Diagnostic accuracy of frozen section in borderline ovarian tumors

Giuseppina Palumbo[1], Giovanna Giordano[2], Andrea Dall'Asta[1], Michela Monica[1], Daniele Mautone[1], Maurizio Di Serio[1], Roberto Berretta[1]

[1] Department of Surgical Sciences, Obstetrics and Gynecology Unit, University of Parma, Parma, Italy; [2] Department of Biomedical, Biotechnological and Translational Sciences, Pathological Anatomy and Histology Unit, University of Parma, Parma, Italy

Summary. *Background:* Borderline ovarian tumors (BOTs) are an intermediate form between benign and malignant neoplasms. BOTs occur more frequently in stage I and in young women who desire progeny. Several studies have shown that conservative treatment (unilateral oophorectomy) or ultra-conservative (cystectomy) are an oncologically safe choice in terms of survival. Frozen section histology is considered reliable to exclude the presence of malignant lesions in suspicious masses. The aim of this study was to evaluate the diagnostic accuracy of intraoperative histological examination in borderline tumors of the ovary. *Patients and methods:* We retrospectively collected 627 patients with a ovarian eteroplasia treated at the University Hospital of Parma between January 1, 1994 and December 31, 2012. 124 of these had a final diagnosis of BOT (19.8%). Among those, 39 adnexal masses were analyzed in the 37 patients included in the study who underwent intraoperative frozen section of the surgical specimen. *Results:* Group 0 included patients whose definitive histological examination disagreed with the extemporaneous examination, while group 1 included those patients in whom intraoperative and final diagnosis agreed. Groups 0 and 1 did not statistically differ in regard to clinical and laboratory features. Histotype and tumor size affected frozen section diagnostic accuracy. Frozen section accuracy was higher in serous BOTs; extemporaneous examination performed best upon maximum diameters of less than 8.6 cm. *Conclusion:* Frozen section is an accurate and useful method for surgical management of suspicious adnexal masses.

Key words: borderline ovarian tumors, intraoperative frozen section, gynecology oncology

«ACCURATEZZA DIAGNOSTICA DELL'ESAME ISTOLOGICO ESTEMPORANEO NEI TUMORI BORDERLINE DELL'OVAIO»

Riassunto. *Background:* I tumori ovarici borderline (BOTs) sono una forma intermedia tra neoplasie benigne e maligne. I BOTs sono più frequenti al I stadio e in giovani donne desiderose di prole. Diversi studi hanno dimostrato che il trattamento conservativo (ovariectomia monolaterale) o ultra-conservativo (enucleazione della neoplasia) rappresentano una scelta oncologicamente sicura. L'esame istologico intraoperatorio è considerato affidabile per escludere la presenza di lesioni maligne in masse annessiali sospette. Lo scopo di questo studio è stata la valutazione dell'accuratezza diagnostica dell'esame istologico intraoperatorio nei tumori borderline dell'ovaio. *Pazienti e metodi:* Abbiamo analizzato retrospettivamente i dati relativi a 627 pazienti con eteroplasia ovarica sottoposte a staging chirurgico dal 1 Gennaio 1994 al 31 Dicembre 2012. 124 di queste hanno avuto una diagnosi finale di BOT (19,8%). Abbiamo considerato eligibili per il nostro studio 39 masse annessiali analizzate con esame estemporaneo intraoperatorio in 37 pazienti. *Risultati:* Le pazienti incluse sono state suddivise in due gruppi: il gruppo 0 ha compreso casi il cui esame istologico definitivo è

risultato discordante con l'esame estemporaneo, mentre il gruppo 1 ha compreso le pazienti in cui la diagnosi intraoperatoria è risultata concordante con l'esame istologico definitivo. I due gruppi di pazienti non sono risultati significativamente differenti in termini di caratteristiche cliniche e laboratoristiche. L'istotipo e le dimensioni della neoplasia si sono dimostrati fattori in grado di influenzare l'accuratezza diagnostica dell'esame estemporaneo intraoperatorio, che è risultata maggiore in BOTs di tipo sieroso e con diametro massimo inferiore a 8,6 centimetri. *Conclusione:* L'esame estemporaneo intraoperatorio è un metodo accurato e utile per la gestione chirurgica delle masse annessiali sospette.

Parole chiave: tumori ovarici, borderline, esame estemperoneo intraoperatorio, oncologia ginecologica

Background

Borderline ovarian tumors (BOTs) are an independent category and form a unique intermediate stage of ovarian neoplasia (1) which accounts for 10-20% of all ovarian tumors. By definition, unlike malignant neoplasms, BOTs do not have metastatic potential and are confined within the basal lamina without stromal invasion; unlike benign tumors, BOT cells present nuclear atypia and an increased mitotic index; they can cause an extraovarian disease in the form of peritoneal "implants". BOTs are epithelial tumors whose main histo-pathological features are 1) epithelial proliferation, 2) low-grade nuclear atypia and 3) no stromal invasion/microinvasion (<10 mm) (2). BOTs are bilateral in 30% of cases; stage I diagnosis occurs in approximately 70% of cases. The most common histological types are the serous (74%) and the mucinous (24%) (3) followed by the endometrioid histotype (4), whereas other histotypes rarely occur.

Clinically, BOTs are often asymptomatic and are occasionally diagnosed during a routine gynecological visit (5). BOTs have an indolent course with good prognosis in terms of survival, but they can recur even 10-15 years after primary surgery (1-3).

Tumoral marker evaluation, especially CA125, CA19-9, CA15-3 and CEA, may help clinicians in guessing the nature of the adnexal mass (6-9). As reported by Fisherova *et al.*, only in 29%-69% of cases are BOTs correctly classified preoperatively by ultrasound. Doppler examination of tumor vascular patterns and three-dimensional ultrasound may slightly increase the percentage of correct specific diagnosis; neither computed tomography (CT) nor magnetic resonance imaging (MRI) can reliably discriminate between BOTs and early-stage low-grade ovarian cancer (10).

BOT surgical treatment in women who do not desire pregnancies is provided by peritoneal washing followed by hysterectomy with bilateral salpingo-oophorectomy, multiple peritoneal omentectomy biopsies (11) (peritoneum subdiaphragmatic left and right, paracolic gutter right and left, Retzius peritoneum, pouch of Douglas) and, occasionally, pelvic lymphadenectomy (12). Despite this, BOTs are frequently diagnosed at an early stage or in young women desirous of having progeny. Several studies have shown that conservative treatment (unilateral oophorectomy) or ultra-conservative (cystectomy) are oncologically safe choices in terms of survival (13), whereas other authors report an increased rate of recurrence after fertility sparing surgery. Currently consensus has not been achieved regarding the identification of those cases which may benefit from fertility sparing surgery rather than a radical approach (1). The aim of this study was to evaluate the diagnostic accuracy of intraoperative histological examination in borderline ovarian tumors.

Materials and methods

This retrospective study was conducted on patients surgically treated for adnexal mass at the University Hospital of Parma. All patients underwent intraoperative histologic examination (frozen section). We collected 627 patients with ovarian cancer treated between January 1, 1994 and December 31, 2012. 124 of these had a final diagnosis of BOT (19.8%).

All patients underwent preoperative evaluation by transvaginal ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) and serum CA-125, CA 19.9 and CA 15.3 dosage.

In accordance with the international literature regarding BOT therapy (1), at our Unit all patients with a final diagnosis of BOT were treated by radical surgery, consisting in total hysterectomy and bilateral salpingo-oophorectomy, infracolic omentectomy, peritoneal cytology, multiple biopsies with or without pelvic/lomboaortic lymphadenectomy and appendectomy in the event of mucinous histology or by fertility sparing surgery in the event of fertile patients who desired to plan pregnancies.

The indication to perform frozen section was based on clinical, laboratory and instrumental evaluation. At the Pathological Anatomy and Histology Unit of the University of Parma surgical specimens underwent specific ovarian investigation according to the guidelines reported in Rosai and Ackerman's Surgical Pathology, 10th edition (14):

Description of the specimen:
1. Size and shape; weight, if enlarged
2. Capsule: thickened? adhesions? hemorrhage? rupture? external surface smooth or irregular?
3. Cut section: character of cortex, medulla, and hilum; cysts (size and content); corpus luteum? calcification? hemorrhage?
4. Tumors: size; external appearance: smooth or papillary? solid or cystic? content of cystic masses; hemorrhage, necrosis, or calcification?

Sections for histology:
1. For cysts: up to three sections of cyst wall (particularly from areas with papillary appearance)
2. For tumors: three sections or one section for each centimeter of tumor, whichever is greater; also, one section of non-neoplastic ovary, if identifiable.

The specimens were first macroscopically examined and the suspect portion of the surgical specimen identified. The lesion was then placed in the gel OCT and frozen (-20C°); finally, after slicing 5 micron specimens and coloring with hematoxylin-eosin, samples were assessed through optical microscopy. Frozen section diagnosis was compared to the final pathology report.

Statistical analysis was performed using SPSS statistical software version 2.0 for Windows. Discrete variables were expressed as absolute numbers and percentages, whereas continuous variables as means ± standard deviation. Whenever possible we performed parametric and nonparametric statistical tests, if possible using the Kolmogorov–Smirnov test. Continuous variables were analyzed by the t-test, and categorical variables were analyzed by the χ^2 test or Fisher's exact test. P values less than 0.05 were considered as significant.

Results

Frozen section intraoperative examination was performed in the 37 patients included, who were divided into Group 0 (13 patients, 35.1%) and Group 1 (24 patients, 64.9%) on the basis of disagreement or agreement between the intraoperative histologic examination and the final pathology report, respectively. Demographic and laboratory features did not statistically differ between the two groups, as reported in Tables 1a and 1b.

Preoperative evaluation stated Stage I disease according to FIGO 2009 Classification in all the patients included. 28 out of 30 fertile patients underwent laparoscopic fertility sparing surgery: we performed

Table 1a. Demographic features.

	Group 0 (n=13)	Group 1 (n=24)	p
Multiparous n (%)	9 (69.2%)	17 (70.8%)	>0.005
Menopause n (%)	9 (69.2%)	15 (62.5%)	>0.005
BMI <23 n (%)	4 (30.7%)	5 (21.7%)	>0.005
Median age (Q1-Q3)	51 (46-55)	61 (44-66)	>0.005

Table 1b. Laboratory features of the patients included.

	Group 0 (n=13) Median (Q1-Q3)	Group 1 (n=24) Median (Q1-Q3)	p
CA 125 UI/ml	15.2 (11.8-27.1)	34.1 (18.3-97.8)	>0.005
CA 15-3 UI/ml	18.0 (17.1-18.9)	17.0 (9.2-24.6)	>0.005
CA 19-9 UI/ml	15.9 (13.7-39886.2)	11.2 (5.3-22.4)	>0.005

13 monolateral cystectomies, 13 monolateral adnexectomies, 2 bilateral cystectomies. Laparoscopic radical surgery was performed in 2 fertile patients who refused fertility sparing surgery and 7 postmenopausal patients were treated with hysterectomy and bilateral adnexectomy. The final pathology report stated grade I tumors in all the patients included. Two group 0 patients had bilateral BOT. The overall specimens analyzed were 39 in number, 15 in Group 0 and 24 in Group 1.

The final pathology report revealed Stage I grade I in all patients included. Tumor size in terms of maximum diameter in cm and distance between the 1st (Q1) and 3rd quartile (Q3) as measured at CT and TVUS

Table 2. Ovarian masses maximum diameter at computed tomography (CT), transvaginal ultrasound (TVUS) and intraoperative pathologic examination.

	Group 0 (n=15) Median value (cm) and interquartile distance (Q1-Q3)	Group 1 (n=24) Median value (cm) and interquartile distance (Q1-Q3)	p
TC max diameter	15 (8.7-19.5)	8.3 (6-14.3)	0.048
TVUS max diameter	16 (9.2-19.7)	8.6 (6.7-12)	0.0158
Surgical specimen max diameter	13 (6.0-20.5)	8.5 (7.15-15.5)	>0.05

statistically differed between the two groups (p <0.05) (Table 2). One potential bias in the surgical specimen diameter assessment was the occasional rupture of the cystic walls and subsequent measurement of their fragments.

When assessing the maximum tumor diameter by TVUS and CT in relation to the reliability of the extemporaneous histological examination we found lesions with a maximum diameter less than 8.6 cm more reliable in predicting disease (Figure 1).

18 cases (46.15%) were mucinous tumors, 18 (46.15%) serous tumors and 3 (7.7%) endometrioid BOTs. Histological type distribution statistically differed between the two groups (Table 3). Mucinous BOTs represented 86.67% of tumors in Group 0 and only 20.83% in Group 1. On the other hand, for serous BOTs we had a 66.67% incidence in Group 1 and 13.33% in Group 0. We found a statistically significant difference in serous and mucinous tumor distribution

Table 3. Pathology reports in Group 0 and Group 1.

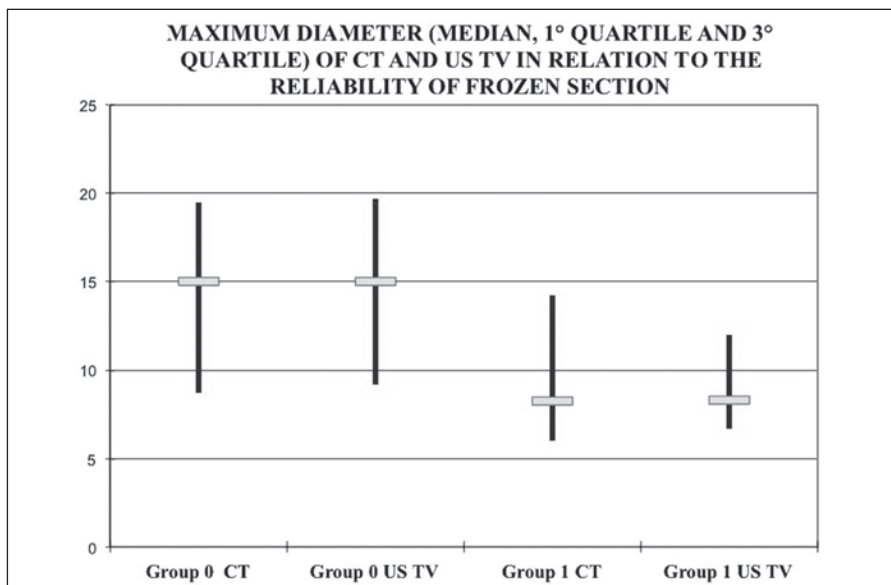|	Group 0 (n=15) n (%)	Group 1 (n=24) n (%)	p
Mucinous tumors	13 (86.67%)	5 (20.83%)	0.02
Serous tumors	2 (13.33%)	16 (66.67%)	0.001
Other tumors	0	3 (12.50%)	0.2

Figure 1. Maximum diameter of CT scan and TVUS (US TV) in relation to the accuracy of frozen section histology.
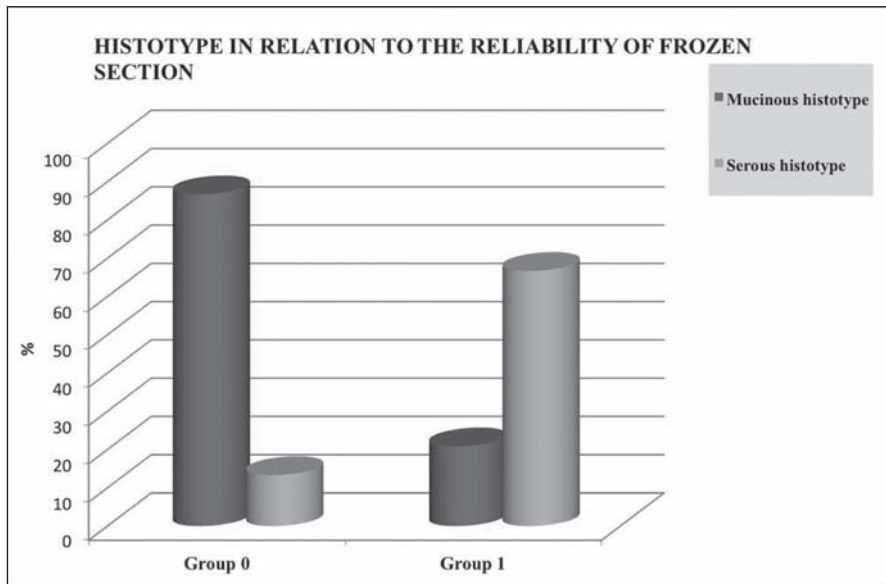
Figure 2. Frozen section diagnostic accuracy in serous and mucinous borderline tumors.

between the two groups (p < 0.05). The frozen section diagnostic accuracy was greater for serous tumors than for mucinous neoplasia. Figure 2 shows the diagnostic accuracy of the intraoperative histologic examination in each histotype.

We reported only 1 false negative case of frozen section in what proved an adenocarcinoma G1 at the final pathologic report but was intraoperatively diagnosed as BOT. Overall, frozen section examination showed 64.68% sensitivity and a 96% positive predictive value.

Discussion

BOTs represent 10-20% of all epithelial ovarian tumors. They usually occur at a younger age and are usually diagnosed at an earlier stage than invasive forms. When managing adnexal masses it is important to differentiate between malignant and borderline pathology before and/or during surgery. Careful evaluation is therefore mandatory when counseling and planning the surgical procedure.

The clinical and instrumental approach towards patients with adnexal masses may provide different algorithms used in assessing the risk of malignancy. The IOTA System assesses morphologic features, whereas the ROMA score also involves other laboratory parameters (15, 16). When preoperative evaluation fails to clear up doubts about the risk of malignancy, extemporaneous histology can give additional information intraoperatively. Frozen section diagnostic accuracy is affected by the pathologist's experience. Diagnostic accuracy between the extemporaneous and definitive report is higher when the intraoperative evaluation is done by an experienced gynecological pathologist (17, 18); moreover, the over- and/or mis-diagnosis rate are lower when frozen section is performed by experienced practitioners, who often formulate a right diagnosis without needing to await the final histological examination. A study by Menzin *et al.* showed that disagreement between intraoperative and definitive pathology report occurred in 8% of cases and 19% of cases in specialist and non-specialist pathologists respectively (p <0.005) (19). In the literature, only one study shows that the experience of the pathologist does not affect the diagnostic accuracy of frozen section examination in patients with BOT (20).

Many studies have shown that patients' clinical features (age, parity, BMI, menopausal status) do not affect frozen section diagnostic accuracy (21-24). In line with the international literature, our study's two groups did not significantly differ regarding the clinical features of patients included.

Kim *et al.* (24) demonstrated that tumor markers could not improve frozen section diagnostic accuracy in BOTs (p = 0.76). Our data agree with these findings: we could not demonstrate any relation between preoperative markers and frozen section accuracy. Frozen section reported sensitivity ranges from 45.4% to 91.4% (24-27). Our study reported 69.4% sensitivity: this result can be explained by the high prevalence of mucinous tumors (46.15% in the whole sample, 86.67% in group 0) and the large dimensions, which may have affected neoplasia sampling procedures.

In our study intraoperative histology showed a higher positive predictive value (96%) in diagnosing BOTs than that reported in the international literature [62.5% (25), 82.9% (24) , 87% (18), 88.9% (26)]. Other studies showed that frozen section had a greater accuracy in distinguishing BOTs from malignant tumors than from benign ones. BOTs have often been misdiagnosed as benign lesions in frozen histology (18). In our study we found only 1 misdiagnosis between BOTs and malignant neoplasias (BOT at extemporaneous examination, invasive carcinoma at the pathology report); other misdiagnosis cases were benign tumors at frozen section with BOT at the final pathology report.

When considering the relationship between histology and frozen section accuracy, several studies showed that mucinous histology is associated with a higher misdiagnosis rate between frozen and pathology reports (18), which can be explained by the fact that mucinous tumors often have a mixed component (benign, borderline and malignant) and a greater size than serous ones (27). Our findings confirm previous studies as we reported a higher mucinous histology rate in the disagreement group (group 0) than in the agreement group (group 1).

The examination time is an additional factor which may affect frozen section diagnostic accuracy: intraoperative histology is a quicker exam than the final pathology report (28), and this can affect the disagreement rate.

Moreover, extemporaneous diagnosis accuracy is related to tumor size; the larger the diameter, the greater the likelihood of benign/borderline or borderline/malignant area coexistence. Previous studies have shown that the diagnosis of a benign tumor through extemporaneous examination is less reliable if the mass is larger than 10 cm (29). In our study we found a cut-off value of 8.6 cm.

37 patients included is a small sample upon which to draw definitive conclusion, so our results will not modify the current clinical approach toward ovarian masses. Furthermore, in our opinion the most important diagnostic challenge in adnexal mass preoperative evaluation is to validate an imaging scoring system combining serum markers such as the He4 assay, which seems to increase the preoperative diagnostic accuracy of adnexal masses as suggested by Gizzo *et al.* (1), or other models such ADNEX as suggested by Van Calster *et al.* (30). On the basis of our findings we conclude that intraoperative frozen section examination is an accurate and useful method for the surgical management of suspicious ovarian masses. Tumor size and histotype affect the diagnostic accuracy, which is higher in small and serous tumors. Because of our small sample cohort we think further studies on larger cohorts are needed to test and confirm our results.

Conclusion

Our study shows a relatively high positive predictive value (96%) of intraoperative histology in diagnosing borderline ovarian tumors (BOTs). Previous studies have shown that histological examination of frozen section has a greater reliability to distinguish malignant tumors from BOTs, compared to benign. The accuracy of frozen section histology differs among histological types, and our study confirms that mucinous histology is more commonly in disagreement with the final examination.

The accuracy of extemporaneous diagnosis is related to tumor size; the greater the tumor diameter, the higher the likelihood of coexistence of benign-borderline-malignant areas, because of this the accuracy of intraoperative frozen section examination seems to the higher in small tumours.

Authors' contribution

Acknowledgement

References

1. Gizzo S, Berretta R, Di Gangi S, *et al.* Borderline Ovarian Tumors and Diagnostic Dilemma of Intraoperative Diagnosis: Could Preoperative He4 Assay and ROMA score Assessment Increase the Frozen Section Accuracy? A multicenter Case-Control Study. Biomed Res Int 2014; 2014: 803598.

2. Messalli EM, *et al.* Borderline ovarian tumors: features and controversial aspects. Eur J Obstet Gynecol Reprod Biol 2012; 167 (1): 86-9.

3. Morice P, Uzan C, Fauvet R, *et al.* Borderline ovarian tumor: pathological diagnostic dilemma and risk factor for invasive or lethal recurrence. Lancet oncology 2012; 13: 103-15.

4. AIOM. Linee guida tumori dell'ovaio. 2013; www.aiom.it; pdf: lg_aiom_ovaio w7_10.08.2013.

5. Shih KK, Zhou Q, Huh J, *et al.* Risk factors for recurrence of ovarian borderline tumors". Gynecologic Oncology 2011; 120: 480-4.

6. Uzan C, Berretta R, Rolla M, *et al.* Management and prognosis of endometrioid borderline tumor of the ovary. Surgical Oncology 2012; 21: 178-84.

7. Vine MF, Ness RB, Calingaert B, *et al.* Types and Duration of Symptoms Prior to Diagnosis of Invasive or Borderline Ovarian Tumor. Gynecologic Oncology 2001; 83: 466-71.

8. Lenhard MS, Nehring S, Nagel D, *et al.* Predictive value of CA 125 and CA 72-4 in ovarian borderline tumors. Clin Chem Lab Med 2009; 47: 537-42.

9. Morotti M, Menada MV, Gillott DJ, *et al.* The preoperative diagnosis of borderline ovarian tumors: a review of current literature. Gynecol Obstet 2012; 285: 1103-12.

10. Fisherova D, Zikan M, Dundr P, *et al.* Diagnosis, treatment on follow-up of borderline ovarian tumors. Oncologist 2012; 17 (12): 1515-33.

11. Gultekin E, Gultekin OE, Cingillioglu B, *et al.* The value of frozen section evaluation in the management of borderline ovarian tumors. J Can Res Ther 2011; 7: 416-20.

12. Tinelli R, Malzoni M, Cosentino F, *et al.* Feasibility, safety, and efficacy of conservative laparoscopic treatment of borderline ovarian tumors. Fertility and Sterility 2009; 92: 736-41.

13. Viganò R, Petrone M, Pella F, *et al.* Surgery in advanced borderline tumors. Fertility and Sterility 2010; 3: 1163-5.

14. Boran N, Cil AP, Tulunay G, *et al.* Fertility and recurrence results of conservative surgery for borderline ovarian tumors. Gynecologic Oncology 2005; 97: 845-51.

15. Rosai J. Rosai and Ackerman's Surgical Pathology. 2nd Volume Set; 10th Edition: Chapter 19. Elsevier, 2011.

16. Timmerman D, Ameye L, Fischerova D, *et al.* Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ 2010; 341: c6839.

17. Karlsen MA, Sandhu N, Høgdall C, *et al.* Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. Gynecologic Oncology 2012; 127: 379-83.

18. Fanfani F, Zannoni GF, Fagotti A, *et al.* Importance of a specialized pathologist for the examination of frozen sections of adnexal masses. Int J Gynecol Cancer 2007; 17 (5): 1034-9.

19. Brun JL, Cortez A, Rouzier R, *et al.* Factors influencing the use and accuracy of frozen section diagnosis of epithelial ovarian tumor. Am J Obstet Gynecol 2008; 199 (3): 244 - e1-7.

20. Geomini P, Bremer G, Kruitwagen R, *et al.* Diagnostic accuracy of frozen section diagnosis of the adnexal mass: a metaanalysis. Gynecologic Oncology 2005; 96: 1-9.

21. Menzin AW, Rubin SC, Noumoff JS, *et al.* The accuracy of a frozen section diagnosis of borderline ovarian malignancy. Gynecologic Oncology 1995; 59: 183-5.

22. Tempfer CB, Polterauer S, Bentz EK, *et al.* Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary: A retrospective analysis of 96 cases and review of the literature. Gynecologic Oncology 2007; 107: 248-52.

23. Gultekin E, Gultekin OE, Cincillioglu B, *et al.* The value of frozen section evaluation in the management of borderline ovarian tumors. J Cancer Res Ther 2011; 7: 416-20.

24. Kim K, Chung HH, Kim JW, *et al.* Clinical impact of under-diagnosis by frozen section examination is minimal in borderline ovarian tumors. J Cancer Surg 2009; 35: 969-73.

25. Kim H, Kim TJ, Park YG, *et al.* Clinical analysis of intraoperative frozen section proven borderline tumors of the ovary. J Gynecol Oncol 2009; 20: 176-80.

26. Maheshwari A, Gupta S, Kane S, *et al.* Accuracy of intraoperative frozen section in the diagnosis of ovarian neoplasms: Experience at a tertiary oncology center. World J Surg Oncol 2006; 4: 12-5.

27. Bige O, Demir A, Saygili U, *et al.* Frozen section diagnoses of 578 ovarian tumors made by pathologist with and without expertise on gynecologic pathology. Gynecologic Oncology 2011; 123: 43-6.

28. Ilvana S, Ramazanoglua R, Ulker Akyildizb E, *et al.* The accuracy of frozen section (intraoperative consultation) in the diagnosis of ovarian masses. Gynecologic Oncology 2005; 97: 395-9.

29. Geomini PM, Zuurendonk LD, Bremer GL, *et al.* The impact of size of the adnexal mass on the accuracy of frozen section diagnosis. Gynecologic Oncology 2005; 99: 362-6.

30. Van Calster B, Van Hoorde K, Valentin L, *et al.* Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. BMJ 2014; 349: g5920.

Received: 2.7.2014
Accepted: 28.7.2014
Address: Andrea Dall'Asta, MD,
Department of Surgical Sciences,
University of Parma
Via Antonio Gramsci 14, 43126 Parma, Italy
Tel. +390521704819
Fax +390521702513
E-mail: andrea.dallasta1@gmail.com