Transvaginal Ultrasound-guided biopsy: a useful tool in the management of suspicious primary advanced ~~or metastatic~~ tubo-ovarian carcinoma

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ABSTRACT

Objective: To assess the accuracy of pathological diagnosis at transvaginal ultrasound (US) -guided biopsy versus surgery in patients with suspicious primary advanced ~~or metastatic~~ tubo-ovarian carcinoma. Feasibility, adequacy, and safety of the procedure were also evaluated.

Methods: Consecutive women with pre-operative suspicious primary advanced ~~or metastatic~~ tubo-ovarian carcinoma presenting at our hospital between July 2019 and September 2021 were enrolled. Feasibility was defined as the number of cases in which US-guided biopsy was possible according to tumour characteristics (morphology and site). Adequacy was defined as the possibility of a conclusive diagnosis in the sample collected. Safety was defined ~~on~~ by the number of major complications. Major complications were defined as hospitalization, surgery, and/or blood transfusion.

Results: 278 patients were eligible for the study; 158 were enrolled, while 120 were excluded due to logistic reasons or patient refusal (Figure 1). Ultrasound-guided biopsy was unfeasible in 30 (19%) patients. The samples obtained in the remaining 128 cases were all adequate (100%), and no major complications were noted. 26 (20%) patients started neoadjuvant chemotherapy on the bases of the diagnosis obtained by ultrasound, whereas 102 (80%) patients underwent surgery. Accuracy of ultrasound-guided biopsy versus surgery was 94% (96/102), with 6 false negative cases at US (6%). Site (pre-vescical peritoneum) and size (< 8mm) of the nodules resulted as major predictive factors for US-guided biopsy failure (false negative). Ultrasound-guided biopsy correctly identified 86 primary invasive tubo-ovarian carcinomas and 10 metastatic tumours.

Conclusions: Ultrasound-guided biopsy is a feasible, safe, and accurate method to provide histologically diagnosis in suspicious advanced or metastatic tubo-ovarian cancer patients.

INTRODUCTION

Primary cytoreductive surgery (PCS) followed by adjuvant platinum-based chemotherapy is a ~~the~~ standard of care in advanced ovarian cancer patients (1).

It often requires major surgical procedures with the risk of post-operative complications, which may delay chemotherapy and affect survival (2). Those patients who are not candidate for PCS, either because too frail or for unresectable disease, can receive neoadjuvant chemotherapy once pathology is confirmed (3-5).

The appropriate selection of patients for upfront surgery is of major importance. Several algorithms have been developed with this purpose (6-8). A laparoscopy-based scoring model centered on the intraoperative presence/absence of some specific cancer features was developed in 2006 (6, 7) and updated in 2015 (8). With this approach, surgical evaluation and histological diagnosis are performed at the same time, and patients considered suitable for PCS can be treated immediately. However, access to the operating room might not be cost-effective in frail women just for sample collection, and an imaging guided biopsy can be offered (9-11).

Traditionally, Computed Tomography (CT) scan has represented the standard imaging technique to stage ovarian cancer patients, and therefore it is commonly used to perform biopsy obtaining tumor samples in these patients. Recently, ultrasound examination performed by an expert examiner has been included in the pre-operative assessment of ovarian tumors providing a good accuracy in detecting intra-abdominal spread (12-15). Ultrasound-guided biopsy-a minimally invasive approach- is used in different tumor types, such as breast and prostate cancers (16-17). It can be performed in an outpatient setting, after the completion of ultrasound examination, as does not require any special preparation of the patient, fasting, or anesthesia. It is less expensive and more cost-effective than both CT scan and diagnostic laparoscopy (18).

In the field of gynecologic oncology, ~~few~~ several studies have investigated the role of US-guided biopsy in the management of abdominal and pelvic tumors demonstrating that the procedure is safe and feasible (10, 19-25).

The primary aim of the study was to evaluate the accuracy of ultrasound-guided biopsy in a prospective series of women with suspicious primary advanced or metastatic tubo-ovarian carcinoma. The secondary aims were to evaluate the feasibility, adequacy, and safety of the procedure.

~~PATIENTS AND~~ METHODS

This is a prospective cohort study carried out at the Gynecologic Oncology Unit, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, in Rome. The protocol was approved by the institutional Ethics Committee (EC nr 2819) and all patients gave their written informed consent for participation. The STAndards for the Reporting of Diagnostic accuracy studies (STARD) statement guidelines, available to the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network were used for the design, analysis, and interpretation of the data, and drafting and revision (26).

All women with peritoneal carcinomatosis from suspicious primary advanced ~~or metastatic~~ tubo-ovarian carcinoma admitted to our Unit from July 2019 to September 2021 were ~~included~~screened. Women with evidence of peritoneal pelvic/abdominal disease at CT scan with either pelvic masses, or ascites, or CA 125 over 500 mUI/mL were eligible to be included in the protocol. Patients who had previously undergone chemotherapy (NACT) and those with recurrence were excluded.

All patients were examined preoperatively with transvaginal/transrectal and transabdominal ultrasound using a standardized examination technique (27-28) to localize and map the disease. The ultrasound examinations were carried out using high-end ultrasound equipment; the frequency of the transvaginal probes varied between 5.0 and 9.0 MHz, and thatof the transabdominal probes between 3.5 and 5.0MHz. US-guided tru-cut biopsies were performed using an automatic bioptic gun (Bio Pince automatic biopsy system, Argon Medical Devices, Inc) with a 18G/25cm core-cut biopsy needle. The approach was chosen depending on tumor localization and best access. In patients with multiple localizations, the target lesion was the one selected for biopsy and its ultrasound characteristics were included in the analysis.

Patients were evaluated for feasibility of ultrasound-guided biopsy. Non-feasible cases were ~~multilocular masses with a small solid component and/or~~ patients in whom the distance between the metastatic tissue and the probe was too large or the tissue considered too thin to take a biopsy from.

No local or general anesthesia was performed during the procedure. The perineum and the abdominal skin were cleaned with chlorhexidine, and sterilely draped. A sterile cover was applied on the transvaginal/transabdominal ultrasound probe, and the sterile needle guide (Biopsy PEC63/H46721R GE and 680-120 PVT-781VT Canon) was attached to the probe.

The needle trajectory was planned and then measured using the distance between the probe

and the target lesion, and then set on the gun before starting the procedure. The tip of the biopsy needle was continuously visualized to achieve optimal sampling and patient safety.

For each target lesion, three specimens were obtained during the same procedure. ~~The tissue was fixed in formalin, embedded in paraffin wax, and stained with hematoxylin and eosin for histological examination. Samples that permitted conclusive histological diagnosis and identification of tumor origin were considered adequate. The minimum immunohistochemical tests performed in each case were p53, WT1, ER, PAX8~~.

Biopsy samples were fixed in formalin for 24–48 h, dehydrated and embedded in paraffin. Four-µm-thick sections were obtained from the paraffin-embedded tissue blocks by microtome, mounted on glass slides, and stained with hematoxylin and eosin. Immunohistochemistry (IHC) was performed, using anti-PAX8, ER and WT1 antibodies, in order to confirm the mullerian origin of the neoplasm and evaluate the percentage of hormone receptor expression. The p53 status was also tested by IHC, classifying it as "wild-type" (focal/isolated positive cells) or "abnormal" (>70% of positive or completely negative cells). Performing the IHC on biopsies should be always considered, due to the better degree of fixation of small specimens compared to surgical ones. However, the presence of an internal positive control is mandatory for the correct interpretation of IHC results. All biopsies that allowed a definitive histological diagnosis, with the identification of the tumor origin, were considered adequate.

Accuracy was defined as the agreement between ultrasound-guided biopsy histology and final surgical histology ~~in patients who underwent surgery~~.

Safety was defined by inverse number of major complications. Major complications were defined as hospitalization, surgery, and/or blood transfusion. Minor complications included procedure-related pain or bleeding that did not require medication or treatment (29). Pain was evaluated through VAS scoring scale and recorded at the time of the procedure.

Patients were observed for 90 minutes after the procedure and then discharged. ~~Neither analgesics nor antibiotics were given before or after procedures. After enrollment in the protocol, all patients were triaged to surgery, except a few~~ 26 ~~cases with poor performance status who underwent neoadjuvant chemotherapy based on histological analysis obtained at ultrasound biopsy.~~

Diagnostic laparoscopy was performed following our internal protocol and patients with a PIV Fagotti score <8 (9) and Vizzielli score <6 (30) suitable for complete surgical resection

underwent primary debulking surgery at the same time. Patients considered unsuitable for surgery based on these scores underwent additional tumor biopsies and received chemotherapy according to diagnosis.

STATISTICAL ANALYSIS

This study was designed to estimate the accuracy of ultrasound-guided biopsy. Based on the asymptotic theory of normal approximation (31-32), assuming a prevalence (of invasive or borderline ovarian disease in the selected population) of 0.8 and a sample sensitivity of 0.95 with a 10% margin of error and a type I error $\alpha = 0.05$, the sample size needed was 92 participants. Anticipating a 28% dropout rate, 128 patients were enrolled in the study. ~~To calculate the accuracy of ultrasound-guided biopsies, only patients were included who underwent surgery following this procedure.~~ Standard descriptive statistics were calculated. Categorical data are expressed as frequencies and percentages and means ± standard deviation is reported for continuous variables. Several variables including age, body mass index (BMI), Ca 125 serum levels, maximum lesion diameter, disease stage, histology, ascites, access for biopsy, site of biopsy, and size of specimen were investigated for their potential association with adequacy and accuracy of the technique. Continuous variables were dichotomised. Parameters were compared using the chi-squared, Fisher's exact, or McNemar's test. All p-values <0.05 were considered statistically significant.

RESULTS

Two hundred and seventy-eight patients met the inclusion criteria and were eligible in the study period. The STARD flow diagram of the patients' population is shown in **Figure 1.**

One hundred and fifty-eight patients were finally enrolled, while 120 were excluded due to logistic reasons, such as patient refusal, or unavailability of the biotic gun and/or of the ultrasound examiner or patient under anticoagulant treatment and unwilling to re-travel. Ultrasound -guided biopsy was feasible in 128 (81%) patients and unfeasible in 30 (19%) because of the presence of thin carcinomatosis (in 21 cases) and lesion characteristics such as absence of clear solid component (in 9 cases).

The clinical, histological and ultrasound characteristics of the 128 patients are presented in **Table 1.** The median BMI was 24 (range, 16–28) kg/m^2. ~~Twelve patients had suspicious metastatic cancer based on biochemical and radiological findings, and personal history.~~ Most patients (62%) had clinical stage IIIC disease.

The ultrasound characteristics of the target lesions are presented in **Table 1.** The largest lesion diameter was 48 (range, 8–211) mm. In most cases, the lesion was solid (112/128, 87%) with irregular margins (127/128, 99%) and moderately to richly vascularised on colour Doppler examination (73/128, 57%).

Almost all biopsies (121/128, 94%) were performed using a transvaginal approach, with only seven (6%) performed transabdominally. The Douglas pouch (60/128, 47%) and pelvic masses (57/128, 44%) were the most frequent site of biopsy. Additionally, biopsy was performed on the prevesical peritoneum in 6 (5%) cases, omentum in 4 (3%), and inguinal lymph nodes in 1 (0.7%).

Table 1. Clinical, histological and ultrasound characteristics of the patients

Variable	**n (%) or median (range)**
All cases	128
Median Age (range) (years)	66 (30–90)
Median BMI (range) (Kg/m^2)	24 (16–28)
Median CA 125 serum levels (range) UI/mL *	822 (12–12.000)
FIGO Stage of disease**	
IIIc	68 (62)

IV	42 (38)
Histology of ultrasound biopsies	
Malignant	122 (95)
High grade serous carcinoma	*96 (79)*
Low grade serous carcinoma	*1 (1)*
Endometrioid adenocarcinoma	*3 (2)*
Carcinosarcoma	*3 (2)*
Undifferentiated sarcoma	*1 (1)*
Metastases from non gynecological tumors	*18 (15)*
Benign	6 (5)
Fibrosis	*1 (17)*
Epithelial cells-No Atypia	*5 (83)*
Ultrasound characteristics	
Median diameter of the lesion (mm) (range)	48 (8–211)
Type of lesion §	
Solid	112 (88)
Multilocular solid	16 (12)
Lesion margins	
Regular	1 (1)
Irregular	127 (99)
Color Score	
1	10 (8)
2	45 (35)
3	44 (34)
4	29 (23)
Site of biopsy	
Douglas pouch	60 (47)
Pelvic mass	57 (45)
Prevesical peritoneum	6 (5)
Omentum	4 (3)
Lymphnode	1 (1)

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics

*Five unknown cases

**Tubo-ovarian carcinoma only

§According to IOTA terminology (27)

No major complications were noted. One patient experienced fever after biopsy but did not require antibiotics. Self-limiting bleeding (not requiring hospitalisation, surgery, or blood transfusion) was observed in all cases. Neither analgesics nor antibiotics were given before or after procedures because it was not part of the protocol. Nonetheless,. no women experienced pain requiring medications during or after the procedure.

All the ultrasound biopsies were adequate for histological diagnosis (100% adequacy), as no inconclusive result was obtained. The median size of the samples collected was 9 (range, 2–20) mm. The absence of inadequate ultrasound -guided biopsies precluded statistical analysis of factors that could contribute to ultrasound-guided biopsies adequacy/inadequacy.

Of the 128 patients undergoing ultrasound -biopsy, 102 underwent subsequent surgical evaluation. The remaining 26 women did not attend the scheduled surgery required by the research plan ~~underwent chemotherapy based on ultrasound -guided biopsy only,~~ because of their inconvenience and overwhelm ~~contraindications to surgery due to either comorbidities and/or extension of the disease.~~ To note, patient dropouts did not negatively affect the study, as it stands, we factored in dropout rate as high as 28 percent into the protocol design.

There were no false positives by definition. The ultrasound -guided procedure proved to be accurate in identifying malignant tumours in 96 (94%) of 102 cases. In 6 cases, ultrasound -guided biopsy did not show presence of cancer cells in the specimen, but all these patients had a positive finding at surgical biopsy. Moreover, 4 cases had cancer cells at ultrasound -guided biopsy, which was not confirmed at the following surgical biopsy performed laparoscopy. These patients underwent chemotherapy based on ultrasound biopsy findings. The overall accuracy of ultrasound guided biopsy was 0.941 with a McNemar test p value of 0.041.

Characteristics of clinical data and parameters comparison in not accurate and accurate specimens are shown in **Table 2**. The false-negative rate of US-guided biopsy was the highest (100%) when the biopsy size was ≤8 mm. Biopsy was performed in the prevesical peritoneum in 50% of false-negative cases. All other parameters analysed were not significant between not accurate and accurate cases.

No port-site metastases were observed in all patients, neither with vaginal nor rectal nor

percutaneous approach after 1 month from the procedure.

Table 2. Characteristics of clinical data in not accurate and accurate US biopsy specimens

Parameter	Not accurate (n = 6)	Accurate (n = 96)	Total (n = 102)	p-value
Age				0.687
≤ 60	2 (33.3%)	40 (41.7%)	42 (41.2%)	
> 60	4 (66.7%)	56 (58.3%)	60 (58.8%)	
BMI				0.882
< 25	3 (50.0%)	51 (53.1%)	54 (52.9%)	
≥ 25	3 (50.0%)	45 (46.9%)	48 (47.1%)	
Ca 125				0.687
≤ 1000	4 (66.7%)	56 (58.3%)	60 (58.8%)	
> 1000	2 (33.3%)	40 (41.7%)	42 (41.2%)	
US guided biopsy access				0.610
Transvaginal	6 (100.0%)	92 (95.8%)	98 (96.1%)	
Transabdominal	0 (0.0%)	4 (4.2%)	4 (3.9%)	
US Site of Biopsy				< 0.001
Pelvic mass	1 (16.7%)	40 (41.7%)	41 (40.2%)	
Douglas Pouch	2 (33.3%)	50 (52.1%)	52 (51.0%)	
Prevesical peritoneum	3 (50.0%)	3 (3.1%)	6 (5.9%)	
Omentum	0 (0.0%)	3 (3.1%)	3 (2.9%)	
US Biopsy size				0.007
≤ 8 mm	6 (100.0%)	42 (43.8%)	48 (47.1%)	
> 8 mm	0 (0.0%)	54 (56.2%)	54 (52.9%)	
Ascites				0.889
No	1 (16.7%)	14 (14.6%)	15 (14.7%)	
Yes	5 (83.3%)	82 (85.4%)	87 (85.3%)	
US characteristics of the tumour				0.701
Solid	5 (83.3%)	85 (88.5%)	90 (88.2%)	
Multilocular solid	1 (16.7%)	11 (11.5%)	12 (11.8%)	
Maximum diameter of the lesion				0.209
≤ 60 mm	5 (83.3%)	55 (57.3%)	60 (58.8%)	
> 60 mm	1 (16.7%)	41 (42.7%)	42 (41.2%)	
Color Score				0.761
1	0 (0.0%)	7 (7.3%)	7 (6.9%)	
2	2 (33.3%)	33 (34.4%)	35 (34.3%)	
3	3 (50.0%)	31 (32.3%)	34 (33.3%)	
4	1 (16.7%)	25 (26.0%)	26 (25.5%)	
Final Histology of Surgery				0.819
HGSC	5 (83.3%)	77 (80.2%)	82 (80.4%)	
LGSC	0 (0.0%)	1 (1.0%)	1 (1.0%)	
Endometroid	1 (16.7%)	3 (3.1%)	4 (3.9%)	
Carcinosarcoma	0 (0.0%)	2 (2.1%)	2 (2.0%)	
Metastatic	0 (0.0%)	8 (8.3%)	8 (7.8%)	
Undifferentiated sarcoma	0 (0.0%)	1 (1.0%)	1 (1.0%)	
Negative	0 (0.0%)	3 (3.1%)	3 (2.9%)	
Not adequate	0 (0.0%)	1 (1.0%)	1 (1.0%)	

US, ultrasound; BMI, body mass index; HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma

DISCUSSION

Summary of main results

This is the first prospective longitudinal study confirming that ultrasound -guided biopsy is a feasible, safe, and accurate method to diagnose patients with suspicious advanced tubo-ovarian ~~or metastatic~~ carcinoma in an outpatient setting.

Results in the context of published literature

The data in the literature are mostly retrospective. Some studies included patients with non-specified abdominal-pelvic tumours who were often previously considered unsuitable for surgery (10, 19-24). Therefore, correlation between ultrasound -guided tru-cut biopsy and final surgical histology is rarely reported (10, 24).

Failure to obtain an adequate sample is described more frequently with cystic or necrotic tumours, which are common in patients with recurrence (10, ,19-24, 29). Moreover, adequacy is strictly related to the overall amount of tissue resected; in the study by Verschuere et al (33), the reported adequacy rate was 80.2% and increased significantly with the number of cylinders. In our series, for each target lesion, three specimens were obtained in all cases, which allowed to achieve 100% adequacy.

Our findings are also in agreement with 85–98 % accuracy rate reported in the literature. Lengyel et al. recently published a large prospective study in 2021 (23); they collected data on 303 cases of gynaecological cancers. In 94 women, they compared ultrasound-guided tru-cut diagnosis with the corresponding surgical histology and found an adequacy of 99% and an accuracy of 88%. They used local anaesthesia in 14% of the patients who underwent the procedure, and general anaesthesia in 3.2%. No major complications were registered, and only three (3.2%) patients had infectious sequelae due to biopsy.

Strengths and Weaknesses

We were able to identify some characteristics to predict the risk of false negatives. Non-accurate diagnosis is generally associated with small sample size (<8 mm) and lesion site (prevesical). In four cases, the accuracy of ultrasound -guided biopsy was better than that of its surgical counterpart, thus showing the advantage of imaging over human eye.

Complications reported in other series were rare and consisted in hemoperitoneum after the transabdominal procedure (10, 24). In our study, no major complications were registered and no patient experienced pain due to the procedure without any anaesthesia and/or analgesic therapy.

The feasibility rate of the procedure is about 46%. Indeed, the main limitations to perform ultrasound -guided biopsy have been the prompt availability of an expert operator and the automatic bioptic gun in the outpatient setting; concurrent medications at high risk of bleeding (anticoagulant treatment); technical difficulties such as tissue location and/or thickness and/or density. A small number of patients also refused the procedure as they felt too invasive without anaesthesia. However, it is conceivable that a better logistic organization will significantly improve feasibility in the future. However, the sample size allows to conclude on the sensitivity of 0.941 of the test versus 0.95 as a priori defined. Specificity and NPV were not calculated as no negative cases were included.

Implications for Practice and Future Research

Ultrasound -guided biopsy has an incredible potential to offer a ~~more democratic,~~ less expensive, less time consuming, and more friendly access to health care system for women with abdominal carcinomatosis of unknown origin.

Transvaginal and transabdominal ultrasound examinations have already shown good performances in the evaluation of disease extension from ovarian cancer, like other standard imaging such as CT scan and MRI (34-35). Therefore, in an ideal outpatient setting, a woman can receive an all-in-one ultrasound based approach, for both staging and diagnosis, providing a sufficiently large tissue sample for detailed histologic analysis, including immunohistochemistry, on which subsequent therapy can be established.

~~On these bases, a more personalized treatment to abdominal carcinomatosis can be hypothesised based on factors which are usually obtained after surgery only.~~

Further applications, such as genetic testing for BRCA mutations and whole genomic profiling, should be developed.

CONCLUSIONS

Ultrasound -guided biopsy can be performed using different approaches depending on the localisation of the lesion (i.e., percutaneous, transvaginal, transrectal, or transabdominal) and it should be ~~always~~ considered in patients with abdominal carcinomatosis to assess origin and characteristics of the tumor.

CONTRIBUTORS

FMa, LQ did the study design, patient recruitment, data analysis and interpretation, statistical analysis, and wrote the report. AF, ACT e GS supervised the whole process. FMo, ACT, AF and GS participated in patient recruitment. LQ, FMa, ADN and MM contributed to data collection and curation. FDF contributed statistical analysis. All authors approved the final report.

COMPETING INTERESTS:

The authors declare that there are no conflicts of interest.

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REFERENCES

[1] M. Peiretti, V. Zanagnolo, G.D. Aletti, et al., Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: surgical and oncological outcomes. Single institution experience, Gynecol. Oncol. 119 (2010) 259–264, https://doi.org/10.1016/j.ygyno.2010.07.032.

[2] Fagotti A, Ferrandina MG, Vizzielli G, Pasciuto T, Fanfani F, Gallotta V, Margariti PA, Chiantera V, Costantini B, Gueli Alletti S, Cosentino F, Scambia G. Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). Int J Gynecol Cancer. 2020 Nov;30(11):1657-1664.

[3] S. Kehoe, J. Hook, M. Nankivell, G.C. Jayson, H. Kitchener, T. Lopes, D. Luesley, T. Perren, S. Bannoo, M. Mascarenhas, S. Dobbs, S. Essapen, J. Twigg, J. Herod, G. McCluggage, M. Parmar, A.M. Swart, Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): An open-label, randomised, controlled, non-inferiority trial, Lancet. 386 (2015) 249–257.

[4] I. Vergote, C.G. Tropé, F. Amant, G.B. Kristensen, T. Ehlen, N. Johnson, R.H.M. Verheijen, M.E.L. van der Burg, A.J. Lacave, P.B. Panici, G.G. Kenter, A. Casado, C. Mendiola, C. Coens, L. Verleye, G.C.E. Stuart, S. Pecorelli, N.S. Reed, Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer, N. Engl. J. Med. 363 (2010) 943–953.

[5] N.R. Gómez-Hidalgo, B.A. Martinez-Cannon, A.M. Nick, K.H. Lu, A.K. Sood, R.L. Coleman, P.T. Ramirez, Predictors of optimal cytoreduction in patients with newly diagnosed advanced-stage epithelial ovarian cancer: Time to incorporate laparoscopic assessment into the standard of care, Gynecol. Oncol. 137 (2015) 553–558.

[6] A. Fagotti, G. Ferrandina, F. Fanfani, A. Ercoli, D. Lorusso, M. Rossi, G. Scambia, A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: A pilot study, Ann. Surg. Oncol. 13 (2006) 1156–1161.

[7] A. Fagotti, G. Ferrandina, F. Fanfani, G. Garganese, G. Vizzielli, V. Carone, M.G. Salerno, G. Scambia, Prospective validation of a laparoscopic predictive model for optimal cytoreduction in advanced ovarian carcinoma, Am. J. Obstet. Gynecol. 199 (2008) 642.e1-642.e6.

[8] M. Petrillo, G. Vizzielli, F. Fanfani, V. Gallotta, F. Cosentino, V. Chiantera, F. Legge, V. Carbone, G. Scambia, A. Fagotti, Definition of a dynamic laparoscopic model for the prediction of incomplete cytoreduction in advanced epithelial ovarian cancer: Proof of a concept, Gynecol. Oncol. 139 (2015) 5–9.

[9] Chojniak R, Isberner RK, Viana LM, Yu LS, Aita AA, SoaresFA. Computed tomography guided needle biopsy: experiencefrom 1,300 procedures. Sao Paulo Med J2006;124: 10 – 14.5. Ultrasound Obstet Gynecol.

[10] M. Zikan, D. Fischerova, I. Pinkavova, P. Dundr, D. Cibula, Ultrasound-guided tru-cut biopsy of abdominal and pelvic tumors in gynecology, Ultrasound Obstet. Gynecol. 36 (2010) 767–772.

[11 Bdour M, Hourani S, Mefleh W, Shababat A, Karadsheh S,Nawaiseh O, Ebous A. Comparison between fine needleaspiration cytology and tru-cut biopsy in the diagnosis of breastcancer.J Surg Pak (Int)2008;13: 19 – 21.

[12]. Moruzzi MC, Bolomini G, Moro F, Mascilini F, Ficarelli S, Beneduce G, Giudice MT, Pasciuto T, Moroni R, Scambia G, Fagotti A, Testa AC Diagnostic performance of ultrasound in assessing the extension of the disease in patients with suspicion of malignant ovarian tumor: correlation between ultrasound parameters and Fagotti's score. Int J Gynecol Cancer. 2021;31:279-285

[13]. Fischerova D, Zikan M, Semeradova I, Slama J, Kocian R, Dundr P, Nemejcova K, Burgetova A, Dusek L, Cibula D. Ultrasound in preoperative assessment of pelvic and abdominal spread in patients with ovarian cancer: a prospective study.
Ultrasound Obstet Gynecol. 2017;49:263-274.

[14]. Fischerova D, Pinto P, Burgetova A, Masek M, Slama J, Kocian R, Frühauf F, Zikan M, Dusek L, Dundr P, Cibula D. Preoperative staging of ovarian cancer: comparison between ultrasound, CT and whole-body diffusion-weighted MRI (ISAAC study).
.Ultrasound Obstet Gynecol. 2022;59:248-262.

[15]. Timmerman D, Planchamp F, Bourne T, Landolfo C, du Bois A, Chiva L, Cibula D, Concin N, Fischerova D, Froyman W, Gallardo G, Lemley B, Loft A, Mereu L, Morice P, Querleu D, Testa C, Vergote I, Vandecaveye V, Scambia G, Fotopoulou C. ESGO/ISUOG/IOTA/ESGE Consensus Statement on preoperative diagnosis of ovarian tumours. Facts Views Vis Obgyn. 202;13:107-130.

[16] N.P. Woodcock, I. Glaves, D.R. Morgan, J. MacFie, Ultrasound-guided Tru-cut biopsy of the breast, Ann. R. Coll. Surg. Engl. 80 (1998) 253–256.

[17] B.K. Park, Ultrasound-guided genitourinary interventions: Principles and techniques, Ultrasonography. 36 (2017) 336–348.

[18] R.L. Faulkner, L. Mohiyiddeen, R. McVey, H.C. Kitchener, Transvaginal biopsy in the diagnosis of ovarian cancer, BJOG An Int. J. Obstet. Gynaecol. 112 (2005) 991–993.

[19] F. Mascilini, L. Quagliozzi, F. Moro, M.C. Moruzzi, I. De Blasis, V. Paris, G. Scambia, A. Fagotti, A.C. Testa, Role of transvaginal ultrasound-guided biopsy in gynecology, Int. J. Gynecol. Cancer. 30 (2020) 128–132.

[20] S.Y. Lin, Y.H. Xiong, M. Yun, L.Z. Liu, W. Zheng, X. Lin, X.Q. Pei, A.H. Li, Transvaginal Ultrasound-Guided Core Needle Biopsy of Pelvic Masses, J. Ultrasound Med. 37 (2018) 453–461.

[21] S.Y. Won, H.-S. Kim, S.Y. Park, Transrectal or transvaginal ultrasoundguided biopsy for pelvic masses: external validation and usefulness in oncologic patients, Ultrasonography. 38 (2019) 149–155.

[22] C. Gao, L. Wang, C. Zhang, X. Li, Transvaginal/transrectal ultrasound-guided aspiration biopsy for diagnosis of pelvic/pelvic floor tumors in females: A retrospective analysis, Exp. Ther. Med. (2019) 352–357.

[23] Dániel Lengyel, Ildikó Vereczkey , Krisztina Kőhalmy , Kiarash Bahrehmand , Zoltán Novák. Transvaginal Ultrasound-Guided Core Biopsy-Experiences in a Comprehensive Cancer Centre. Cancers (Basel). . 2021 May 25;13(11):2590.

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Codice campo modificato

[24] D. Fischerova, D. Cibula, P. Dundr, M. Zikan, P. Calda, P. Freitag, J. Slama, Ultrasound-guided tru-cut biopsy in the management of advanced abdomino-pelvic tumors, Int. J. Gynecol. Cancer. 18 (2008) 833–837.

[25] E. Epstein, B. Van Calster, D. Timmerman, S. Nikman, Subjective ultrasound assessment, the ADNEX model and ultrasound-guided tru-cut biopsy to differentiate disseminated primary ovarian cancer from metastatic non-ovarian cancer, Ultrasound Obstet. Gynecol. 47 (2016) 110–116.

[26] J.F. Cohen, D.A. Korevaar, D.G. Altman, D.E. Bruns, C.A. Gatsonis, L. Hooft, L. Irwig, D. Levine, J.B. Reitsma, H.C.W. De Vet, P.M.M. Bossuyt, STARD 2015 guidelines for reporting diagnostic accuracy studies: Explanation and elaboration, BMJ Open. 6 (2016) 1–17.

[27] D. Timmerman, L. Valentin, T.H. Bourne, W.P. Collins, H. Verrelst, I. Vergote, Terms, definitions and measurements to describe the sonographic features of adnexal tumors: A consensus opinion from the International Ovarian Tumor Analysis (IOTA) group, Ultrasound Obstet. Gynecol. 16 (2000) 500–505.

[28] I. Vergote, S. Marquette, F. Amant, P. Berteloot, P. Neven, Port-site metastases after open laparoscopy: A study in 173 patients with advanced ovarian carcinoma, Int. J. Gynecol. Cancer. 15 (2005) 776–779.

[29] G.A. Hawker, S. Mian, T. Kendzerska, M. French, Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF, Arthritis Care Res. 63 (2011) 240–252.

[30] G. Vizzielli, B. Costantini, L. Tortorella, I. Pitruzzella, V. Gallotta, F. Fanfani, S. Gueli Alletti, F. Cosentino, C. Nero, G. Scambia, A. Fagotti. A laparoscopic risk-adjusted model to predict major complications after primary debulking surgery in ovarian cancer: A single-institution assessment. Gynecol. Oncol. 142 (2016) 19–24.

[31 Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform. 2014;48:193-204.

[32] Buderer NM. Statistical methodology: I. Incorporating the prevalence of disease into the sample size calculation for sensitivity and specificity. Acad Emerg Med. 1996;3(9):895-900.

[33] Verschuere H, Froyman W, Van den Bosch T, Van Hoefs M, Kaijser J, Van Schoubroeck D, Van Rompuy AS, Vergote I, Timmerman D. Safety and efficiency of performing transvaginal ultrasound-guided tru-cut biopsy for pelvic masses. Gynecol Oncol. 2021 Jun;161(3):845-851.

[34] R. Eitan, Y. Peled, G. Sabah, H. Krissi, A. Ben Haroush, I. Meizner, D. Danon, R. Bardin, A. Jakobson-Setton, L. Salzer, R. Mashiach, Diagnosis of deep pelvic masses on a gynaecology service: Trans-vaginal ultrasound-guided needle aspiration of pelvic solid and cystic lesions, Aust. New Zeal. J. Obstet. Gynaecol. 57 (2017) 197–200.

[35] M.C. Moruzzi, G. Bolomini, F. Moro, F. Mascilini, S. Ficarelli, G. Beneduce, M.T. Giudice, T. Pasciuto, R. Moroni, G. Scambia, A. Fagotti, A.C. Testa, Diagnostic performance of ultrasound in assessing the extension of the disease in patients with suspicion of malignant ovarian tumor: Correlation between ultrasound parameters and Fagotti's score, Int. J. Gynecol. Cancer. 31 (2021) 279–285.