sparing surgery [5]. In the present study, we found a recurrence rate of 4.3 %, occurring in 21 out of 483 patients after a median follow-up of 81.2 months (range, 17.8–236.0 months). Our findings seem to confirm that recurrence is a rare event in postmenopausal women undergoing removal of both adnexa, highlighting the crucial role of residual ovarian tissue as a recurrence risk factor [4,14]. On the other hand, the prognostic role of hysterectomy appears not well defined in the literature. Indeed, international guidelines differ for indication to hysterectomy among postmenopausal patients [1,3,13,16]. In particular, while National Comprehensive Cancer Network (NCCN) guidelines recommend hysterectomy [1], British Gynecological Cancer Society (BGCS) do not recommend it [16], Collège National des Gynécologues et Obstétriciens Français (CNGOF) recommend it only for endometroid histotype [13], and European Society for Medical Oncology - European Society of Gynecological Oncology (ESMO-ESGO) consensus does not provide specific guidance on hysterectomy among postmenopausal women [3], allowing the decision to remove or preserve the uterus to be made on a case-by-case basis. This remarkable heterogeneity regarding indications for hysterectomy among postmenopausal women with BOT reflects the lack of data on the impact of hysterectomy alone on survival outcomes.

Recently, a meta-analysis was carried out to clarify the impact of hysterectomy on survival outcomes in women with BOT [4], reporting a significantly lower risk of recurrence among women who underwent hysterectomy compared to those who had uterine-sparing surgery, while no significant differences in the risk of death due to BOT and death of any cause were observed between the two groups [4]. Nevertheless, patients undergoing uterine-sparing surgery without ovarian preservation

could not be excluded from the analysis. In contrast to the findings of this meta-analysis [4], a multicenter retrospective study [5] found that uterine preservation did not increase risk of recurrence or death of any cause compared to hysterectomy among postmenopausal women. However, the results of this study, based on a small sample size, required validation with a larger patient cohort [5].

4.3. Clinical implications

In this study, hysterectomy was found to be a protective factor for recurrence among postmenopausal women, reducing the risk of recurrence by 74.7 %.

An explanation for the risk of recurrence of BOT associated with uterine preservation might be the possible cytoreductive role of hysterectomy regarding microscopic foci or cells of BOT disseminated on the peritoneum removed during hysterectomy. Peritoneal spread of these microscopic foci or cells of BOT might explain the higher risk of peritoneal (also extra-pelvic) BOT recurrences in the no-hysterectomy group.

Considering the findings of this study, hysterectomy should be included in the surgical management of BOT among postmenopausal women. However, women should be informed that recurrence rate of BOT remains very low in menopause when both adnexa are removed. Thus, in case of women with challenging hysterectomy (e.g. large uterus, high BMI, previous pelvic surgery, previous pelvic inflammatory disease and/or endometriosis), high surgical risk and/or low performance status, uterine preservation can be reasonably proposed.

4.4. Research implications

This study includes patients treated from 2005 to 2017, a relatively long period during which the diagnostic criteria for the histologic subtypes of BOT have evolved, with the most recent updates introduced in the 2014 WHO Classification of Tumors of the Female Genital Organs [7]. This edition presented new terminology for non-invasive implants associated with serous BOT, while any invasive foci (formerly defined invasive implants) were classified as peritoneal LGSC (low-grade serous carcinoma), reflecting their biological behavior more accurately. Despite the latest classification, the diagnosis of BOT remains challenging in certain cases, particularly those involving

microinvasion, intraepithelial carcinoma, and non-invasive peritoneal implants. The complexities in diagnosis and the updated histopathological terminology highlight the need for further studies including a centralized reevaluation of surgical specimens to validate our findings. Additionally, future studies should further clarify the prognostic impact of incomplete surgical staging by assessing the risk of BOT recurrence in women who have not undergone a complete exploration of the abdomen.

Finally, a cost-effectiveness study comparing hysterectomy and uterine-sparing surgery would be valuable to evaluate the efficiency and sustainability of both approaches for the surgical treatment of BOT in postmenopausal women.

4.5. Strengths and limitations

An important strength of our study is the large size of the study population: indeed, an adequate control of type II error, achieved through an a priori sample size calculation based on a preliminary study [5], allows to generalize these results, clarifying the impact of hysterectomy alone on survival outcomes among women with BOT. Another strength of our study is the follow-up length: a mean follow-up of 79.3 months in the hysterectomy group and 86.0 months in the no-hysterectomy group. However, our study has some limitations. As above-mentioned, most patients in the no-hysterectomy group underwent incomplete surgical staging with the risk of being potentially understaged. Furthermore, despite the methodology adopted per protocol to minimize confounding factors, our results may be limited by the retrospective nature of the study and lack of centralized pathological evaluation of the surgical specimens. Finally, we recognize that the study is not powered enough to fully examine OS and DSS, due to the high number of patients lost at follow-up after 5 years and the low number of deaths.

5. CONCLUSION

In postmenopausal women, hysterectomy seems to decrease the risk of recurrence, but not the risk of death from any cause and the risk of death due to BOT. Hysterectomy should be routinely included

in the surgical staging of BOT among postmenopausal women.

curation. Maria Giovanna Vastarella: Visualization, Validation, Investigation, Data curation. Davide Calandra: Visualization, Validation, Investigation, Data curation. Alexandro Paccapelo: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Jacopo Lenzi: Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. Luigi Cobellis: Visualization, Validation, Investigation, Data curation. Giovanni Scambia: Visualization, Validation, Supervision, Investigation, Data curation. Giuseppe Vizzielli: Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. Renato Seracchioli: Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

ETHICS STATEMENT

The study received approval from the Institutional Review Board of the IRCCS Azienda Ospedaliero-Universitaria di Bologna (Id: CE-AVEC 827/2021/Oss/AOUBo) and the other participating centers. The study was carried out in accordance with the Helsinki Declaration. All patients signed an informed consent for the use of their data with previous anonymization.

FUNDING DETAILS

No financial support was received for this study.

COMPETING INTERESTS

The authors report no conflict of interest.

REFEENCES

[1] Liu J, Berchuck A, Backes FJ, Cohen J, Grisham R, Leath CA, Martin L, Matei D, Miller DS, Robertson S, Barroilhet L, Uppal S, Hendrickson AW, Gershenson DM, Gray HJ, Hakam A, Jain A, Konecny GE, Moroney J, Ratner E, Schorge J, Thaker PH, Werner TL, Zsiros E, Behbakht K, Chen LM, DeRosa M, Eisenhauer EL, Leiserowitz G, Litkouhi B, McHale M, Percac-Lima S, Rodabaugh K, Vargas R, Jones F, Kovach E, Hang L, Ramakrishnan S, Alvarez RD, Armstrong DK. NCCN Guidelines® Insights: Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer, Version 3.2024. J Natl Compr Canc Netw. 2024 Oct;22(8):512-519. doi: 10.6004/jnccn.2024.0052. PMID: 39413835.

[2] Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. Oncologist. 2012;17(12):1515-33. doi: 10.1634/theoncologist.2012-0139. Epub 2012 Sep 28. PMID: 23024155; PMCID: PMC3528384.

[3] Colombo N, Sessa C, Bois AD, Ledermann J, McCluggage WG, McNeish I, Morice P, Pignata S, Ray-Coquard I, Vergote I, Baert T, Belaroussi I, Dashora A, Olbrecht S, Planchamp F, Querleu D; ESMO–ESGO Ovarian Cancer Consensus Conference Working Group. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer. 2019 May 7;29(4):728-760. doi: 10.1136/ijgc-2019-000308. PMID: 31048403.

[4] Raimondo D, Raffone A, Zakhari A, Maletta M, Vizzielli G, Restaino S, Travaglino A, Krishnamurthy S, Mabrouk M, Casadio P, Mollo A, Scambia G, Seracchioli R. The impact of hysterectomy on oncological outcomes in patients with borderline ovarian tumors: A systematic review and meta-analysis. Gynecol Oncol. 2022 Apr;165(1):184-191. doi: 10.1016/j.ygyno.2022.01.019. Epub 2022 Jan 26. PMID: 35090745.

[5] Raimondo D, Raffone A, Scambia G, Maletta M, Lenzi J, Restaino S, Mascilini F, Trozzi R, Mauro J, Travaglino A, Driul L, Casadio P, Mollo A, Fagotti A, Vizzielli G, Seracchioli R. The impact of hysterectomy on oncological outcomes in postmenopausal patients with borderline ovarian

tumors: A multicenter retrospective study. Front Oncol. 2022 Oct 27;12:1009341. doi: 10.3389/fonc.2022.1009341. PMID: 36387131; PMCID: PMC9647053.

[6] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014 Dec;12(12):1495-9. doi: 10.1016/j.ijsu.2014.07.013. Epub 2014 Jul 18. PMID: 25046131.

[7] Hauptmann S, Friedrich K, Redline R, Avril S. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. Virchows Arch. 2017 Feb;470(2):125-142. doi: 10.1007/s00428-016-2040-8. Epub 2016 Dec 27. PMID: 28025670; PMCID: PMC5298321.

[8] Abouleish, Amr E. M.D., M.B.A; Leib, Marc L. M.D., J.D.; Chair; Cohen, Neal H. M.D., M.P.H., M.S.; Chair. ASA Provides Examples to Each ASA Physical Status Class. ASA Monitor 79(6):p 38-49, June 2015. doi: 10.1097/01.ASM.0001073116.40041.ee.

[9] Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014 Jan;124(1):1-5. doi: 10.1016/j.ijgo.2013.10.001. Epub 2013 Oct 22. PMID: 24219974.

[10] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL, Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009 Aug;250(2):187-96. doi: 10.1097/SLA.0b013e3181b13ca2. PMID: 19638912.

[11] Donnez J, Munschke A, Berliere M, Pirard C, Jadoul P, Smets M, Squifflet J. Safety of conservative management and fertility outcome in women with borderline tumors of the ovary. Fertil Steril. 2003 May;79(5):1216-21. doi: 10.1016/s0015-0282(03)00160-2. PMID: 12738521.

[12] du Bois A, Ewald-Riegler N, de Gregorio N, Reuss A, Mahner S, Fotopoulou C, Kommoss F, Schmalfeldt B, Hilpert F, Fehm T, Burges A, Meier W, Hillemanns P, Hanker L, Hasenburg A, Strauss HG, Hellriegel M, Wimberger P, Keyver-Paik MD, Baumann K, Canzler U, Wollschlaeger K, Forner D, Pfisterer J, Schröder W, Münstedt K, Richter B, Kommoss S, Hauptmann S;

Arbeitsgmeinschaft Gynäkologische Onkologie (AGO) Study Group. Borderline tumours of the ovary: A cohort study of the Arbeitsgmeinschaft Gynäkologische Onkologie (AGO) Study Group. Eur J Cancer. 2013 May;49(8):1905-14. doi: 10.1016/j.ejca.2013.01.035. Epub 2013 Mar 13. PMID: 23490647.

[13] Canlorbe G, Lecointre L, Chauvet P, Azaïs H, Fauvet R, Uzan C. Tumeurs frontières de l'ovaire. Recommandations pour la pratique clinique du CNGOF – Prise en charge thérapeutique des stades précoces [Borderline Ovarian Tumours: CNGOF Guidelines for Clinical Practice - Therapeutic Management of Early Stages]. Gynecol Obstet Fertil Senol. 2020 Mar;48(3):287-303. French. doi: 10.1016/j.gofs.2020.01.016. Epub 2020 Jan 28. PMID: 32004786.

[14] Sangnier E, Ouldamer L, Bendifallah S, Huchon C, Collinet P, Bricou A, Mimoun C, Lecointre L, Graesslin O, Raimond E. Risk factors for recurrence of borderline ovarian tumors in France: A multicenter retrospective study by the FRANCOGYN group. J Gynecol Obstet Hum Reprod. 2021 Apr;50(4):101961. doi: 10.1016/j.jogoh.2020.101961. Epub 2020 Oct 28. PMID: 33127559.

[15] Westermann T, Karabeg E, Heitz F, Traut A, Plett H, Moubarak M, Welz J, Heikaus S, Lax S, du Bois A, Harter P. Role of fertility-sparing surgery and further prognostic factors in borderline tumors of the ovary. Int J Gynecol Cancer. 2024 Jun 3;34(6):898-905. doi: 10.1136/ijgc-2023-005214. PMID: 38627034.

[16] Moss E, Taylor A, Andreou A, Ang C, Arora R, Attygalle A, Banerjee S, Bowen R, Buckley L, Burbos N, Coleridge S, Edmondson R, El-Bahrawy M, Fotopoulou C, Frost J, Ganesan R, George A, Hanna L, Kaur B, Manchanda R, Maxwell H, Michael A, Miles T, Newton C, Nicum S, Ratnavelu N, Ryan N, Sundar S, Vroobel K, Walther A, Wong J, Morrison J. British Gynaecological Cancer Society (BGCS) ovarian, tubal and primary peritoneal cancer guidelines: Recommendations for practice update 2024. Eur J Obstet Gynecol Reprod Biol. 2024 Sep;300:69-123. doi: 10.1016/j.ejogrb.2024.06.025. Epub 2024 Jun 21. PMID: 39002401.

TABLES

Table 1. Demographic and clinical characteristics of the whole study population and per study groups.

Characteristic	Study population	No-hysterectomy group	Hysterectomy group	p-value
	$n = 483$	$n = 144$	$n = 339$	
Age [years], mean ± SD	67.4 ± 11.9	63.0 ± 13.0	69.3 ± 10.9	<0.001
BMI [kg/m²], mean ± SD	25.8 ± 4.9	25.6 ± 5.6	25.8 ± 4.6	0.711
Parity ≥ 1, n (%)	355 (73.5)	110 (76.4)	245 (72.3)	0.348
ASA score, n (%)				
I-II	402 (83.2)	121 (84)	281 (82.9)	0.792
III	81 (16.8)	23 (16)	58 (17.1)	
Previous abdominal surgery, n (%)	221 (45.8)	57 (39.6)	164 (48.8)	0.090
CA 125 > 35 U/ml, n (%)	150 (31.1)	25 (17.4)	125 (36.9)	<0.001
CA 19–9 > 37 U/ml, n (%)	62 (12.8)	18 (12.5)	44 (13.0)	1.000

SD = standard deviation; CA = cancer antigen; BMI = Body Mass Index; ASA = American Society of Anesthesiologists; BOT = borderline ovarian tumor.

Table 2. Surgical data of the whole study population and per study groups.

Characteristics	Study population n = 483	No-hysterectomy n = 144	Hysterectomy n = 339	p-value
Laterality of BOT, n (%)				
- Right	206 (42.7)	56 (38.9)	150 (44.2)	
- Left	184 (38.1)	70 (48.6)	114 (33.6)	0.003
- Bilateral	93 (19.3)	18 (12.5)	75 (22.1)	
Surgical approach, n (%)				
- LPT	256 (53.0)	38 (26.4)	218 (64.3)	
- LPS	214 (44.7)	102 (70.8)	114 (33.6)	
- Robot	1 (0.2)	0	1 (0.3)	<0.001
- Vaginal	2 (0.4)	0	2 (0.6)	
- LPS-LPT	8 (1.7)	4 (2.8)	4 (1.2)	
Salpingo-oophorectomy, n (%)				
- Unilateral	39 (8.1)	21 (14.6)	18 (5.3)	0.002
- Bilateral	444 (91.9)	123 (85.4)	321 (94.7)	
Peritoneal biopsies, n (%)	318 (65.8)	82 (56.9)	236 (69.6)	0.009
Peritoneal washing, n (%)	402 (83.2)	99 (68.8)	303 (89.4)	<0.001
Appendectomy, n (%)	60 (12.4)	14 (9.7)	46 (13.6)	0.292
Omentectomy, n (%)	160 (33.1)	9 (6.3)	151 (44.5)	<0.001
Omental biopsies, n (%)	141 (29.2)	37 (25.7)	104 (30.7)	0.325
Peritonectomy, n (%)				
- No	473 (97.9)	144 (100.0)	329 (97.1)	
- Pelvic	9 (1.9)	0	9 (2.7)	0.114
- Extrapelvic	1 (0.2)	0	1 (0.3)	
Incomplete staging, n (%)	248 (51.3)	110 (76.4)	138 (40.7)	<0.001
Operative time [min], mean ± SD	83.0 ± 39.8	120.2 ± 54.7	245 ± 52.3	<0.001
Intraoperative blood loss [ml], mean ± SD	94.0 ± 105.2	146.4 ± 199.5	165.9 ± 221.8	0.001
Hospitalization [days], mean ± SD	3.6 ± 2.0	4.6 ± 2.5	5.1 ± 2.6	<0.001

SD = standard deviation; BOT = borderline ovarian tumors; LPT = laparotomy; LPS = laparoscopy; LPS-LPT = conversion from laparoscopy to laparotomy.

Table 3. Pathological data of the whole study population and per study groups.

	Study population	No-hysterectomy group	Hysterectomy group	p-value
	n = 483	n = 144	n = 339	
FIGO stage, n (%)				
- IA	319 (66.0)	109 (75.7)	210 (61.9)	
- IB	33 (6.8)	12 (8.3)	21 (6.2)	
- IC1	51 (10.6)	10 (6.9)	41 (12.1)	
- IC2	11 (2.3)	2 (1.4)	9 (2.7)	
- IC3	15 (3.1)	4 (2.8)	11 (3.2)	0.059
- IIA	7 (1.4)	0	7 (2.1)	
- IIB	24 (5.0)	3 (2.1)	21 (6.2)	
- IIIA1	4 (0.8)	1 (0.7)	3 (0.9)	
- IIIA2	2 (0.4)	1 (0.7)	1 (0.3)	
- IIIB	17 (3.5)	2 (1.4)	15 (4.4)	
Tumor size [mm], mean ± SD	117.5 ± 85.5	88.0 ± 65.5	130.8 ± 90.1	<0.001
Histotype, n (%)				
- Mucinous	183 (37.9)	50 (34.7)	133 (39.2)	
- Endometrioid	12 (2.5)	1 (0.7)	11 (3.2)	
- Serous	257 (53.2)	84 (58.3)	173 (51.0)	0.229
- Brenner	8 (1.7)	1 (0.7)	7 (2.1)	
- Sero-mucinous	23 (4.8)	8 (5.6)	15 (4.4)	
Stromal microinvasion, n (%)	32 (6.6)	4 (2.8)	28 (8.3)	0.027
Micropapillary pattern, n (%)	28 (5.8)	8 (5.6)	20 (5.9)	0.370
Intraepithelial carcinoma, n (%)	55 (11.4)	16 (11.1)	39 (11.5)	1.000
Positive peritoneal cytology, n (%)	44 (9.1)	7 (4.9)	37 (10.9)	0.038

SD = standard deviation; FIGO = International Federation of Gynecology and Obstetrics; BOT = borderline ovarian tumors.

Table 4. Oncological outcomes and peri-operative complications of the whole study population and per study groups.

Characteristic	Study population	No-hysterectomy group	Hysterectomy group	p-value
	n = 483	n = 144	n = 339	
Intraoperative complications, n (%)	13 (2.7)	4 (2.8)	9 (2.7)	1.000
- No complications	470 (97.3)	140 (97.2)	330 (97.3)	0.889
- Bowel injury	5 (1.0)	2 (1.4)	3 (0.9)	
- Ureteral injury	1 (0.2)	0	1 (0.3)	
- Hemorrhage	6 (1.2)	2 (1.4)	4 (1.2)	
- Major vascular injury	1 (0.2)	0	1 (0.3)	
Clavien-Dindo post-operarative complicationa, n (%)	33 (6.8)	7 (4.9)	26 (7.7)	0.327
- I	10 (2.1)	2 (1.4)	8 (2.4)	0.723
- II	15 (3.1)	3 (2.1)	12 (3.5)	
- IIIA	2 (0.4)	2 (1.4)	0	
- IIIB	6 (1.2)	0	6 (1.8)	
Recurrence, n (%)	21 (4.3)	12 (8.3)	9 (2.7)	0.012
Death from any cause, n (%)	21 (4.3)	6 (4.2)	15 (4.4)	1.000
Death due to BOT, n (%)	5 (1)	1 (0.7)	4 (1.2)	1.000

SD = standard deviation; FIGO = International Federation of Gynecology and Obstetrics; LPT = laparotomy. BOT = borderline ovarian tumors.

Table 5. Results of a Cox proportional hazards models used to study the association between clinical variables and DFS.

Disease-free survival	Univariate models			Multivariate model (backward stepwise approach)		
Disease-free survival	HR	95 %CI	*p*-value	HR	95 %CI	*p*-value
Hysterectomy	0.312	0.131–0.740	0.008	0.253	0.103–0.618	0.003
Age (years)	0.969	0.931–1.008	0.113			
Increased CA 125	1.171	0.439–3.120	0.752			
ASA score III	0.838	0.247–2.847	0.778			
Advanced FIGO stage (IIIA1, IIIA2, IIIB)	5.135	1.727–15.268	0.003	7.419	2.402–22.915	<0.001
Tumor size ≥100 mm	1.313	0.533–3.232	0.554			
Histotype	/	/ – /	0.972			
Intraepithelial carcinoma	0.382	0.051–2.844	0.347			
Micropapillary pattern	0.801	0.108–5.969	0.829			
Stromal microinvasion	0.701	0.094–5.222	0.729			
Surgical Approach (LPS vs. LPT)	0.623	0.248–1.562	0.313			
Omentectomy	0.824	0.319–2.123	0.688			
Incomplete staging	0.822	0.349–1.938	0.655			

HR = hazard ratio; CA = cancer antigen; FIGO = International Federation of Gynecology and Obstetrics; CI = confidence interval; LPS = laparoscopy; LPT = laparotomy.

FIGURES

Figure 1. Kaplan–Meier estimates of DFS according to the presence of hysterectomy in the surgical treatment.