TRUTH – TRU-cut biopsy in Tumor cHaracterisation

Version:	**2.0**
Date:	**1-JAN-2024**
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Study design:	**Prospective cohort**

DECLARATION OF THE MAIN INVESTIGATOR

Title: A single arm, prospective, cohort study to evaluate the feasibility of a complex classification of pelvic and abdominal tumors by tru-cut biopsy with immunohistochemistry, next-generation sequencing, and immunological examination.

Acronym: TRUTH

Protocol version: 2.0

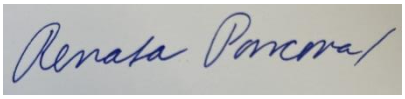
The undersigned confirms that the above-referenced protocol has been acknowledged and accepted, he agrees to conduct the study in compliance with the approved protocol, and will adhere to the ICH guidelines, the most recent version of the Declaration of Helsinki, the EU General Data Protection Regulation 2016/679 (GDPR), relevant Czech laws implementing the GDPR, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agrees not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the study, without prior written consent from the sponsor.

Center: Department of Obstetrics and Gynecology
General University Hospital and First Faculty of Medicine Charles University
Prague

Main investigator: Renata Poncová

Date: 1-JAN-2024

Signature: 

SYNOPSIS

Title	A prospective study to evaluate the feasibility of a complex classification of pelvic and abdominal tumors by tru-cut biopsy with immunohistochemistry, next-generation sequencing, and immunological examination.
Acronym	TRUTH
Type	Prospective cohort
Objective	The objective of this prospective study is to evaluate if a complex classification of pelvic and abdominal tumors using tissue samples obtained by tru-cut biopsy (TCB) is feasible.
Primary endpoint	The primary endpoint is the adequacy of samples obtained by TCB for histopathological examination.
Secondary endpoint	The secondary endpoints are the adequacy of samples obtained by TCB for: 1. next-generation sequencing examination 2. immunohistochemistry examination 3. immunologic examination
Additional endpoints	1. To evaluate which factors affect the primary and secondary endpoints, including: a. tumor origin b. size of the tumor c. presence of ascites d. body mass index (BMI) e. biopsy site f. biopsy approach (transvaginal, transrectal vs. transabdominal) g. disease status – first diagnosis, recurrence or progression h. previous treatment modality – chemotherapy, anti-angiogenic therapy, PARP inhibitor therapy, hormonal therapy, or radiotherapy 2. To evaluate the overall safety of TCB 3. To evaluate the overall accuracy of TCB for complex classification of pelvic and abdominal tumors
Inclusion criteria	1. Presence of a pelvic/abdominal lesion with suspicion of malignancy: a. new diagnosis of a presumed gynecologic tumor b. suspicious recurrence or progression of a known gynecologic malignancy c. pelvic/abdominal spread or recurrence of a non-gynecologic tumor (primary tumor or metastasis) d. pelvic/abdominal spread of a tumor of unknown origin 2. Age ≥18 years 3. Eastern Cooperative Oncology Group (ECOG) performance status grade <3 4. Not pregnant

	5. Signed informed consent form
Exclusion criteria	1. Considered by the investigator to be unsuitable for any treatment 2. Early stage disease 3. Age <18 years
Time frame and sample size	A total of 250 consecutive patients Start date: 1-FEB-2024 End date: 31-JAN-2026

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LIST OF ABBREVIATIONS

ADNEX	Assessment of Different NEoplasias in the adneXa (model)
AE	Adverse Events
BMI	Body Mass Index
BOT	Border-line Ovarian Tumor
CT	Computed Tomography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EC	Ethical Committee
FNAB	Fine Needle Aspiration Biopsy
GCP	Good Clinical Practice
HGSC	High Grade Serous Carcinoma
ICF	Informed Consent Form
IHC	Immunohistochemistry
ICH	International Conference on Harmonisation
LGSC	Low Grade Serous Carcinoma
LMWH	Low Molecular Weight Heparin
MI	Main Investigator
MRI	Magnetic Resonance Imaging
NACT	Neoadjuvant Chemotherapy
NGS	Next-Generation Sequencing
NOAC	New Anticoagulants
PI	Principal Investigator
PARP	Poly-ADP Ribose Polymerase
PET	Positron Emission Tomography
REDcap	Research Electronic Data Capture
TAS	Transabdominal Ultrasound
TCB	Tru-cut Biopsy
TIL	Tumor Infiltrating Lymphocytes
TMB	Tumor Mutational Burden
TVS	Transvaginal Ultrasound
US	Ultrasound

ROLES AND RESPONSIBILITIES

The principal investigator (PI) is responsible for the conduct of the study at his/her participating site, and for protecting the rights, safety, and well-being of all participants. As such, the PI must ensure adequate supervision of the study at the local site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated the specified study-related duties. The PI will ensure that adequate training is provided and documented for all study staff, before they conduct the assigned activities. Even when certain activities are delegated, the PI will ultimately remain responsible for the conduct of the study.

The main investigator's (MI) responsibility is to supervise the general conduct of the study, including study progress, communications, protocol training and support of the participating sites, annual reporting to the ethical committee (EC), end of study notification(s), and reporting of the results. The MI fulfils both investigator and sponsor responsibilities, as outlined in the International Conference on Harmonisation – good clinical practice (ICH-GCP) and applicable regulations.

1. BACKGROUND AND RATIONALE

Image-guided diagnostic interventions are valuable tools in gynecologic oncology clinical practice. Several procedures are available, including core needle (tru-cut) biopsy (TCB) and fine needle aspiration biopsy (FNAB).

The purpose of performing biopsies in gynecologic practice is to obtain a representative tissue sample for a valid morphological examination. Biopsies are particularly useful for patients who are deemed unsuitable for more invasive interventions, and accelerate the process from diagnosis to therapy without the need for a period of recovery [1, 2]. In addition, in the era of personalized medicine, biopsies of gynecological cancers, either from primary, recurrent or progressive disease, have become important for characterizing the cellular pathways of the disease and to plan subsequent targeted therapy [3].

Tru-cut biopsy (TCB) is a minimally invasive method to obtain an adequate sample from the lesion and hence tailor the subsequent management avoiding unnecessary surgery. In gynecologic oncology, this technique is predominantly used in advanced ovarian cancers if primary cytoreductive surgery with no residual disease is not feasible and for patients indicated for neoadjuvant chemotherapy. Furthermore, it is useful to verify recurrent disease [4] and can be used in cases with tumors of presumed non-gynecologic origin that, in the pelvis, are mostly metastases derived from the gastrointestinal tract or breast cancer [5]. TCB can be used in combination with subjective ultrasound (US) assessment or with the assessment of different neoplasias in the adnexa (ADNEX) model to evaluate the nature of the majority of the pelvic tumor [6].

The Gynecologic Oncology Centre of the General University Hospital in Prague was among the first centers to start using TCB. Also, one of the largest retrospective studies published on this topic was done in our center. In the previous study, 190 patients were enrolled, and an adequate sample was obtained in more than 93% of all cases. In patients indicated for primary surgery or secondary debulking surgery, less than 2% of tru-cut biopsies did not coincide with the final histologic diagnoses. Regarding safety, only two bleeding complications, which were resolved by surgery, were recorded [7].

The samples obtained by TCB using an appropriate thick needle is usually sufficient for histopathological examination, immunohistochemistry (IHC), and next-generation sequencing (NGS). Although there is not yet strong evidence to show whether thick needle specimens are sufficient for the assessment of the tumor microenvironment based on immune monitoring, the available data are promising [8]. By contrast, FNAB only permits cytological examination with several crucial limitations to establish the final diagnosis [9, 10].

Modern examination methods (IHC, NGS, immunology) can give new information about the tumor's characteristics that can substantially affect the clinical prognosis and efficacy of different types of targeted treatment. Now, de novo biopsy in cases of disease recurrence or progression is strongly recommended because it can reveal the alterations of these characteristics that occur during the course of treatment and improve the therapeutic strategies. In ovarian cancer, high temporal heterogeneity of tumor biopsies has been demonstrated, with a significant clinical impact [11].

TCB can be considered the smartest way to histopathologically verify a gynecologic malignancy because it is minimally invasive, is performed in an outpatient basis, and is well tolerable with a low complication rate. Furthermore, TCB has an excellent cost–benefit ratio.

2. ENDPOINTS

2.1. Primary endpoint

The primary endpoint is the adequacy of samples obtained by TCB for histopathological diagnosis at the Gynecologic Oncology Center of the General University Hospital in 3 years.

2.2. Secondary endpoint

The secondary endpoint is the adequacy of samples obtained by TCB for next generation sequencing, immunohistochemistry, and immunologic examination.

2.3. Additional endpoints

1. To evaluate which factors affect the primary and secondary endpoint, including:
    a. tumor origin
    b. size of the tumor
    c. presence of ascites
    d. body mass index (BMI)
    e. biopsy site
    f. biopsy approach transvaginal, transrectal vs. transabdominal
    g. disease status – the first diagnosis, the first and other recurrence or progression
    h. previous treatment modality – chemotherapy, anti-angiogenic therapy, PARP inhibitor therapy, hormonal therapy, or radiotherapy
2. To evaluate the overall safety of TCB
3. To evaluate the overall accuracy of TCB for complex classification of pelvic and abdominal tumors

2.4. Definitions of endpoints

The feasibility of TCB will be calculated as the proportion of patients in whom TCB was performed among all patients enrolled in the study.

Adequacy is defined as the proportion of patients in whom an adequate sample was obtained for a particular examination from among those patients who underwent TCB.

Accuracy will only be evaluated in patients in whom an adequate sample was obtained by TCB who underwent surgery with biopsy. Accuracy is defined as the concordance between the examination of samples obtained by TCB and the results of surgery with TCB to the final histopathology. The outcome of the final histopathological examination will be considered the reference standard.

For accuracy and adequacy, the impact of selected variables (e.g., approach, number of biopsies, and target lesion size) will be assessed in a multivariable analysis.

Safety is defined as the rate of complications related to TCB, including events occurring during the procedure, events within 24 hours after the procedure (early events), and events within 30 days of the procedure (late events).

3. ELIGIBILITY CRITERIA

3.1. Inclusion criteria

Patients will be eligible for the study if they satisfy all of the following criteria:

1. Presence of a pelvic/abdominal lesion with suspicion of a primary malignancy, disease recurrence, or disease progression
    a. new diagnosis of a presumed gynecologic tumor
    b. suspected recurrence or progression of a known gynecologic malignancy
    c. pelvic/abdominal spread or recurrence of a non-gynecologic tumor (tumor itself or metastasis)
    d. pelvic/abdominal spread of a tumor of unknown origin.
2. Age ≥18 years
3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade <3
4. Not pregnant
5. Signed informed consent form

3.2. Exclusion criteria

Patients will be excluded from the study for the following reasons:

1. Considered by the investigator to be unsuitable for any treatment
2. Early stage disease
3. Age <18 years

4. STUDY DESCRIPTION

Patients referred to the Gynecologic Oncology Centre with a new or recurrent progressive abdominal/pelvic tumor will be clinically examined. The standard of care imaging method will be performed as part of preoperative work-up, including expert transvaginal US (TVS), transrectal and transabdominal US (TAS) or computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)/CT scan.

Eligible women meeting all the inclusion criteria will be identified by a clinician. They will be provided with the "Informed consent" and "Information for patients" documents, and the objectives and the course of the study will be discussed with them. After obtaining written consent, patients will be registered into the database using the REDCap (Research Electronic Data Capture, www.project-redcap.org) electronic data capture tool. This is a secure, web-based application with controlled access designed to support data capture for research studies, hosted at MD Anderson. Basic clinical data about patients will be compiled using the *Clinical data form.* The REDCap service complies with GDPR/data regulations.

Before the procedure, the patient's risk factors for bleeding (e.g. history of bleeding, and current use of antiplatelet or anticoagulant agents) will be carefully evaluated. In patients with any risk factors, their platelet (PLT) count and coagulation status will be tested and controlled by the physician performing TCB. In patients with thrombocytopenia or a prolonged prothrombin time and activated thromboplastin time, preventive measures should be discussed with a hemostasis specialist. PLT count > 50 × 10^9/L and an international normalized ratio (INR) > 1.5 are considered safe [12, 13]. In patients using low molecular weight heparin (LMWH), TCB should be not be performed within 12 h after the loading dose, or within 24 h after a therapeutic dose. In patients using vitamin K antagonists, TCB should be performed at least 5 days after last tablet [14]. In patients using new anticoagulant drugs (NOAC), it is only necessary to skip a single dose before and after TCB. Patients who are unable to undergo TCB due to hematologic complications will be excluded from the trial.

4.1. DESCRIPTION OF TCB

Because of the very low rate of complications associated with pelvic TCB, it is considered a low-risk procedure and, as such, can be performed in an outpatient basis. It does not require any special preparation of the patient, laboratory tests (except in patients with high risk of bleeding), fasting, or general anesthesia, and it involves a short procedure time. Anxious, risky patients and those who are unable to tolerate US should be offered conscious sedation or general anesthesia in an inpatient setting. Patients referred for surgical treatment according to clinical staging will undergo TCB just

before main surgery under anesthesia. For the other patients, TCB should be done as soon as possible after US, with a maximum interval of 1 week.

The physician who performs TCB according to US will choose the best suitable approach, such as vaginal/ transrectal or abdominal/percutaneous; in some cases, both routes may be used. If the lesion is accessible by two different approaches (transvaginal and percutaneous), the preferred approach is transvaginal because the needle is easier to control, the needle tip can be continuously monitored easily, the higher resolution of the endovaginal probe, and the gynecologist usually has greater experience of this approach. All biopsies will be performed by physicians with training in performing gynecologic US and TCB.

Antibiotic prophylaxis is recommended after transrectal biopsy if the needle passes through the rectal wall into the peritoneal cavity and in immunocompromised patients [15, 16]. The main principles of clean contaminated procedures must be followed when performing invasive procedures to minimize the risk of infection.

4.1.1. Transvaginal TCB

The patient will be placed in the lithotomic position in an US room or operating theatre. The needle will be inserted into an automatic biopsy gun. For the transvaginal approach, an 18G needle with a length of 30 cm will be used. The sample length may be 15 or 22 mm, and the required length of sample will be set. After disinfecting the vagina, the endovaginal probe with the needle held in the gun will be introduced into the vagina by the physician. The tip of the biopsy needle will be continuously visualized during the whole procedure for optimal sampling and ensure patient safety. The operator can use color/power Doppler US to increase the safety of the procedure by avoiding injuring large vessels when inserting the biopsy needle. In addition, Doppler US can help the operator identify a viable portion of the lesion without necrotic/cystic tissue, and thus minimize the risk of obtaining a sample inadequate for histological examination. When the needle is in a correct position and the penetration depth is checked, the gun will be activated by depressing the trigger button to fire the needle. After confirming successful tissue retrieval, the sample will be removed and placed into a labelled container with 10% buffered formalin. To ensure that the sample will be suitable for histological examination, we will require at least three passages of the needle into a neoplastic lesion [17, 18]. The collected tissue will be delivered to the Department of Pathology for examination and storage. At the end of the procedure, US should be continued to detect any signs of internal bleeding (e.g., “fountain sign”/turbulent flow) or other complications adjacent to the site of the biopsy. Mild internal bleeding from the biopsy site usually resolves spontaneously. If the patient suffers bleeding from the biopsy site in the vagina or in the vaginal wall, a hemostatic tamponade will be inserted inside the vagina. If an adverse event (AE) occurs, the patient will be hospitalized in the Oncogynecologic Department, depending on the severity of the AE. Data from TCB will be recorded using *TCB*

evaluation form, and details of AEs will be recorded using *the AE evaluation form.* AEs will be prospectively assessed according to the Clavien–Dindo classification (Attachment 1) [19]. AEs will be reported separately according to whether they occurred during the procedure, within 24 hours after the procedure, or within 30 days after the procedure. Furthermore, the patients will be contacted by telephone within 72 hours to enquire about their subjective assessment of the procedure.

4.1.2. Transabdominal/percutaneous TCB

The patient will lie on a bed in the US room or operating theatre. Local anesthetic will be infiltrated into the abdominal wall. For patients without a known allergy, trimecaine will be applied as a local anesthetic, and injected immediately before performing the procedure, approximately 5 minutes before TCB. The needle will be inserted into an automatic biopsy gun. For the percutaneous approach, a 16G needle with a length of 20 cm will be used. After disinfecting the skin, the operator will puncture the skin with the needle in place in the biopsy gun held in one hand, with guidance with an abdominal probe placed in the operator's other hand. The rest of procedure will be same as described in 4.1.1 Transvaginal TCB. If bleeding occurs, pressure will be applied to the site of bleeding. If pressure does not help, a stitch will be applied. AEs will be managed according to local recommendations.

4.2. DESCRIPTION OF THE EXAMINATION METHODS

4.2.1. Histopathological examination

Standard histopathological examinations will be performed for all TCB samples. To guarantee the high quality of the results, only pathologists who are highly experienced with examining TCB samples will be responsible for the histopathological examinations and other examinations.

4.2.2. Immunohistochemistry (IHC)

IHC is a pathological method to detect specific tumor antigens. IHC uses monoclonal or polyclonal antibodies to determine the distribution of tumor antigens, which may be expressed de-novo or up-regulated in a particular type of cancer [20]. IHC is often performed on tumors of unknown origin if the morphological results are inconclusive. Tumor cells may express specific intermediate filaments, such as keratin, desmin, vimentin, neurofilaments, and glial fibrillary acidic proteins [21]. By determining the expression of these and other proteins, IHC can precisely classify a tumor. Therefore, IHC is indicated by a pathologist in order to make an accurate diagnosis. Some gynecological tumors are

hormonally dependent, which means their growth is regulated by a hormone. Using IHC, we can determine the expression and distribution of hormonal receptors distribution, enabling more effective personalized treatment. IHC can also provide information about prognostic markers by identifying the enzymes, tumor-specific antigens, oncogenes, tumor suppressor genes, and tumor cell proliferation markers expressed by the tumor cells [20]. IHC can help us identify which patients are eligible for genetic screening (mismatch repair proteins – MLH1, PMS2, MSH2, MSH6 and Lynch syndrome screening) and to assess their potential eligibility for targeted therapies [22]. The gynecologist/oncologist may therefore indicate IHC to determine the patient's prognosis and choose the appropriate treatment. Thus, a great deal of information can be obtain from IHC, as for NGS, and comparing the result can be valuable.

4.2.3. Next-generation sequencing (NGS)

NGS is massively parallel sequencing that enables us to identify previously unrecognized genomic alterations in many malignancies and enable targeted therapy. NGS can be targeted using DNA or RNA panels. Using NGS, we can identify germline and somatic mutations, molecular aberrations, and specific RNA fusions, as well as their associations with malignancies. NGS can also reveal the mechanism of resistance to specific treatments. However, the main limitation of of NGS is its cost. It is also questioned how often the result of NGS will have a clinical impact and will change the patient's therapeutic strategy [22]. NGS-guided therapies include hormone therapies, pathway-specific therapies, and immunotherapies, which are associated with longer progression-free interval and longer overall survival. In gynecological tumors, the most commonly detected mutations are located in the genes *TP53*, *MYC*, *KRAS* and *BRCA1/2*. NGS examination and molecular classification can be performed at any time during the treatment course. Specific mutations can be detected in the tumor genome at initial diagnosis, or when can occur as acquired new resistance alterations after previous treatment lines. The results of NGS can optimize the therapeutic regimen and increase the opportunity for targeted therapy [23] [24]. For example, genomic profiling of endometrial cancers led to the reclassification of endometrial cancer into four groups that are distinct from the previous histological classification and are relevant to the consequent treatment of the patients [25].

NGS can also determine the tumor mutational burden (TMB), defined as the number of somatic mutations, that varies across malignancies. TMB can improve the predictive accuracy for immunotherapy outcomes, and has the potential to expand the number of candidates for treatment with immune checkpoint inhibitors [26].

We now have great expectations of liquid biopsy examination. Liquid biopsy is an essential non-invasive diagnostic test that evaluates circulating tumor cells and tumor DNA, as well as other blood markers that may be useful for guiding precision medicine. Although liquid biopsy is not a

routinely used diagnostic test, the potential applications in the diagnosis and prognosis in ovarian cancer are rapidly growing [27].

4.2.4. Immunologic examination

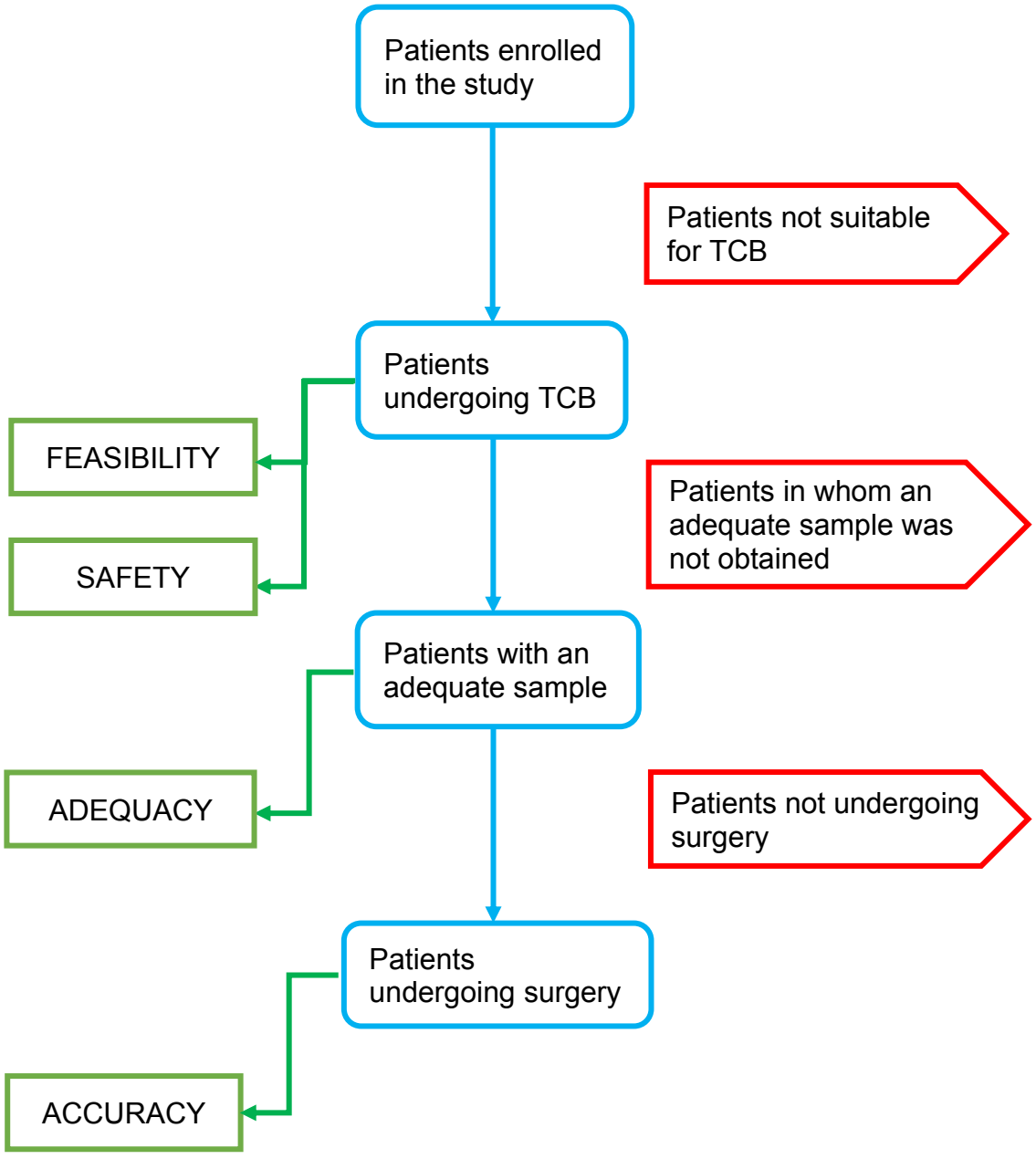
It is accepted that the origin and development of cancer is enabled by the evasion of immunosurveillance due to the loss of antigenicity and/or immunogenicity, and by coordinating an immunosuppressive microenvironment [28] [29]. Specific oncological treatments, including chemotherapy, radiotherapy and immunotherapy, induce an immune response beyond the expected antitumor activity. This immune response can be evaluated by immunological testing. There are some immunological indicators that are relevant to the prognosis and prediction of a treatment response, including the density, functional state, and organization of tumor infiltrating lymphocytes (TIL) [30]. Specialized methods can be used to analyze the immune contexture of tumors, and to determine biomarkers that could permit the adaptation of individual treatment approaches, as well as monitoring the response to therapy [31]. Interesting information can also be obtained by comparing the T cell profiles of samples obtained at de novo diagnosis with those obtained upon recurrence after specific therapy and is therefore useful as part of the long-term follow-up. Immunologic examination of TCB will be done consequently after the standard pathologic tests (IHC and NGS) have been performed.

STUDY DESCRIPTION

1. **Referral to the Gynecologic Oncology Department**
Clinical examination Expert US
2. **Inclusion and exclusion criteria assessment**
Inclusion criteria 1. Presence of a pelvic/abdominal lesion with suspicion of malignancy 2. Age ≥18 years 3. Eastern Cooperative Oncology Group performance status grade <3 4. Not pregnant 5. Signed informed consent form **Exclusion criteria** 1. Considered by the investigator to be unsuitable for any treatment 2. Early stage disease 3. Age <18 years
3. **Informed consent signature**
Included: informed consent form signed Excluded: informed consent form not signed
4. **Registration on the TRUTH electronic database**
Clinical data form
5. **Index tests** - US
US evaluation form
6. **TCB**
TCB evaluation form *AE evaluation form* – including telephone call to identify AEs occurring within 72 hours after the procedure
7. **Histopathological report for TCB**
Pathology, NGS, immunohistochemistry, and immunology evaluation form
8. **Histopathological report from surgery** *Final pathology evaluation form*

AE: adverse event; NGS: next-generation sequencing TCB: tru-cut biopsy; US: ultrasound

Figure 1 Flow chart describing the design and patient flow in the TRUTH trial



5. STATISTICAL ANALYSIS

The power analysis was computed for adequacy/feasibility of immunological examination based on published data and a pilot study for samples obtained by TCB.

The sample size analysis was calculated for adequacy of samples obtained by TCB for histopathological diagnosis. The calculation was computed under the assumption of sample adequacy between 50-90%. The evaluated parameter was the width of 95% confidence interval for the proportion of adequate sample (Table 1-2).

With the expected adequacy of the samples in the range of 70-90%, we plan to enroll at minimum 250 subjects, in order to achieve confidence interval of ≤10%.

The analysis was computed using PASS 16 Power Analysis and Sample Size Software (2018) NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass, by Institute of Biostatistics and Analyses (Faculty of Medicine, Masaryk University, Brno). [32, 33]

Standard descriptive statistics will be applied for the exploratory analysis, including absolute and relative frequencies for categorical variables and medians with 5^{th}–95^{th} percentiles and/or means with standard deviations or confidence intervals (95%) of point estimates. The statistical significance of differences in categorical variables will be assessed using the maximum likelihood chi-square test. The accuracy, adequacy, and safety will be assessed by performing receiver operator characteristic (ROC) curve analysis, after selecting appropriate predictors, and with a standard set of descriptive statistics alongside confidence intervals related to the individual predictors (area under the curve, sensitivity, specificity, positive and negative predictive value, overall accuracy).

Statistical analyses will be performed using SPSS 24.0.0.0 (IBM Corporation, 2015) statistical software.

6. STUDY TIMELINE AND SAMPLE SIZE

At Gynecologic Oncology Centre of the General University Hospital in Prague, approximately 100 women undergo TCB per year. According to the power analysis, the required study sample size is 250 cases. Therefore, the required number of the patients undergoing TCB is expected to be achieved in 2-3 years. All participants will be followed-up for 30 days after TCB to monitor any AEs. The total duration of the project is 3 years, depending on the main endpoint and power analysis.

7. EXPECTED OUTCOMES

This prospective study is to our knowledge the first study registered on www.clinicaltrials.gov designed to prospectively evaluate the quality of samples obtained by TCB for comprehensive classification of pelvic and abdominal malignant tumors by IHC, NGS, and immunological evaluation, and allowing evaluation based on location, size, and other factors. Our study is also expected to confirm the known feasibility and safety of TCB, and demonstrate its high adequacy and accuracy. The findings should also provide an update to the promising results of a previous retrospective analysis of TCB in a larger study population.

8. ETHICAL COMMITTEE APPROVAL

Before the start of the study, this protocol and other related documents must be submitted for review to the Ethical Committee for authorization. The study will not commence until such approvals have been obtained and until other relevant essential documents, such as the signed contract agreements and evidence of adequate study financing, are prepared.

The study must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the study data are credible, reliable and reproducible.

The study will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR). Any personal data will always be treated as confidential including during collection, handling and use, or processing, and the personal data (including in any electronic format) shall always be stored securely, with all technical and organizational security measures necessary for compliance with EU and national data protection legislation (whichever is more stringent). The sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9. DATA HANDLING AND MONITORING

Data collection, handling, processing, and transfer for the purpose of the study will be performed in compliance with applicable regulations, guidelines for clinical studies and internal procedures. It remains the responsibility of the investigator to check that all data are entered into the electronic Case Report Form (eCRF) in accordance with the instructions provided and that the forms are filled out accurately, completely, and in a timely manner.

The study will use the REDCap (Research Electronic Data Capture, www.project-redcap.org) electronic data capture tool. It is a secure, web-based application with controlled access designed to support data capture for research studies, hosted at MD Anderson. Access will be restricted to authorized users only.

The study will be monitored by the study coordinator and the main investigator, who are responsible for checking the accuracy, completeness, and plausibility of all data, as well as compliance the study protocol and GCP requirements.

10. FUNDING AND SUPPORT

The TRUTH study is a non-commercial trial that is not receiving any support from the industry. The participating site and patients will not receive any financial compensation for participation in the study. All expenses related to the trial (administration, statistics, electronic data capture system, monitoring) will be covered by a research grant.

Patients enrolled in the TRUTH trial will be insured according to the laws and regulations of our country TCB and the new examination methods are considered routine procedures as part of the standard workup, including disease recurrence/progression, for evaluation of tumour characteristics according to international guidelines. Therefore, procedures are reimbursed as part of standard clinical care. No separate insurance is requested for the project.

11. PUBLICATION PLAN

All publications will be coordinated by the main investigator. Authorship will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and the requirements of the respective medical journal.

12. REFERENCES

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