Gemelli
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

PROTOCOL TITLE

Image-guided ultrasound robotic intraoperative evaluation of lymph-nodes status in gynecological malignancies

(R-LYNUS prospective trial)

Scientific Director
Prof. Giovanni Scambia

PI
Prof.ssa Antonia Testa

Sub -Investigator
Prof. Denis Querleu

PhD Candidate
Dott. Matteo Pavone

Collaborators
Dott.ssa Elena Teodorico
Dott. Nicolo' Bizzarri
Dott. Valerio Gallotta
Dott.ssa Simona Fragomeni

Statistician
Prof.ssa Diana Giannarelli

Synopsis

TITLE	**Image-guided ultrasound robotic intraoperative evaluation of lymph-nodes status in gynecological malignancies (R-LYNUS prospective trial)**
CENTERS	Dipartimento per la salute della Donna e del Bambino e della Salute Pubblica, Fondazione Policlinico Universitario A. Gemelli, IRCCS, UOC Ginecologia Oncologica, Rome, Italy.
BACKGROUND	The assessment of lymph node status is of crucial importance in gynaecological malignancies. Indeed, the prognosis and adjuvant treatment regimens are strongly influenced by the presence of nodal involvement. Systematic extensive lymphadenectomies are often performed for staging, diagnosis of skip metastases and to define the radiation field when radiotherapy treatments are required. Nevertheless, these can lead to significant short-term and long-term lymphatic complications, which are difficult to justify if the lymph nodes are free from metastasis. To avoid unnecessary comprehensive procedures in early-stage cancers, evaluation of the sentinel lymph node has acquired a valuable role even if limitations are still present (rate of frozen section false negative, “empty packets” and mapping failure). The introduction of an intra-operative non-invasive imaging technique capable of describing the presence and characteristics of lymph nodes could help in (1) eliminating the risk of empty packet, (2) orienting the intraoperative decision while avoiding the drawbacks of frozen section (time and resources, partial destruction of the tissue material), (3) orientate the pathological section if frozen section is used. To date, technological advancements have paved the way for enhanced intra-operative assessment of cancerous organs and lesions. Over the past decade, the evolution of robotic surgery combined with advancements in image-guided surgery techniques has led to the introduction of ultrasound probes designed specifically for intraoperative ultrasound during robotic surgery (RIOUS). Apart from the conventional rigid laparoscopic probes, which can be inserted through an accessory trocar, there are robotic probes tailored to fit device arms, and drop-in flexible probes that are becoming increasingly relevant in the scientific panorama. Notably, the latter drop-in probes feature a rigid segment designed for compatibility with robotic graspers, leveraging the dexterity and rotational manoeuvrability inherent to robotic surgery. Such probes, already proven effective in evaluating liver and kidney lesions as well as tumour margins, hold promise for intraoperative lymph node assessments due to the possibility of reaching difficult anatomical spaces thanks to the robotic-assisted movements.
PRIMARY ENDPOINT	The aim of this prospective trial is to report the sensibility of RIUS in the metastasis detection (macro, micro and ITCs) from fresh, unstained in vivo lymph node samples.
SECONDARY ENDPOINT	The secondary endpoint is to assess the lowest size detectable with the adopted drop-in robotic ultrasound probe.
TYPE OF STUDY	Interventional, prospective monocentric clinical trial
INCLUSION CRITERIA	- Women undergoing robotic surgery for gynecological malignancies (ovarian, endometrial, cervical cencers) - Need for nodal excision (staging or cytoreductive reasons) - 18-99 years old - Absence of contemporary lymphatic diseases - Absence of previous oncological disease in the last 5 years - Willingness to participate in the study and to provide informed consent
EXCLUSION CRITERIA	- Previous radiotherapy treatments in the area of analysed lymph nodes - Previous chemotherapy treatments

MATERIAL AND METHODS	Women undergoing radical surgery for gynecological cancers who meet the inclusion criteria in absence of exclusion criteria will be considered candidate for the study. Intraoperative robotic ultrasound will be performed on in vivo lymph nodal samples. Lymph nodes morphology and imaging characteristics will be evaluated. The gold standard will be definitive pathology.
SAMPLE SIZE	The primary endpoint of this study is the sensitivity of RIOUS in detecting metastases. We will consider the number of nodes rather than the number of patients; the sample size is based on a 10% risk of metastasis. A total of 351 nodes will ensure to estimate a sensitivity of about 90% with a 95% confidence interval semi-width of 10% and will allow to obtain a precision of 4% for the specificity. Considering that an average of 2-3 nodes is sampled by patients, the number of patients can be estimated to 160.

1. Background:

The assessment of lymph node status is of crucial importance in gynaecological malignancies (ovarian, endometrial, cervical and vulvar cancers) (1,2). The rate of positive lymph nodes in apparently early stage cancers is far to be low (14.2% ovarian, 10% endometrial, cervical 15% and vulvar cancers 10%) (3–6). Indeed, the prognosis and adjuvant treatment regimens are strongly influenced by the presence of nodal involvement (7). Systematic extensive lymphadenectomies are often performed for staging, diagnosis of skip metastases and to define the radiation field when adjuvant radiotherapy treatments are required. Nevertheless, pelvic and/or para-aortic lymphadenectomy can lead to significant short-term and long-term complications. The main reported postoperative complications include lymphoceles in up to 38% of cases and the development of lymphedemas in the lower limbs, which greatly diminish the quality of life for patients (8–10). In vulvar cancer surgery, inguinofemoral lymphadenectomy carries a risk of wound infection or breakdown in 20% to 40% of cases and a risk of lymphedema in 13% to 48% of patients (11). Despite the high morbidity associated with these procedures, systematic lymphadenectomies have been performed for many years because accurately determining lymph node involvement is crucial for care assessing. In cases of endometrial cancer, the recurrence-free survival rate drops from 87% in patients without lymph node involvement to 71% and 36% in women with pelvic and aortic node involvement, respectively (12). Similarly, in cervical cancer, lymph node invasion has been recognized as a critical prognostic factor, as reflected in the latest FIGO classification (13). Lymphatic spread is a characteristic feature also of epithelial ovarian cancer (EOC) even at early stages (14). Studies aiming to assess nodal involvement in all EOC stages, by performing systematic lymphadenectomy, have reported up to 55% rates of pelvic and para-aortic nodal metastases in patients with stage III and IV disease (15).

However, what makes the burden of surgical morbidity even more difficult to bear is that in most cases, regardless of the type of pelvic malignancy, the lymph nodes are free from metastasis (16,17). This means that the majority of patients undergo an unnecessary, risky, and burdensome procedure that has no proven impact on their survival. To solve this issue in early stages cancers, evaluation of the sentinel

lymph node (SLN) has acquired a valuable role allowing node-negative patients to be spared from the surgical comorbidities associated with total lymphadenectomy (18–21). Sentinel node frozen section analysis tough is not routinely performed also due to its disadvantage in terms of time consumption and not accurate results for micro-metastasis detection (2,22). Furthermore, in some case it is reported the inadvertent failure to harvest nodal tissue (it can reach the 8% in obese patients with endometrial cancer) with "empty packets" that may lead to overtreatment for patient safety (23). Additionally, sometimes SLN mapping may fail, leading the surgeon to the need to extend the lymphadenectomy or making the SLN technique unuseful and the patient unstaged. Even if efforts are focused on tailoring the lymph nodes removal to avoid the complications of extensive lymphadenectomies, the detection of pathological lymph nodes with micro or macro metastases is still an open challenge for pre-operative imaging techniques (24). While FDG PET/CT is the most accurate imaging examination for lymph node evaluation, it nevertheless results in false negative diagnoses (25,26). As an example, a study in 60 patients with stage IB2 to IVA cervical cancer found that 12 % of those with no finding of positive paraaortic nodes on PET/CT had pathologically positive paraaortic nodes (25).

The introduction of an intra-operative imaging technique capable of describing the presence and characteristics of lymph nodes could help in the identification of the diseased ones tailoring surgical procedures and decreasing the risks associated with unuseful extensive lymphadenectomies (27).

To date, advances in imaging guided surgery and artificial intelligence software are offering alternative solutions in the intraoperative diagnosis of nodal involvement (27).

Among the novel intraoperative bedside imaging guided surgery techniques Full-Field Optical Coherence Tomography (FFOCT) (27), High-Frequency Ultrasound (HFUS) (28,29) and Intraoperative Ultrasound (IOUS) (30) appear as the most promising in the scientific panorama. The ultrasound lymph nodal morphology in gynecological malignancies has been extensively described. However, the intra-operative assessment of lymph nodal status is far to be fully achieved.

Intraoperative ultrasound (IOUS) is commonly utilized during open surgery with linear or finger probes, particularly in the hepato-biliary (HPB) and urological fields (31,32). Laparoscopically (LIOUS), ultrasound probes for guidance in MIS are more challenging to handle (33). To overcome this limitation, innovative approaches for robotic platforms integrate ultrasound imaging to facilitate its use in MIS

(34). Image-guided robotic approaches, that can integrate also three-dimensional (3D) imaging, augmented reality (AR), and machine learning algorithms, offer advantages in the era of digital surgery (35). Real-time, non-invasive, cost-effective and dynamic intraoperative imaging of complex anatomy is the ultimate goal in computer-assisted surgery to attain unparalleled precision. In this landscape, IOUS has become the imaging modality of choice with the introduction of articulated robotic ultrasound probes (36). Image augmentation and fusion of imaging modalities is especially beneficial to delineate healthy and neoplastic tissue in oncological surgery (37).

The navigation of ultrasound probes manoeuvred by articulated robotic graspers, can give access to anatomical spaces and angles that are inconvenient for rigid laparoscopic probes. First reports of applications of intraoperative ultrasound during robotic surgery (RIOUS) have been published in similar fields as open surgery with encouraging results (31,38).

RIOUS has demonstrated superior performance compared to conventional LIOUS in liver surface exploration and tool manipulation. RIOUS' success rate exceeded the one of LIOUS in liver surface exploration (85% vs. 73%, P = .030) and in tool manipulation (79% vs. 57%, P = .028)(33). Facilitating probe positioning in RIOUS results in enhanced precision while reducing the physical strain on surgeons during complex procedures (31) opportunity to identify otherwise undetected lesions, such as in pancreatic lesions (39).

Similarly, rectal tumours were successfully detected using RIOUS, a finding that highlights its effectiveness in determining the optimal transection line for rectal surgeries, particularly in tumours too high for transanal palpation (40). A remarkable 100% success rate was demonstrated in identifying kidney lesions with RIOUS (41) to optimise tumour identification, thereby enhancing renal tissue preservation via partial nephrectomy, and without compromising oncological safety (34). In transoral robotic tongue base resection for obstructive sleep apnoea RIOUS has emerged as an invaluable tool. to locate the lingual artery and assess laryngeal tissues. The integration of RIOUS significantly enhanced efficiency by substantially reducing the risk of detrimental intraoperative bleeding complications (42).

There are no studies in the literature reporting the use of RIOUS in lymph nodal assessment.

The RIOUS image rendering, could be an useful tool in the definition of in vivo lymph nodes from gynecological malignancies (43,44).

2. Purposes and objective of the clinical trial

The identification of an image-guided surgery technique capable of intraoperatively detecting the presence of lymph node metastases would overcome the disadvantages and complications of extensive staging lymphadenectomies.

3. Experimental design

Primary endpoint

The aim of this prospective trial is to report the sensibility of RIOUS in the metastasis detection (macro, micro and ITCs) from fresh, unstained in vivo lymph node samples.

Secondary endpoint

The secondary endpoint is to assess the lowest size detectable with the adopted imaging technique.

Setting

Patients referred to the Gynecology Oncology Unit in Fondazione Policlinico A. Gemelli IRCCS, Italy, Rome with a diagnosis of gynecological malignancy requiring surgical lymph nodes harvest will be evaluated for the enrolment.

Experimental plan

Interventional, prospective monocentric clinical trial.

4. Study enrolment

Inclusion criteria

- Women undergoing robotic surgery for gynecological malignancies (ovarian, endometrial, cervical cancer)
- Need for nodal excision (staging or cytoreductive reasons)
- 18-99 years old
- Absence of contemporary lymphatic diseases

- Absence of previous oncological disease in the last 5 years
- Willingness to participate in the study and to provide informed consent

Exclusion criteria

- Previous radiotherapy treatments
- Previous chemotherapy treatments
- Recurrence of disease

5. Treatments

Robotic intraoperative ultrasound

Women undergoing radical surgery for gynecological cancers who meet the inclusion criteria will be enrolled. RIOUS will be performed on in vivo nodal samples collected during surgeries at Department of Gynecology Oncology, Fondazione Policlinico A. Gemelli IRCCS. Lymph nodes morphology and imaging characteristics will be evaluated. Comparison with the definitive pathology will be made to accomplish the study endpoints.

The robotic drop-in ARIETTA L51K probe (Hitachi, Tokio, Japan) will be used to describe normal and pathological lymph node by a gynecologist expert in oncological ultrasound and surgery. Lymph nodes images will be evaluated in order to investigate the presence or the absence of morphological parameters to be significant in the macroscopic disease detection according to the VITA (Vulva International Tumor Analysis) group consensus (28,29): nodal shape; inhomogeneous echo structure; intranodal deposits (described as a hyperechoic or hypoechoic area detected within the node); hilum anomalies (absence, displacement or interface distortion); cortical thickening; and nodal grouping. Moreover, the following dimensional parameters will be recorded: long-axis (L) and short-axis (S); L/S ratio, considering as suspicious a value < 2; cortical (C) and medullar (M) thickness of the node; and C/M thickness ratio, considering as suspicious a value > 1. Three additional morphological parameters will be assessed, which comprised: presence of perinodal hyperechoic ring (as a sign of inflammatory

perinodal stroma); cortical interruption (as a sign of extracapsular tumor spread); and presence of rich vascularization. A microscopic evaluation will be then carried out. Observational parameters will be recorded and Doppler images of intra-nodal vascularization scored as 0-3. Detection of macro and micro metastases (< 2mm) or ITCs (< 0.2mm) will be recorded. After collecting these morphological and dimensional parameters, a morphometric ultrasound pattern (MUP) will be expressed. The classification system is based on the tool for breast imaging published by the American College of Radiology (ACR), the breast imaging-reporting and data system (BI-RADS®) provides the following categories for assessment: negative; benign; probably benign; suspicious; and highly suggestive of malignancy. Based on this model, we will classify the LN status into five groups, according to a subjective assessment: normal (U1); reactive-but-negative (U2); minimally suspicious/probably groups U3, U4 and U5 as positive. Finally, specimens will be given to the pathologist for the histological evaluation.

6. Sample size

The primary endpoint of this study is the sensitivity of RIOUS in detecting metastases. We will consider the number of nodes rather than the number of patients; the sample size is based on a 10% risk of metastasis. A total of 351 nodes will ensure to estimate a sensitivity of about 90% with a 95% confidence interval semi-width of 10% and will allow to obtain a precision of 4% for the specificity. Considering that an average of 2-3 lymph nodes is sampled by patients, the number of patients can be estimated to 160.

7. Statistical analysis

In general, data will be summarized using appropriate summary statistics: Categorical data will be described using absolute counts and percentages. Continuous variables will be evaluated using the following standard descriptive summary statistics: number of observations, arithmetic mean and standard deviation, median and interquartile range. Results will be reported at lymph nodes and patients level. Punctual estimates regarding primary and secondary endpoints will be presented with their

confidence intervals. Analysis and reporting will follow the Standard for Reporting Diagnostic Accuracy Studies (STARD) guidelines.

The secondary endpoint will be evaluated with paired test either parametric or not according to the deviation form normality assumptions evaluated with the Kolmogorov-Smirnov test.

9. Administrative and ethical considerations

Ethics considerations

a) Risk-benefit considerations

The RIOUS evaluation will be made during the scheduled surgeries. The patients will not have any additional discomfort due to the imaging exam. The result of the following study will in no way influence the patients' subsequent therapies or the usual standard of care. In this study we will not propose any different treatment compared to the standard of care for patients with gynecological malignancies.

b) Data protection and privacy

The data collection will be performed pseudonymously, and the patient's name will not appear. All collected data will be kept confidential. This study is performed in accordance with the revision of the Declaration of Helsinki.

c) Institutional review board / ethics committee

Study protocol, patient information and informed consent will be submitted to the ethics committee of the FPG-IRCCS and collaborators centres for approval. The study will start after being approved by the ethics committee. The principal investigator will inform the ethics committee about any changes in the

study protocol which could interfere with patient's safety. Furthermore, the committee will be informed of the planned or premature end of the study. The investigators are obliged to consult their responsible ethics committee and to wait for approval before including patients into the study, as well as to inform their ethics committee of changes in the protocol and end of study.

d) Informed consent

Before enrolment in the study, the treating investigator informed the patient about the nature of the procedure, its aims, expected advantages as well as possible risks. Each patient must consent in writing to participate in the study. The patient must be given enough time and opportunity to decide on participation and to clarify questions before inclusion in the trial. The informed consent will be signed by both patient and treating investigator. The original document is kept by the investigator.

Publications

The study's results will be published irrespective of the nature of the results. The coordinating principal investigator, the other investigators, the statistician, the study coordinators and other authors will be included depending on recruitment numbers and absolute number of authors allowed for the respective journal.

Adherence to protocol and protocol amendments

The study protocol must be thoroughly adhered, and any deviation must be documented and justified by the investigator. Changes or supplements to the study protocol can only be decided on and authorised by the coordinating principal investigator (amendment), the study coordinators and the biometrician.

8. Quality assurance/monitoring

According to the guidelines of Good Clinical Practice the study monitoring will be done by personal which is assigned by the coordinating principal investigator. The applicable directives for data protection law will be kept. It is the responsibility of the Clinical or Field Monitor to follow the study via telephone contact, written correspondence, and regular visits to the Investigator and study sites to review records. The Clinical or Field Monitor will maintain current, personal knowledge of the study through observation, review of the records, comparison with source documents, and discussion of the conduct of the study with the investigators. Within this trial a 100% SDV (Source Data Verification) will be performed for the inclusion and exclusion criteria, verification of treatment compliance by surgery reports, histopathological results, primary and secondary endpoints and complications. Other trial data will undergo 100% SDV for 20% of patients. The participation of the patient in the clinical trial has to be documented in the patient record.

9. Data management

Data will be prospectively collected by principal investigator or co-investigator, or by trainees under direct supervision. Data from registration will be entered to an eCRF (electronic Case Report Form) for every patient. Study data will be managed using REDCap electronic data capture tools hosted at Fondazione Policlinico Universitario A. Gemellli, IRCCS (https://redcap-irccs.policlinicogemelli.it/). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (A metadata-driven methodology and workflow process for providing translational research informatics support . Research electronic data capture (REDCap). Only people officially registered as study investigators or data managers will receive a user login to access the REDCap web platform and enter/manage data.

Storage of study documents

Originals of all central study documents will be kept in the study office for a period of 10 years after preparation of the final report. The investigator keeps accrued administrative documents (correspondence with ethics committee, surveillance authority, study coordinators, central study office), the patient identification list, signed informed consent, and general study documents (protocol, amendments) for the above-mentioned period. Original data of study patients (medical records) must be stored according to the archiving period valid at the respective study site, but not less than 10 years.

REFERENCES:

1. Jiang L, Liu L, Yang X. Different approaches to compare the curative effect of laparoscopic resection of para-aortic lymph nodes in gynecological malignant tumors: A systematic review and meta-analysis. Asian J Surg. 2022 Dec;45(12):2965–7.

2. Balaya V, Guani B, Benoit L, Magaud L, Bonsang-Kitzis H, Ngô C, et al. Diagnostic value of frozen section examination of sentinel lymph nodes in early-stage cervical cancer at the time of ultrastaging. Gynecol Oncol. 2020 Sep;158(3):576–83.

3. Kleppe M, Wang T, Gorp TV, Slangen BFM, Kruse AJ, Kruitwagen RFPM. Lymph node metastasis in stages I and II ovarian cancer: A review. Gynecol Oncol. 2011 Dec 1;123(3):610–4.

4. Dong Y, Cheng Y, Tian W, Zhang H, Wang Z, Li X, et al. An Externally Validated Nomogram for Predicting Lymph Node Metastasis of Presumed Stage I and II Endometrial Cancer. Front Oncol [Internet]. 2019 [cited 2023 Jul 11];9. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2019.01218

5. Sponholtz SE, Mogensen O, Hildebrandt MG, Schledermann D, Parner E, Markauskas A, et al. Sentinel lymph node mapping in early-stage cervical cancer – A national prospective multicenter study (SENTIREC trial). Gynecol Oncol. 2021 Sep;162(3):546–54.

6. Rychlik A, Bidzinski M, Rzepka J, Piatek S. Sentinel lymph node in vulvar cancer. Chin Clin Oncol. 2021 Apr;10(2):19–19.

7. ASTEC study group, Kitchener H, Swart AMC, Qian Q, Amos C, Parmar MKB. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet Lond Engl. 2009 Jan 10;373(9658):125–36.

8. Franchi M, Ghezzi F, Riva C, Miglierina M, Buttarelli M, Bolis P. Postoperative complications after pelvic lymphadenectomy for the surgical staging of endometrial cancer. J Surg Oncol. 2001 Dec;78(4):232–7; discussion 237-240.

9. Kim SI, Lim MC, Lee JS, Lee Y, Park K, Joo J, et al. Impact of lower limb lymphedema on quality of life in gynecologic cancer survivors after pelvic lymph node dissection. Eur J Obstet Gynecol Reprod Biol. 2015 Sep;192:31–6.

10. Hayes SC, Janda M, Ward LC, Reul-Hirche H, Steele ML, Carter J, et al. Lymphedema following gynecological cancer: Results from a prospective, longitudinal cohort study on prevalence, incidence and risk factors. Gynecol Oncol. 2017 Sep;146(3):623–9.

11. Wills A, Obermair A. A review of complications associated with the surgical treatment of vulvar cancer. Gynecol Oncol. 2013 Nov;131(2):467–79.

12. Morrow CP, Bundy BN, Kurman RJ, Creasman WT, Heller P, Homesley HD, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991 Jan;40(1):55–65.

13. Macdonald OK, Chen J, Dodson M, Lee CM, Gaffney DK. Prognostic significance of histology and positive lymph node involvement following radical hysterectomy in carcinoma of the cervix. Am J Clin Oncol. 2009 Aug;32(4):411–6.

14. Morice P, Joulie F, Camatte S, Atallah D, Rouzier R, Pautier P, et al. Lymph Node Involvement in Epithelial Ovarian Cancer: Analysis of 276 Pelvic and Paraaortic Lymphadenectomies and Surgical Implications. J Am Coll Surg. 2003 Aug;197(2):198–205.

15. Tzanis AA, Antoniou SA, Zacharoulis D, Ntafopoulos K, Tsouvali H, Daponte A. The role of systematic pelvic and para-aortic lymphadenectomy in the management of patients with advanced epithelial ovarian, tubal, and peritoneal cancer: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2023 Jun 1;285:198–203.

16. Hacker NF, Berek JS, Lagasse LD, Leuchter RS, Moore JG. Management of regional lymph nodes and their prognostic influence in vulvar cancer. Obstet Gynecol. 1983 Apr;61(4):408–12.

17. Havrilesky LJ, Leath CA, Huh W, Calingaert B, Bentley RC, Soper JT, et al. Radical hysterectomy and pelvic lymphadenectomy for stage IB2 cervical cancer. Gynecol Oncol. 2004 May;93(2):429–34.

18. Balaya V, Guani B, Morice P, Querleu D, Fourchotte V, Leblanc E, et al. Long-term oncological safety of sentinel lymph node biopsy in early-stage cervical cancer: A post-hoc analysis of SENTICOL I and SENTICOL II cohorts. Gynecol Oncol. 2022 Jan;164(1):53–61.

19. Garganese G, Collarino A, Fragomeni SM, Rufini V, Perotti G, Gentileschi S, et al. Groin sentinel node biopsy and 18F-FDG PET/CT-supported preoperative lymph node assessment in cN0 patients with vulvar cancer currently unfit for minimally invasive inguinal surgery: The GroSNaPET study. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2017 Sep;43(9):1776–83.

20. Uccella S, Nero C, Vizza E, Vargiu V, Corrado G, Bizzarri N, et al. Sentinel-node biopsy in early-stage ovarian cancer: preliminary results of a prospective multicentre study (SELLY). Am J Obstet Gynecol. 2019 Oct;221(4):324.e1-324.e10.

21. Restaino S, Finelli A, Lucidi A, Ercoli A, Scambia G, Fanfani F. Step-by-step surgical procedures for a correct identification of the sentinel lymph node in endometrial cancer. Facts Views Vis ObGyn. 2021 Jan 8;12(4):309–14.

22. Blakely M, Liu Y, Rahaman J, Prasad-Hayes M, Tismenetsky M, Wang X, et al. Sentinel Lymph Node Ultra-staging as a Supplement for Endometrial Cancer Intraoperative Frozen Section Deficiencies. Int J Gynecol Pathol Off J Int Soc Gynecol Pathol. 2019 Jan;38(1):52–8.

23. Thomaier L, Jager L, Stone R, Wethington S, Fader A, Tanner EJ. Risk of empty lymph node packets in sentinel lymph node mapping for endometrial cancer using indocyanine green. Int J Gynecol Cancer. 2019 Mar;29(3):513–7.

24. Gong Y, Wang Q, Dong L, Jia Y, Hua C, Mi F, et al. Different imaging techniques for the detection of pelvic lymph nodes metastasis from gynecological malignancies: a systematic review and meta-analysis. Oncotarget. 2016 Oct 27;8(8):14107–25.

25. Ramirez PT, Jhingran A, Macapinlac HA, Euscher ED, Munsell MF, Coleman RL, et al. Laparoscopic extraperitoneal para-aortic lymphadenectomy in locally advanced cervical cancer: a prospective correlation of surgical findings with positron emission tomography/computed tomography findings. Cancer. 2011 May 1;117(9):1928–34.

26. Leblanc E, Gauthier H, Querleu D, Ferron G, Zerdoud S, Morice P, et al. Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. Ann Surg Oncol. 2011 Aug;18(8):2302–9.

27. Pavone M, Spiridon IA, Lecointre L, Seeliger B, Scambia G, Venkatasamy A, et al. Full-field optical coherence tomography imaging for intraoperative microscopic extemporaneous lymph node assessment. Int J Gynecol Cancer Off J Int Gynecol Cancer Soc. 2023 Nov 9;ijgc–2023–005050.

28. Garganese G, Fragomeni SM, Pasciuto T, Leombroni M, Moro F, Evangelista MT, et al. Ultrasound morphometric and cytologic preoperative assessment of inguinal lymph-node status in women with vulvar cancer: MorphoNode study. Ultrasound Obstet Gynecol. 2020;55(3):401–10.

29. Fischerova D, Garganese G, Reina H, Fragomeni SM, Cibula D, Nanka O, et al. Terms, definitions and measurements to describe sonographic features of lymph nodes: consensus opinion from the Vulvar International Tumor Analysis (VITA) group. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2021 Jun;57(6):861–79.

30. Mascilini F, Quagliozzi L, Moro F, Moruzzi MC, Gallotta V, Alletti SG, et al. Role of Intraoperative Ultrasound to Extend the Application of Minimally Invasive Surgery for Treatment of Recurrent Gynecologic Cancer. J Minim Invasive Gynecol. 2018;25(5):848–54.

31. Glaysher MA, Beable R, Ball C, Carter NC, Knight BC, Pucher PH, et al. Intra-operative ultrasound assessment of the biliary tree during robotic cholecystectomy. J Robot Surg. 2023 Aug 26;

32. Kaczmarek BF, Sukumar S, Petros F, Trinh QD, Mander N, Chen R, et al. Robotic ultrasound probe for tumor identification in robotic partial nephrectomy: Initial series and outcomes. Int J Urol Off J Jpn Urol Assoc. 2013 Feb;20(2):172–6.

33. Schneider CM, Peng PD, Taylor RH, Dachs GW, Hasser CJ, DiMaio SP, et al. Robot-assisted laparoscopic ultrasonography for hepatic surgery. Surgery. 2012 May;151(5):756–62.

34. Di Cosmo G, Verzotti E, Silvestri T, Lissiani A, Knez R, Pavan N, et al. Intraoperative ultrasound in robot-assisted partial nephrectomy: State of the art. Arch Ital Urol E Androl. 2018 Sep 30;90(3):195–8.

35. Lecointre L, Verde J, Goffin L, Venkatasamy A, Seeliger B, Lodi M, et al. Robotically assisted augmented reality system for identification of targeted lymph nodes in laparoscopic gynecological surgery: a first step toward the identification of sentinel node. Surg Endosc. 2022 Dec 1;36(12):9224–33.

36. Guerra F, Amore Bonapasta S, Annecchiarico M, Bongiolatti S, Coratti A. Robot-integrated intraoperative ultrasound: Initial experience with hepatic malignancies. Minim Invasive Ther Allied Technol MITAT Off J Soc Minim Invasive Ther. 2015;24(6):345–9.

37. Sokolenko A, Preobrazhenskaya E, Marchetti C, Piermattei A, Zagrebin F, Kuligina E, et al. Origin of residual tumor masses in BRCA1/2-driven ovarian carcinomas treated by neoadjuvant chemotherapy: selection of preexisting BRCA1/2-proficient tumor cells but not the gain of second ORF-restoring mutation. Pathobiol J Immunopathol Mol Cell Biol. 2023 Aug 14;

38. Sun Y, Wang W, Zhang Q, Zhao X, Xu L, Guo H. Intraoperative ultrasound: technique and clinical experience in robotic-assisted renal partial nephrectomy for endophytic renal tumors. Int Urol Nephrol. 2021 Mar;53(3):455–63.

39. Liu Y, Ji WB, Wang HG, Luo Y, Wang XQ, Lv SC, et al. Robotic spleen-preserving laparoscopic distal pancreatectomy: a single-centered Chinese experience. World J Surg Oncol. 2015 Sep 17;13(1):275.

40. Otani K, Kiyomatsu T, Ishimaru K, Kataoka A, Hayashi Y, Gohda Y. Usefulness of real-time navigation using intraoperative ultrasonography for rectal cancer resection. Asian J Endosc Surg. 2023;16(4):819–21.

41. Gunelli R, Fiori M, Salaris C, Salomone U, Urbinati M, Vici A, et al. The role of intraoperative ultrasound in small renal mass robotic enucleation. Arch Ital Urol Androl Organo Uff Soc Ital Ecogr Urol E Nefrol. 2016 Dec 30;88(4):311–3.

42. Chang CC, Wu JL, Hsiao JR, Lin CY. Real-Time, Intraoperative, Ultrasound-Assisted Transoral Robotic Surgery for Obstructive Sleep Apnea. The Laryngoscope. 2021 Apr;131(4):E1383–90.

43. Yang H, Zhang S, Liu P, Cheng L, Tong F, Liu H, et al. Use of high-resolution full-field optical coherence tomography and dynamic cell imaging for rapid intraoperative diagnosis during breast cancer surgery. Cancer. 2020;126(S16):3847–56.

44. Ignatov A, Lebius C, Ignatov T, Ivros S, Knueppel R, Papathemelis T, et al. Lymph node micrometastases and outcome of endometrial cancer. Gynecol Oncol. 2019 Sep;154(3):475–9.