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Ovarian borderline tumors, a subtype of neoplasm with controversial behavior. Role of Ki67 as a prognostic factor

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ABSTRACT

Introduction: Ovarian borderline tumors (OBT) are tumors with an intermediate grade of malignancy whose diagnosis is purely based on morphological criteria. They usually occur in young women (under 40 years) and are characterized by a cellular proliferation with slight nuclear atypia and lacking stromal invasion with a destructive pattern. Aim of this study was to explore the immunohistochemical expression of Ki67 proliferative index in OBT and to correlate it with known clinicopathologic prognostic factors in patients older than 40 years.
Material and methods: Twenty cases of OBTdiagnosed in the period ranging from 2016 to 2018 were retrieved. Each specimen was taken from hysterectomy or adnexectomy surgery. Immunohistochemical studies were performed on the most representative sample of the tumor. Positive signal was nuclear and it was evaluated by three independent pathologists.
Results: Ki67 Labelling Index (L.I.) value ranged from 2% to 40%, with an average value of 14% and a median of 10%. Higher Ki67 L.I. was observed in patients older than 40 years ($p$value = 0.0194) and in those with tumors with a maximum diameter ≥ 10 cm ($p$value = 0.0547). Furthermore, a direct correlation was evident between tumor size value and Ki67 L.I. (p value < 0.0001, r = 0.7745). Hitherto no known prognostic factor correlated with high Ki67 L.I.
Conclusions: Overall, OBT are tumors with greater risk of evolution at a more advanced age and when they are greater in size. The assessment of Ki67 could be a valid support in the diagnosis of a more aggressive tumor. Further studies are needed to assess possible correlation with data concerning recurrences rate, that in our cases were not available.

1. Introduction

Ovarian borderline tumors (OBT) are epithelial neoplasms characterized by a cellular proliferation with slight nuclear atypia and lacking stromal invasion with a destructive pattern [1] and usually affecting young women (< 40 years). The definition “borderline” derives from the biological behavior of this tumor that is nearly benign, despite the presence of peritoneal involvement. However, by the years it was observed that the behavior of these neoplasms was highly heterogeneous and many parameters have been investigated [2] as possible prognostic markers.

It is difficult to identify a borderline tumor clinically, radiologically and serologically. In most patients the diagnosis is incidental, during a routine ultrasound examination. Symptoms are aspecific and related to mass effect, as abdominal pain, pelvic pain, impaired intestinal transit or dyspareunia. Echografic [3] as well as Magnetic Resonance Imaging (MRI) [4] findings are not highly sensitive to predict this diagnosis. Indeed, a three-stage multimodal screening strategy [5] is being implemented for the pre-surgical identification of these tumors. It would consist of a first line based on blood assays, followed by a second line echografy that could be integrated by a third line MRI in case where the first two examination were discordant.

According to the current World Health Organization (2014 WHO) Classification [1], these tumors are also called atypical proliferative tumors. Six histologic subtypes are distinguished on the base of the epithelial cell type they derive from: serous OBT, that represent around

Abbreviations: OBT, Ovarian Borderline Tumor; L.I., Labelling Index; MRI, Magnetic Resonance Imaging; WHO, World Health Organization; NET, neuroendocrine tumor; EDTA, Ethylenediamine tetraacetic acid; FIGO, International Federation of Gynecology and Obstetrics

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Table 1
Characteristics of 20 cases included in the study.

Cases	Age (y)	Size (cm)	Site	Surface	Surgery	FIGO stage	Histotype	Prognostic factors	Ki67	Recurrence
1	71	5.7	LO	intact	a	IIb	S	microinvasion, implants	20%	no
2	25	7	LO	intact	h	IIb	M	implants	7%	no
3	54	17	LO	intact	a	Ia	M	no	25%	yes
4	43	16	LO	intact	h	Ia	M	no	27%	no
5	44	3	RO	interrupted	h	Ic	S	no	2%	no
6	51	5 and 3	RO, LO	intact	h	IIb	S	implants	6%	no
7	55	9 and 0.4	LO, RO	intact	h	Ib	S	no	20%	no
8	67	31	RO	intact	h	Ia	S	i. c.	40%	no
9*	31	4.5 and 3.5	RO, LO	intact	a	Ib	S	no	7%	no
10*	32	6 and 4	RO, LO	intact	a	Ib	S	no	9%	no
11	43	5	RO	intact	h	Ia	S	no	10%	no
12	22	4	RO	intact	h	Ia	S	no	10%	no
13	33	3	RO	intact	a	Ia	S	no	12%	no
14	61	25	RO	intact	h	Ia	M	i.c.	25%	no
15	66	5	RO	intact	h	Ia	S	no	25%	yes
16	34	2.5	LO	intact	a	Ia	S	no	5%	no
17	21	3	RO	intact	a	Ia	S	no	9%	no
18	45	4	RO	intact	a	Ia	M	no	10%	no
19	73	16 and 2.5	RO,LO	intact	a	Ib	S	no	10%	no
20	20	9	RO	intact	h	Ia	M	i.c.	5%	no

LO: left ovary; RO: right ovary; a: adnexectomy; h: hysterectomy; M: mucinous; S: serous; i.c.: intraglandular carcinoma; * same patient.

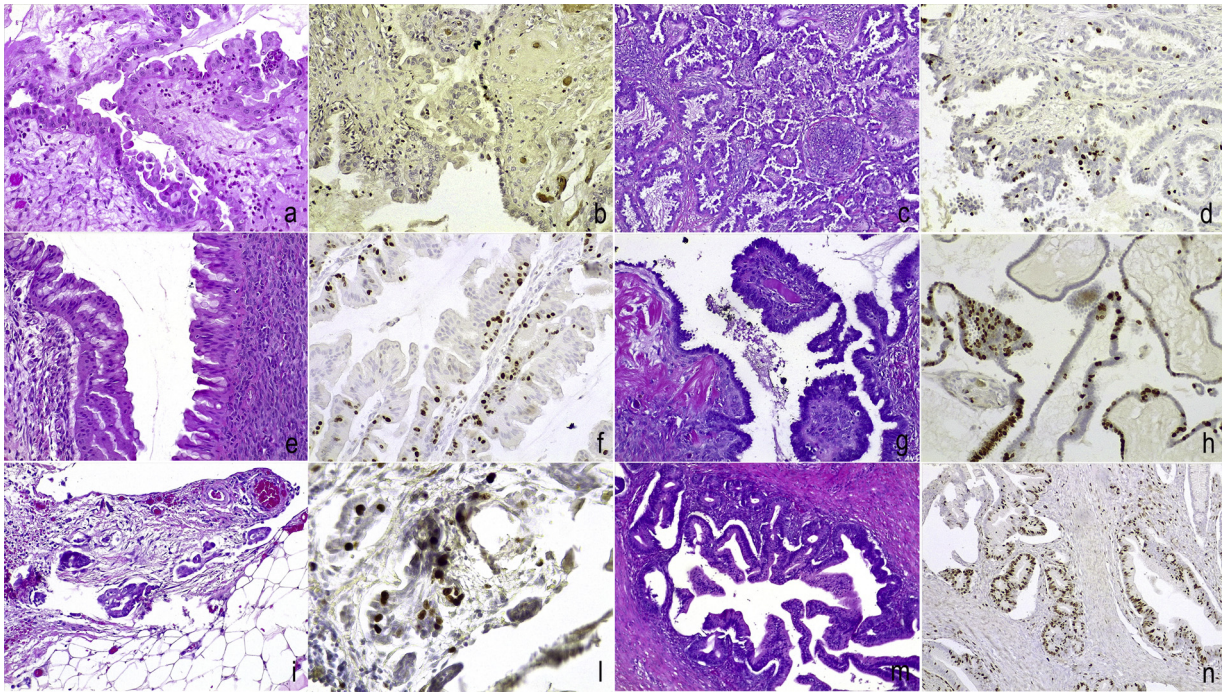

Fig. 1. a–b) Case nr16. SerousOBT (a, Hematoxylin and eosin stain, 20x magnification): in this case Ki67 L.I. (b, 20x magnification) was around 5%; **c-d) Case nr12**. Serous micropapillaryOBT (c, Hematoxylin and eosin stain, 10x magnification): in this case Ki67 L.I. (d, 20x magnification) was around 10%; **e-f) Case nr14**. Mucinous OBT with intraepithelial adenocarcinoma (e, Hematoxylin and eosin stain, 40x magnification): in this case Ki67 L.I. (f, 20x magnification) was around 25% in carcinomatous foci; **g-h) Case nr15**. SerousOBT within serous cystoadenoma (g, Hematoxylin and eosin stain, 20x magnification): in this case Ki67 L.I. (h, 20x magnification) was around 25%; **i-l) Case nr1**. Focus of non-invasive peritoneal implant from serous OBT (i, Hematoxylin and eosin stain, 20x magnification) where Ki67 L.I. was around 20% (l, 40x magnification) **m–n) Case nr8**. Intraglandular adenocarcinoma was evident within a seromucinous OBT (m, Hematoxylin and eosin stain, 40x magnification) and in those areas Ki67 L.I. was around 40% (n, 20x magnification).

50% of all cases, mucinous around 45% and other rare subtypes (endometrioid, clear cell and Brenner) that account for the rest of the cases.Most of the knowledge about the prognosis of OBT derive from the serous subtype that represents the most common type. Bilaterality, surface involvement, capsular rupture [6], presence of micropapillary/cribriform pattern [7–9], microinvasion [10], advanced stage at presentation [11,12], implant type [13] and residual disease are usually associated with more aggressive disease in serous histotype. The American Joint Committee on Caner (AJCC) and the International Federation of Gynecology and Obstetrics (FIGO) developed a staging system for OBT but the latter is the most used [14]. However, tumours without all the known prognostic features can be associated with recurrencesor low-grade serous carcinoma. Furthermore, the concept of microinvasion is controversial and not fully overlapping to what is observed in other organ systems because a significant destructive stromal response is missing.Fivepatterns of stromal microinvasion have been described: “classic” microinvasion (single eosinophilic cells and cell clusters), single and non-complex branching papillae, inverted

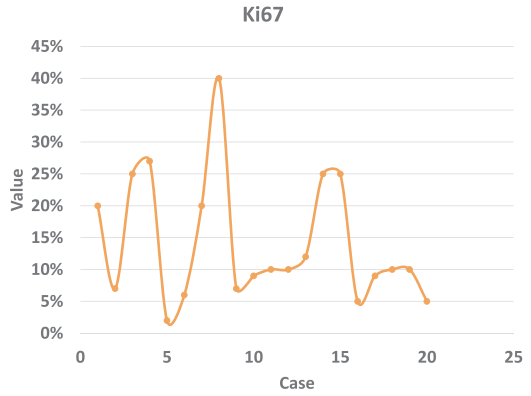

Fig. 2. Ki67 L.I. value ranged from 2% to 40%, with an average value of 14% and a median of 10%.

macropapillae, cribriform glands and micropapillae. The last three may be associated with a higher risk of disease progression [2,8]. According to the current WHO criteria [1], the extension of these foci ofstromal microinvasion must not exceed 5 mm in linear extent. As regards implant types, the previous subdivision into invasive and non-invasive implants was completely abandoned: all cases with peritoneal lesionsandwith invasion of underlyingsubperitoneal tissue or omental fat, once defined invasive implants, now are designated as foci of lowgrade serous carcinoma. In the case of mucinous subtype, the overall survival of patients with OBT with intraepithelial carcinoma is around 95% [1] in early stage disease. In all other subtypes, the prognosis is excellent. The complex plot of factors that come into play in delineating the prognosis of these intriguing tumor subtypes makes it useful to identify a factor that is easy to use and with immediate clinical impact. Ki67 is an antibody that labels nuclei of proliferatingcells including tumor cells and recognizes a nuclear protein(encoded by the MKI 67 gene) which is involved in nuclearremodeling during proliferation [15]. It is widely used in the evaluation of proliferative activity of neoplastic cells in several neoplasms (eg. in breast cancer, together with the assessment of hormonal status, it is a useful tool for risk stratification and for therapeutic decisions). In neuroendocrine tumors (NET) of the gastrointestinal tract, it was shown a strong independent prognostic power for this factor so that it was included in the current classification, that is a Ki67-based grading system [16]. Almost 10 years from the introduction of this classification, this proliferative marker survived to all the problems related to its assessment, including intertumoralandintratumoral staining heterogeneity and counting methods [15].

Aims of our study were to evaluate the possible application of NET Ki67 counting method on OBT and to correlate the results with known clinicopathologic prognostic factors in patients older than 40 years.

2. Materials and methods

Twenty cases of ovarian borderline tumors were retrieved from the archives of the Institute of Pathology of Federico II University Hospital of Naples. They were diagnosed in the period ranging from 2016 to 2018, according to the current WHO classification of tumours of the Female Reproductive Organs. Data concerning the recurrence rate were available but we decided not to include them in the study because not reliable, given the too short follow-up time. Each specimen was taken from hysterectomy ± unilateral or bilateral salpingooferectomy surgery. An extensive sampling of all the lesion was available in all cases. The most representative sample of the tumor was chosen to perform immunohistochemical studies. In the case of coexistent intraglandular carcinoma, a section including both types of neoplasms was selected. For immunohistochemical stain, after deparaffinization, slides were submerged in either sodium citrate buffer or Tris–EDTA buffer for heat induced epitope retrieval at 97 °C for 20 min. The immunostaining was performed with Ventana Detection System and the Ki67 antibody used was clone 30-9 (Rabbit, Dako).Positive signal was nuclear and it was evaluated by three independent pathologists. In general, for the evaluation of Ki67 Labeling Index, “hot spot” areas were chosen at low magnification and an average of the values obtained on 5 adjacent fields (at least 500 neoplastic cells) was calculated [17].When the score was discordant, it was assessed again, collegially, by manually counting unlabeled and labeled nuclei on a camera-captured, printed image.The study of association between the Ki67 Labelling Index (L.I.) and clinicopathological features (age, site, tumor size, histotype, surface status, known prognostic factors, recurrence and FIGO stage) was carried out by Fisher’s exact test. Pearson correlation test was used to examine the correlation between Ki67 score and size.

A p value ≤ 0.05 was considered statistically significant. All tests were two sided and carried out with GraphPad Prism 5 software (GraphPad Software, LaJolla, CA, USA).

2.1. Ethical approval

All procedures performed in studies, involving human participants, were in accordance with the ethical standards of the institutional board and with the 1964 Helsinki declaration including signed informed consent for study participation.

3. Results

The median age of 19 analyzed patients (Table 1) was of 54 years, ranging from 21 to 73 years and all of them were affected by OBT that originated from the right ovary (RO) in 11 cases, from the left ovary (LO) in 5 cases, and was bilateral in 3 cases. In one patient (case 9) bilateral biopsies were taken before and the surgical specimen of both the ovaries (case 10) was examined one year later. Tumor FIGO stage was Ia, Ib, Ic and IIb, respectively in 12, 4, 1 and 3 cases.The size of the lesions ranged from 0.4 cm (with a coexistent contralateral mass that measured 9 cm) to a mass of 31 cm, with an average value of 9.035 cm and a median size of 17 cm. The histotype (Fig. 1) was mucinous (M) in 6 cases (30%) and serous (S) in 14 cases (70%). The percentage of borderline tumor was variable within the benign cystadenoma and in 3 cases (cases 8, 14 and 20) intraglandular carcinoma was coexistent. In three cases (cases 1, 2 and 6) implants were detected; in one case (case 1) a small focus of microinvasion was evident. The capsule was always intact, except for one case (case 5). The tumor was removed by hysterectomy surgery in 11 cases and by adnexectomy in 9 cases. Ki67 L.I. value ranged from 2% to 40% (Figs. 1 and 2), with an average value of 14% and a median of 10%. In studies of association between Ki67 and clinical-pathological parameters, it emerged that higher L.I. ($\geq$10%) was more common in patients older than 40 years (p value = 0.0194) and with tumors with maximum diameter $\geq$ 10 cm (p value = 0.0547) (Fig. 3) although in the absence of statistical significance. Furthermore, a direct correlation was evident between tumor size value and Ki67 L.I. (p value < 0.0001, $r = 0.7745$) (Fig. 4) when evaluated with Pearson correlation test. No association was evident between known prognostic factors (at least one among implants, microinvasion and intraglandular carcinoma) and Ki67 $\geq$ 10% (p value = 0.6424), nor with the FIGO stage (p value = 0.2347) or the recurrence (p value = 0.5211). In 2 of 3 cases with coexistent intraglandular carcinoma, Ki67 L.I. was $\geq$10%. In absence of overlying carcinoma cases with Ki67 value $\geq$ or $<$ 10% were equally distributed (p value = 1.000).

4. Discussion

Aim of our study was to deepen our knowledge on the proliferative dynamics of OBT, which are, by definition, of intermediate grade of malignancy. In our small series, there were tumors of serous and mucinous histotype. We analyzed a group of patients older than 40 years in order to assess whether there was a difference in proliferation in this

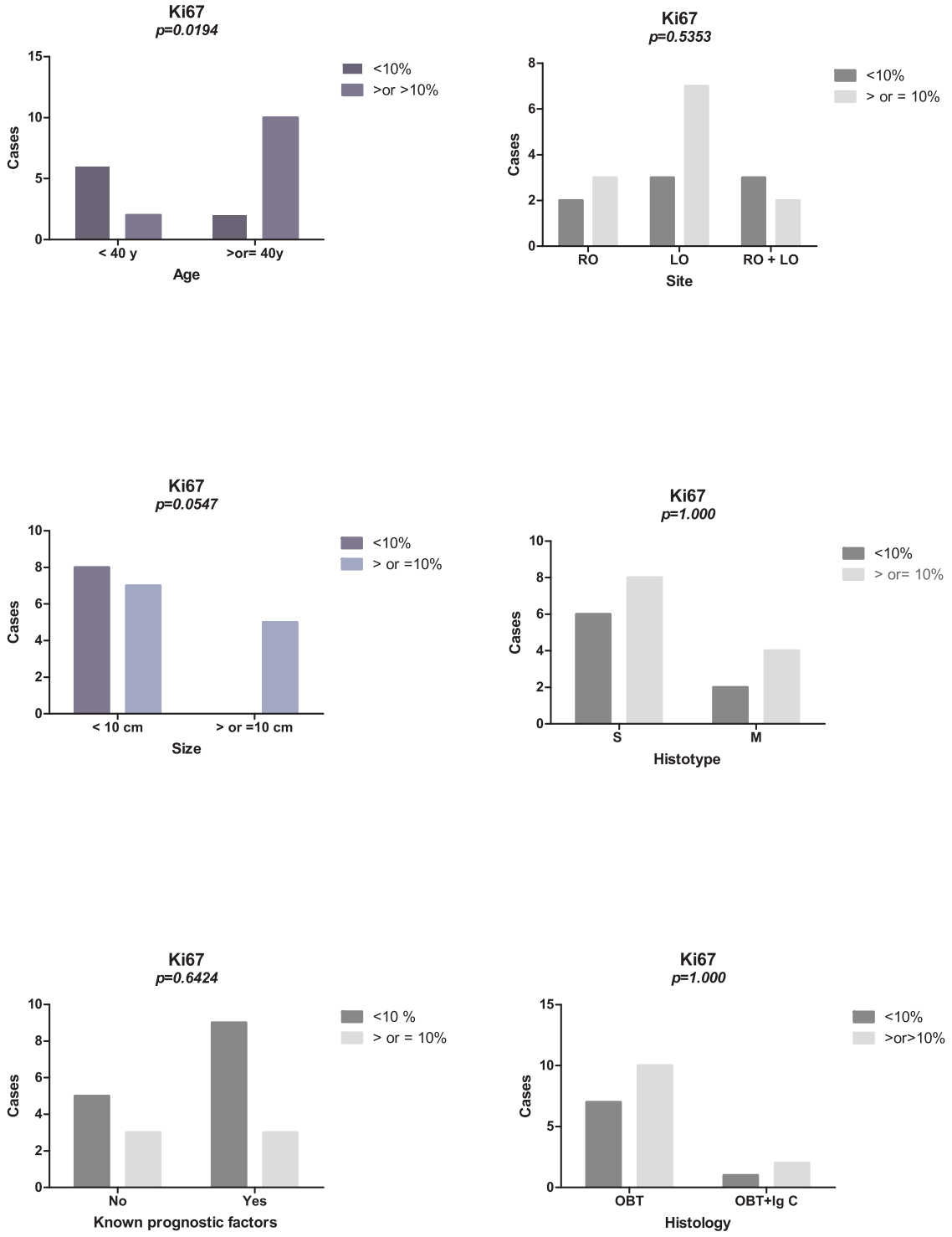

Fig. 3. Statistical analyzes performed by Fisher's exact test showed that Ki67 L.I. ≥ 10% was more common in patients older than 40 years (p value = 0.0194) and with tumors greater than 10 cm in diameter ($p$value = 0.0547).

particular population of patients. The decision to divide the population into a group older than 40 years and another younger than 40 years was completely arbitrary. No rarer forms such as endometrioid, Brenner cell or the clear cell forms were present.

It was observed a heterogeneous expression of the Ki67 index among different types of tumors that belong to the same risk category, including forms expressing very low values and forms with much higher values. In our series, there was a tendency to register higher values among larger tumors and in subjects of higher age. In patient number 9, the value of Ki67 did not increase within a year, and the lesions had increased by about 1 cm. Borderline tumors are, essentially, slow-growing tumors, which are likely to have a greater risk of evolution at an advanced age, when they already had enough time to increase their size and thus to transform itself. It derives that age is among the most determinant factors in addressing the best therapeutic approach in borderline tumors.

Giurgea LN et al. (2012) evidenced that Ki67 immunostaining was highly expressed in malignant ovarian neoplasms, compared to benign

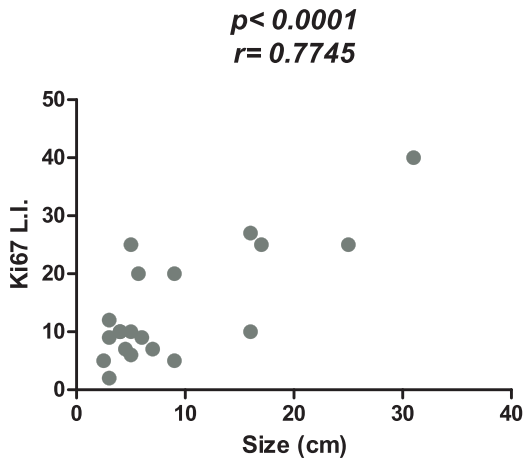

Fig. 4. Tumor size was directly correlated to Ki67 L.I. (p value < 0.0001, r = 0.7745) by Pearson's correlation test.

and borderline forms [18].In our series, the average value of Ki67 was about 14%, slightly higher than that observed in the literature [18,19], where there were values around 6–9.5%. It could be attributable to the counting methodology that we choosed to apply to our cases. We decided to take advantage from the almost ten-years lasting experience acquired with the application of the 2010 WHO classification system for neuroendocrine tumors of the gastro-enteric district, where it was possible to obtain an effective risk stratification based on a meticulous count of Ki67 L.I.OBT usually have an excellent prognosis, with a 10-year survival rate of 97% for all the combined stages [1,2], even if, albeit rarely, recurrences and malignant transformation can be observed. Most of the knowledge accumulated on this regard belongs to the serous histotype. It is well known that ovarian carcinoma subtypes are different diseases because of their different pathogenesis: molecular analysis demonstrated that serous OBTs share the same molecular and genetic alterations with low grade serous carcinoma, which, in turn, is different from the high grade form; furthermore, mucinous OBT is distinct from clear cell and endometrioid OBT because they both derive from endometriotic disease. These findings have important implications in biomarkers studies. It was shown that Ki67 [20] was higher than 13% in high grade serous carcinomas and intermediate in mucinous forms, providing, hence, a prognostic role to this marker. In our study, Ki67 did not show any difference between subtypes.The role of Ki67 in ovarian neoplasms is controversial. In a dated study [21], 92 patients affected by early stage ovarian cancer were followed for recurrence and analyzed for overall survival data. It was observed that the neoplasm never recurred in case of Ki67 lower than 10% and that disease relapse occurred more often with Ki67 higher than 15%. This finding was retained to be extremely important for the decision to start with adjuvant chemotherapy in case with early stage ovarian cancer. Later, a relevant study [22] assessed the expression of Ki67 on a larger collective (880 cases). Ki67 overexpression (> 10%) was observed in 12% of OBT and in 51% of ovarian carcinomas and, among carcinomas, it was associated with increased FIGO stage and grade. Focusing only on the serous OBT subtype [23], Ki67 was more expressed, compared to benign forms, in 46.3% of cases. A trend towards a correlation between the patient's age and Ki67 value and a direct significant association between tumor size (≥10 cm) and Ki67 L.I was found also by others [24] in a study performed on 42 OBT cases. Our findings confirm what was observed by others. This evidence could support the hypothesis that part of these tumors follow a progressive evolution [25] over time and most proliferative tumors are more likely to undergo malignant transformation.

5. Conclusions

In conclusion, the assessment of Ki67 could be a valid support in the diagnosis of a more aggressive tumor. In case of ovarian borderline tumors, it would be essential to be capable of identifying other prognostic factors that can help to predict disease progression, especially in young women, where it would be useful to implement a therapeutic strategy aimed at preserving, whenever possible, fertility. Since in our cases data concerning recurrences rate were not, reliable, because of a too short follow-up time, further studies are needed to assess this possible correlation.

Key message

Ki67 may be useful in the diagnosis of tumors more aggressive than OBT considering that a higher L.I. (≥10%) emerged to be more common in patients older than 40 years (p value = 0. 0194) and with tumors with a maximum diameter ≥ 10 cm.

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Nothing to declare.

Author Contribution

E Guadagno, S Pignatiello, G Borrelli, M Cervasio: Project development, Data Collection, Manuscript writing
L Della Corte: Data collection
G Bifulco: Manuscript editing
L Insabato: Project development and manuscript editing.

Declaration of Competing Interest

We have no conflicts of interests to declare

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Nothing to declare.

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