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FEMaLe

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H2020 Specific Programme – Council Decision 2013/743/EU of 3 December 2013 establishing the Specific Programme Implementing Horizon 2020 - The Framework Programme for Research and Innovation (2014-2020) (OJ L 347, 20.12.2013, p. 965).

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Rules of Application (RAP) – Commission Regulation (EC, Euratom) No 1268/2012 of 29 October 2012 on the rules of application of l Regulation (EC, Euratom) No 966/2012 of the European Parliament and of the Council on the financial rules applicable to the general budget of the Union (OJ L 298, 26.10.2012, p.1).

Finding Endometriosis using Machine Learning: FEMaLe

1. INTRODUCTION TO THE WORK PACKAGE 6, DIAGNOSIS

1.2 Abstract

To develop a computer vision tool that enables a **semi-automatic and objective confirmation of the diagnosis** and assessment of the stage and extension of endometriosis evaluated during **laparoscopy**. Only complete standardisation, using a numeric tool, will allow a reliable definitive assessment. The annotation of the laparoscopic images performed by surgeons will enable machine learning technology to automate the recognition of the endometriosis specific lesion. **The algorithm will be integrated in the SurgAR software** to allow a semi-automatic assessment of the #ENZIAN score.

The #ENZIAN score obtained semi-automatically using the trained algorithm and additional information (MRI location and size information) will be compared to the score manually determined by the expert surgeons to validate the algorithm and the numeric tool. The aim of the algorithm will therefore be to standardise the recognition of endometriosis lesions.

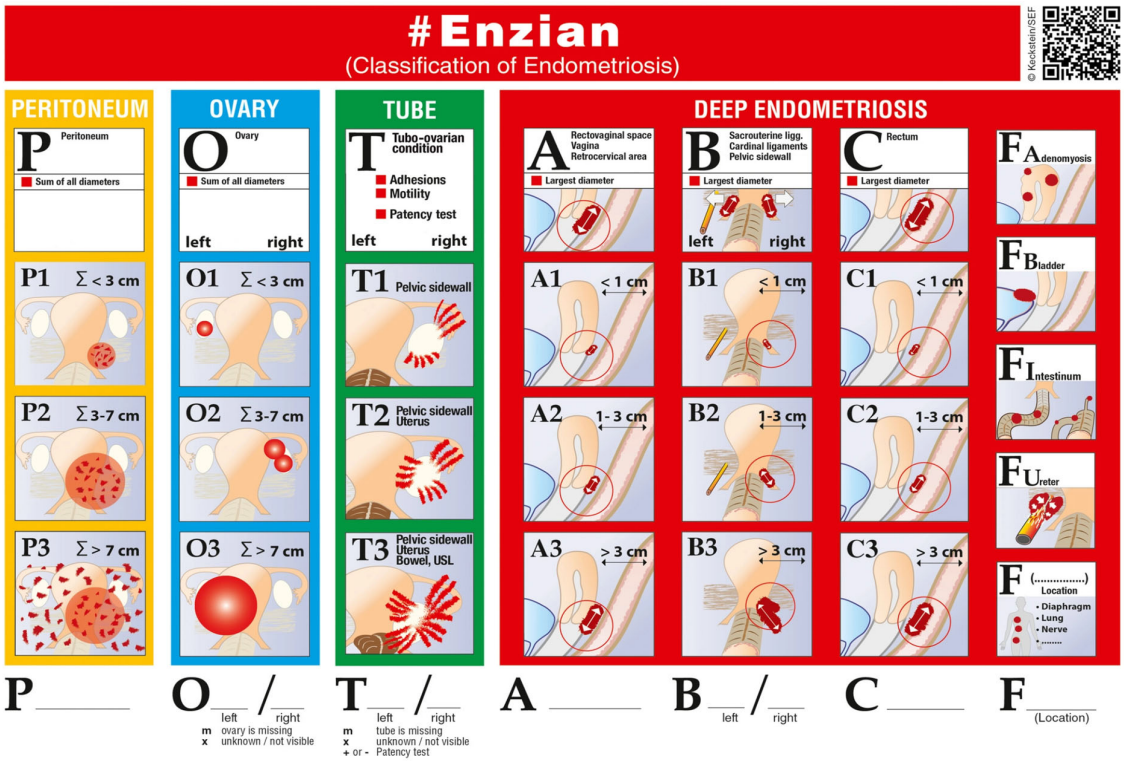


Figure 1: #Enzian: classification of Endometriosis[3]

[3] Keckstein, J., & Gernot, H. (2021). P–331 The #Enzian classification : A comprehensive non-invasive and surgical description system for endometriosis. *Human Reproduction*, *36*(Supplement_1). https://doi.org/10.1093/humrep/deab130.330

1.2 Goals and specifications

WP	6	Lead	Goal	Content	Gantt (M3 - M38)
	6.1	SWU	Collecting videos with metadata	200 surgeries	M3 - M9*
	6.2	AUH	Annotation of laparoscopic videos	Between 50,000-100,000 images or short videos will be annotated.	M9 - M18
	6.3	RTU	Developing deep learning algorithm to automatic r-ASRM/ENZIAN classification	Deep learning algorithm to automatically determine the stage of endometriosis. Machine learning technology to automate the evaluation of the endometriosis specific score.	M18 - M26
	6.4	SURGAR	Integration to the software and real time assessment of algorithm	Integration to the software and real time asComputer vision-based software for real time assessment of endometriosis. The tool allows an automatic and objective confirmation of the diagnosis and assessment of the stage and extension of the disease evaluated during laparoscopy.sessment of algorithm	M26- M32
	6.5	SURGAR	Clinical validation of the algorithm		M32-M38

*Figure 2: Tasks and contents of the work package 6 (*extended to month 12)*

The workflow for endometriosis work package 6 is based on the diagnostic phase: the surgeon will be asked to take standardized pictures of sequenced abdominopelvic quadrants; the machine will carry out the analysis of endometriosis present in these pictures; we will have a final result such as: endometriosis present or not, superficial or deep infiltrating with a score of probability.

1.3 Overview of the project and work process

The FEMaLe project aims to develop artificial intelligence tools to improve laparoscopic endometriosis surgeries.

To such extents, surgical videos are collected from hospitals or clinics, stored on SurgAR's servers and annotated/reviewed by surgeons. To ensure an automated and secure pipeline for video collection and processing, all data are anonymized or pseudonymized (depending on hospital preferences) when submitted to SurgAR or Riga Tehniska Universitate (RTU).

At the hospital, videos are transferred to a dedicated storage. Then the data will be annotated and reviewed by surgeons using a self-hosted annotation platform 'Supervisely'.

Then, RTU and SurgAR will design and test AI algorithms related to the work packages. Finally, the algorithm will be integrated into SurgAR's software suite.

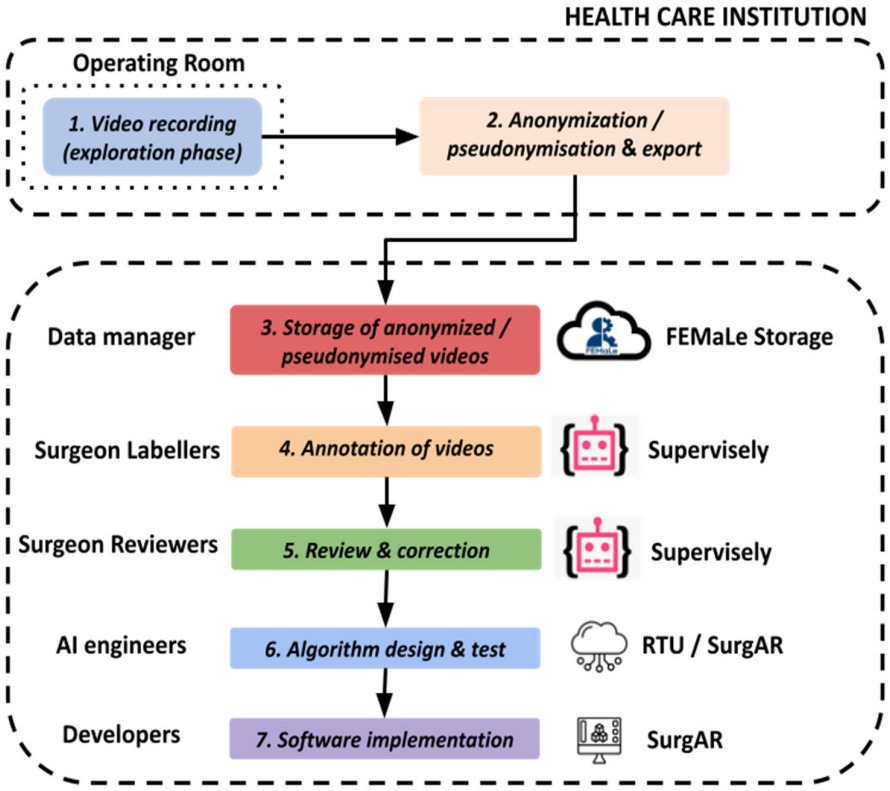


Figure 3: General scheme of the workflow

1.3.1 Video recording

In the operating room, surgical videos are recorded using a recorder directly connected to the laparoscopic tower (any brand and at minimum HD resolution). Endometriosis-related and other gynaecologic interventions are needed for the project in a ratio of 9 for 1. Videos are in MP4 (or MKV) file extension. These videos are accompanied by the metadata necessary for the development of the project (particularly the #ENZIAN score).

One stage of video recording is particularly important and is required of surgeons for better exploitation of surgical videos. This stage takes place in the first few minutes of the surgery, it is the abdominal cavity exploration. This exploration allows the various endometriosis lesions to be sought and examined.

1.3.2 Anonymization / pseudonymisation & export

The videos are irreversibly anonymized (removal of identifying metadata) or pseudonymized (depending on hospital preferences) and safely sent to a dedicated storage. This is the last step within the hospital.

1.3.3 Storage of anonymized / pseudonymised videos

Anonymized or pseudonymised videos are stored on Health Data Protection (HDP) certified storage (server). SurgAR's data manager supervises the data workflow and security from step 4 to 8.

1.3.4 Annotation / Segmentation of videos

First, it is necessary to extract the sequences of interest from the surgical videos. These sequences are usually between 30 seconds and 2 minutes long. Then the video sequences are uploaded to the right Supervisely (annotation platform) workspace Endometriosis.

The annotations will be made by the labelers team on Supervisely platform. Each labeler has previously followed an annotation workshop, validated an entrance exam and has a medical background (**Fig.4**). All these preliminary steps are required to justify the data quality.

Secondly, new jobs will be created and assigned to specific labelers (junior/senior surgeons). A reviewer (senior/expert surgeons) will also be associated with each annotation job.

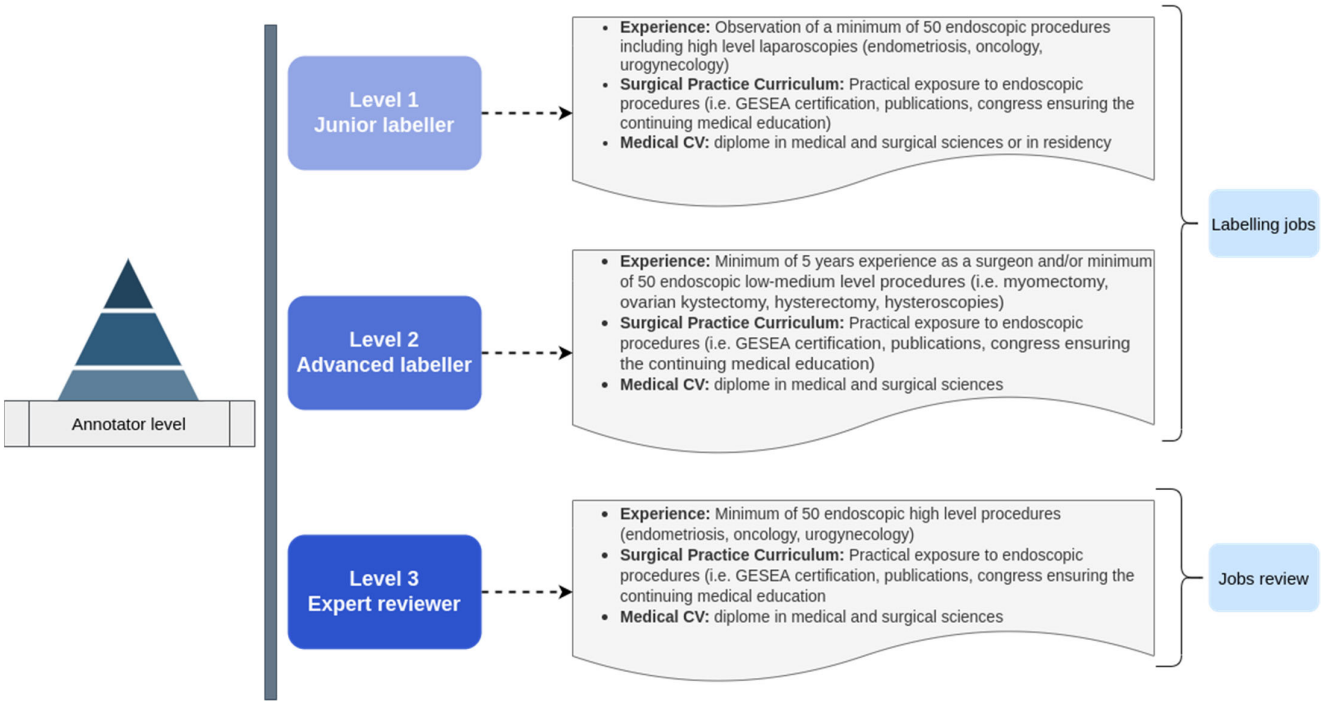


Figure 4: Annotators profile

Finally after the job creation, labelers will receive a notification and will be able to log in to the annotation platform. Using Supervisely tools, labelers will annotate video frames and will submit their annotation job for review.

1.3.5 Review and correction

Senior or expert surgeons will check and correct a sample of each annotation job. If the frames reviewed are validated, they can be exported to the server and used to train the algorithm.

1.3.6 Algorithm creation & test

RTU will have access to anonymized or pseudonymised data on their local storage to design algorithms and test them according to WP6 and 7 goals. SurgAR will also test and validate the algorithms on their local storage using different datasets.

1.3.7 Software implementation

This last step corresponds to software development and implementation of algorithms for the final deliverables.

2. TASK 6.1: DATA COLLECTION

2.1 Scientific research collaborations contracts and legal aspects

Data collection is achieved through scientific research collaboration contracts with several health institutions. The collaboration contract defines the framework of the project, the data workflow, the data processing in compliance with the RGPD and contains a patient information notice.

The data collected in the framework of the FEMaLe project are the surgical videos combined with metadata of patients who meet a specific list of inclusion criteria in order to be selected to participate in this study. The criteria are as follows:

- Non-pregnant women
- Age: 18 years or older
- Must undergo laparoscopy for treatment or diagnostic purposes

The collected surgical videos start at the beginning of the exploration phase of the abdominal cavity and conclude at the end of the surgical procedure. The exploration of the abdominal cavity is particularly interesting and rich in information. It allows an overview of the various endometriosis lesions (macroscopic description, size, location, etc.), and in addition to the preoperative MRI, enables to establish the #ENZIAN score.

This Work Package 6.1 required more time than initially planned (extended to M12). Access to health data (personal data) is highly regulated: National legislation applicable to the project is strictly followed. The data manager and the project coordinator will ensure full compliance with the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679). All our data are stored in the European Union and anonymized or pseudonymized to meet the safety requirements. Depending on the procedures and processes implemented by the hospitals collecting the data, pseudonymization can be chosen over anonymization.

Collaborations have been established with the university hospitals of Semmelweis (Hungary) and Clermont-Ferrand (France), but the ethics committee of the university hospital of Aarhus has refused to collaborate on the project. We are also still in discussion with three health institutions with which it would be particularly interesting for the project to obtain a data-sharing partnership.

2.2 Constitution of the dataset

The dataset is composed of surgeries from health institutions with which a collaboration contract has been established as previously mentioned.

Currently, we have at our disposal 132 surgeries, but the dataset contains 64 processed surgeries (not all the videos are currently used in the dataset due to their complexity but may be included in the future and some have just been shared on the HDP certified storage and therefore not yet processed) from the university hospitals of Semmelweis and Clermont-Ferrand. The Dataset distribution according to the different healthcare establishments can be seen in Fig.5.

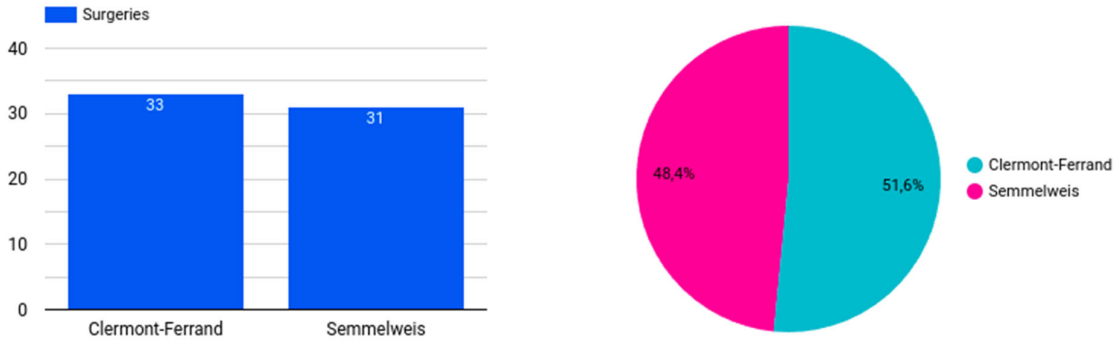


Figure 5: Dataset distribution according to the places of surgery origin (percentages)

2.3 Video sequences annotation

Short video sequences are extracted, actually 114 video sequences, from the laparoscopic videos at certain key moments, particularly at the beginning of the surgery when the abdominal cavity is explored or when the endometriosis lesions are clearly visible.

The annotation will be performed on these short video sequences (generally not exceeding 2 minutes in duration) extracted from laparoscopic surgeries. The labeller will be asked to annotate a certain number of frames on the selected video sequence. Unlike image annotation, video annotation provides a context for the labellers. This context allows a better understanding of the selected frame, provides additional useful information and can reduce annotation errors.

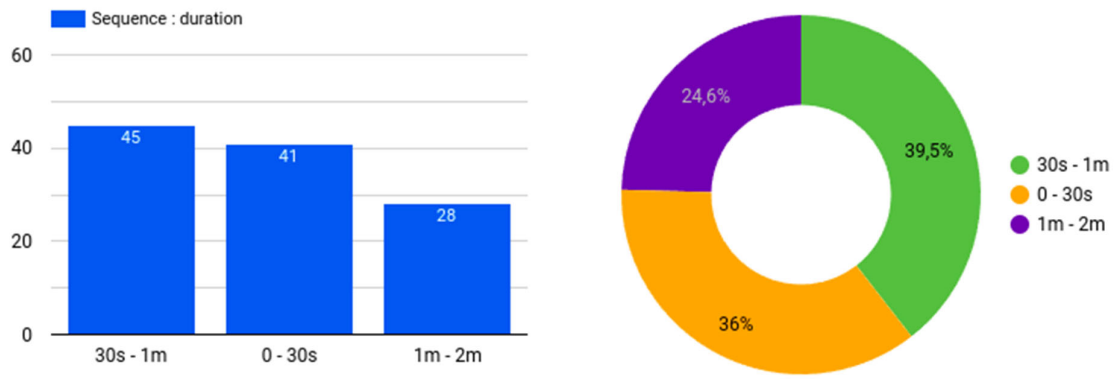


Figure 6: Duration of video sequences

3. TASK 6.2 DATA ANNOTATION

The "Annotation of laparoscopic videos" is the second task of work package 6. It started in parallel with the data collection task. An exploratory phase was necessary to select the most appropriate annotation method for the task.

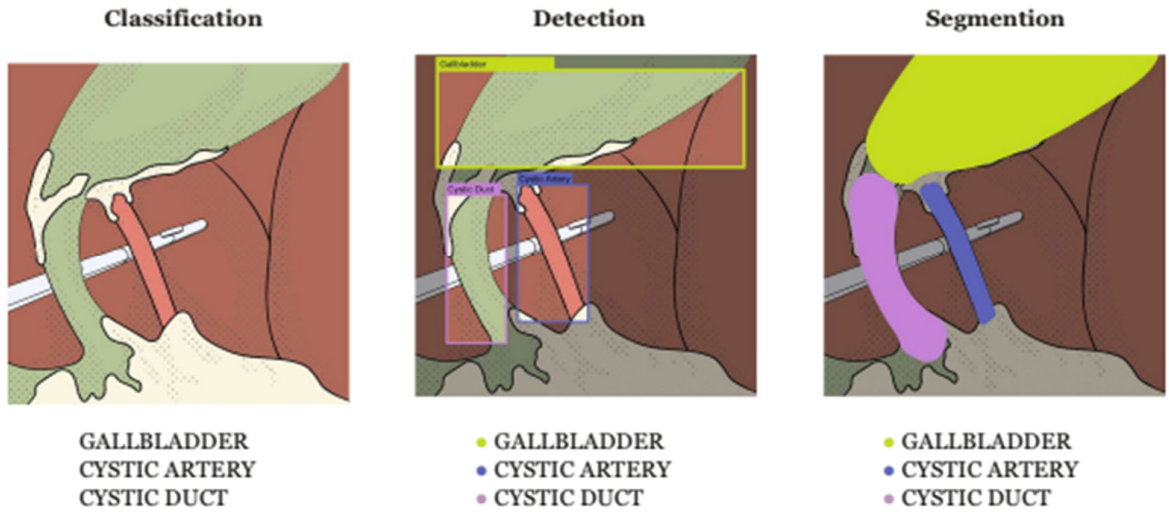


Figure 7: Example of Image analysis techniques from Anteby et al., 2021[4] in the case of cholecystectomy

The most common annotation methods are classification, detection and segmentation, as illustrated in Fig.7:

- **Classification** consists in assigning a specific class to an entire image.
- **Detection** introduces a notion of localisation by identifying the location of an object of interest (lesion, anatomical structure, instrument, etc.) by using bounding boxes, for example.
- **Segmentation** allows defining the precise pixel-wise boundaries of an object of interest (lesion, anatomical structure, instrument, etc.)[2]

[4] Anteby, R., Horesh, N., Soffer, S., Zager, Y., Barash, Y., Amiel, I., Rosin, D., Gutman, M., & Klang, E. (2021). Deep learning visual analysis in laparoscopic surgery : a systematic review and diagnostic test accuracy meta-analysis. *Surgical Endoscopy*, *35*(4), 1521-1533. https://doi.org/10.1007/s00464-020-08168-1

3.1 Research strategy: What is the most appropriate annotation method?

At the launch of the tasks 6.2 "Semantic annotation of laparoscopic videos" we set objectives which, with the benefit of hindsight and after several tests, proved to be very difficult to achieve.

Initially, annotators were asked to segment, on static frames, the delimitation of each endometriosis lesion and to indicate its size and type based on a very large and **detailed** ontology (Appendix 1). The objective of this very accurate classification is to be able to calculate the #ENZIAN score associated with each patient.

The main problematics of this approach are:

- The complexity of the ontology (Appendix 1)
- The complexity of identifying the location of a lesion in the abdominal cavity on a single image.
- The impossibility to evaluate the size of lesion on static frames
- The lack of a complete overview of the abdominal cavity
- The absence of MRI images
- The unclear delimitations (Huge variance inter-annotator) : not accurate and very time consuming annotation method (Fig.8)

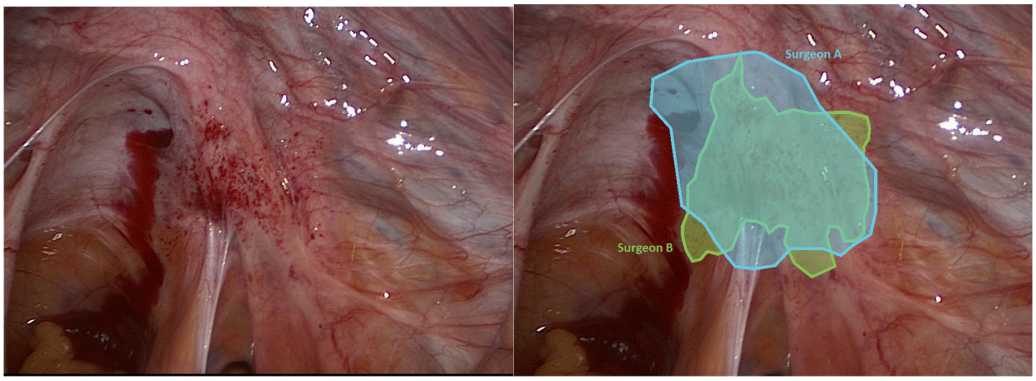


Figure 8: Segmentation of the endometriosis lesion on images extracted from laparoscopic videos

For all these reasons, it was necessary to look for a better annotation strategy. We therefore opted for the application of the Delphi method to establish consensus between medical experts on an optimal ontology. The objective is to reach a consensus among experts on the right way to annotate endometriosis lesions which are highly variable and different. The development of this new annotation method is carried out by SurgAR in collaboration with medical doctors (Antoine Netter) and residents (Fanny Duchateau and Henrique Abrao) from two French University Hospitals.

Our Delphi strategy is detailed in Fig.9 (below).

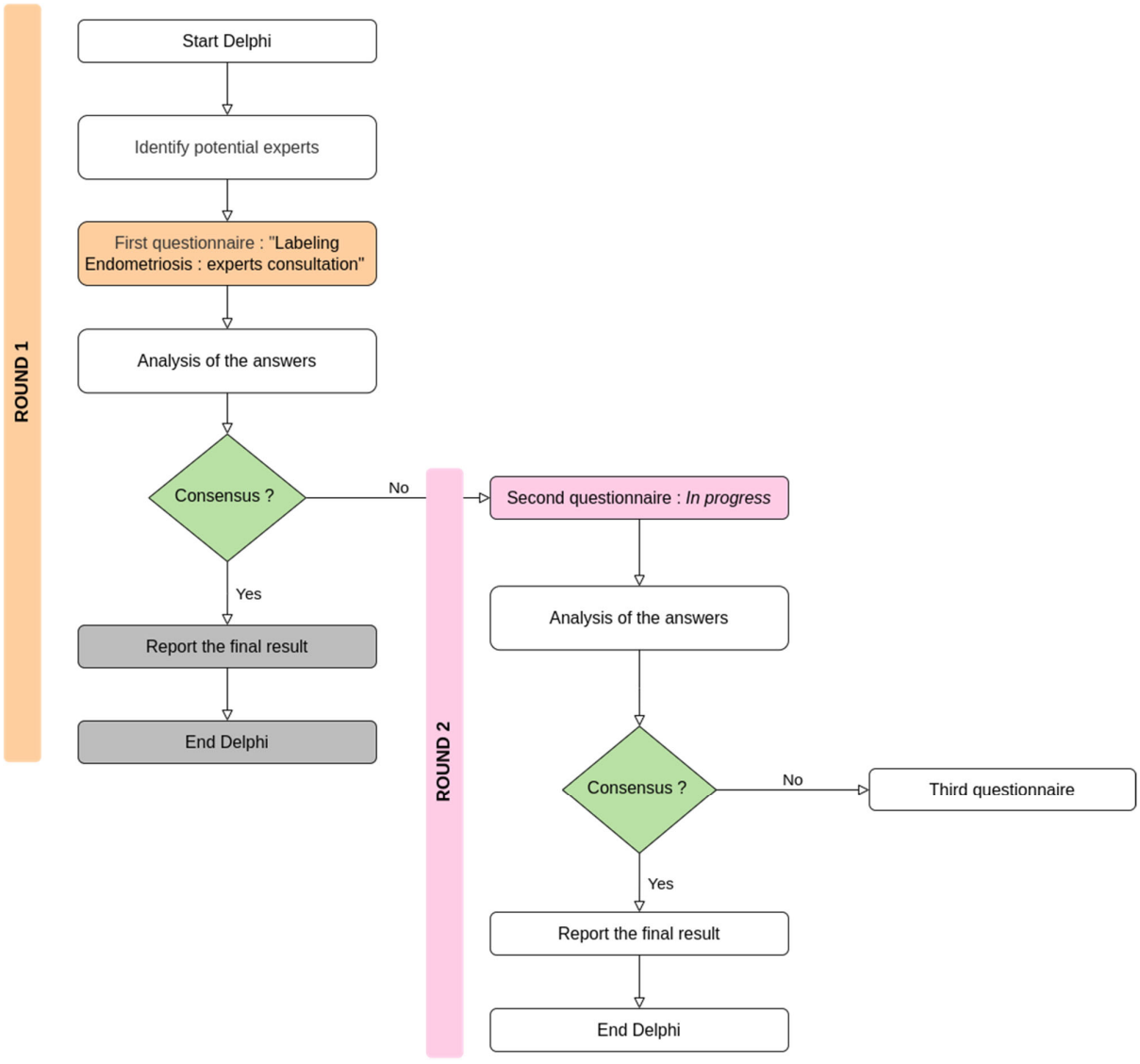
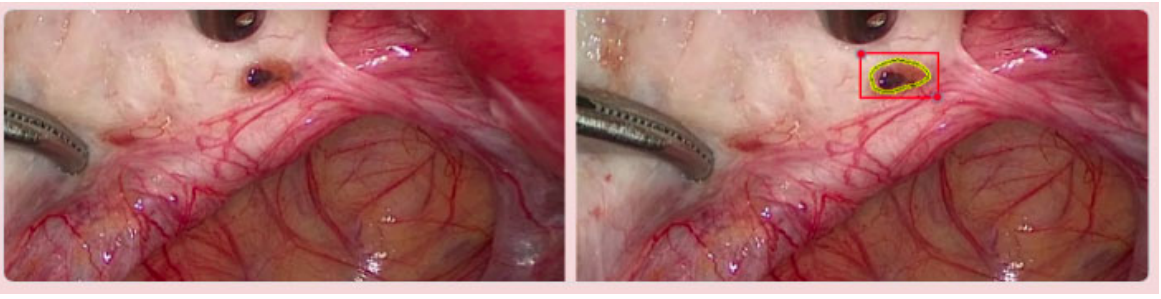


Figure 9: Delphi survey flowchart

3.1.1 Round 1

A first questionnaire was already sent to experts. This round consists of open-ended questions to identify disagreement among experts on the ontological classification and annotation of endometriosis lesions. It is a preliminary work for the labelling of endometriosis lesions and therefore the first essential step in the recognition of these lesions in deep learning.



Labelling Endometriosis: Experts consultation. A. Netter, H.Abrao, N. Bourdel.

Figure 10: First round questionnaire: Labelling Endometriosis : Experts consultation"

This preliminary questionnaire completed by 14 participants (surgeons and expert surgeons) from 7[5] countries revealed the difficulty of segmenting endometriosis lesions and challenged the annotation method initially selected. It was possible to observe difficulty to establish a consensus on all the issues.

An analysis of the results of the first round is currently being written and will be sent to the experts who participated in this first round.

[5] France, Germany, Denmark, Greece, Hungary, Austria, Brasil

3.1.2 Round 2

Based on the answer of the first questionnaire, a series of close questions on the right way to annotate endometriosis lesions. This crucial step is to:

- Validate the ontology
- Obtain a more consensual annotation method for endometriosis lesions

This questionnaire is designed to be as time efficient as possible for experts with an already busy schedule (10-15 minutes).

This second round is currently being finalised and should be sent to the experts who participated in the first round in March-April 2022, attached with the analysis of the results of the first round.

3.2 The type of annotation selected: Detection

Delphi preliminary results suggest that the annotation of data for WP6 should be done by using **bounding boxes on video sequences** to perform **object detection**. The labels used to perform this detection are those specified in the new ontology defined with the Delphi Method (Fig.12). Bounding boxes can be a fast annotation method, are less prone to variability between annotators and are a "raw estimation" of the lesion position on images. So, annotation corresponds to concepts that might be easier to learn (contrary to segmentations of some lesions that have a really high inter-annotator variability, which could lead to difficulties in the learning process). The annotation will be done on each previously selected frame of the video sequence.

The objective of WP6 will be to detect endometriosis lesions and determine the #ENZIAN score. This will be done thanks to the information detected by the algorithm and completed by the surgeon (MRI and the location of the lesions detected during the operation). Each endometriosis lesion should be framed individually by a bounding box (Fig.11).

Figure 11: Detection of Multiple distinct superficial subtle lesions of endometriosis in the Douglas Pouch.

3.2.1 The ontology for automatic detection and classification of endometriotic lesions

The role of ontology is to set up a common vocabulary and to classify data in order to extract relevant information with a clinical impact from laparoscopic videos.

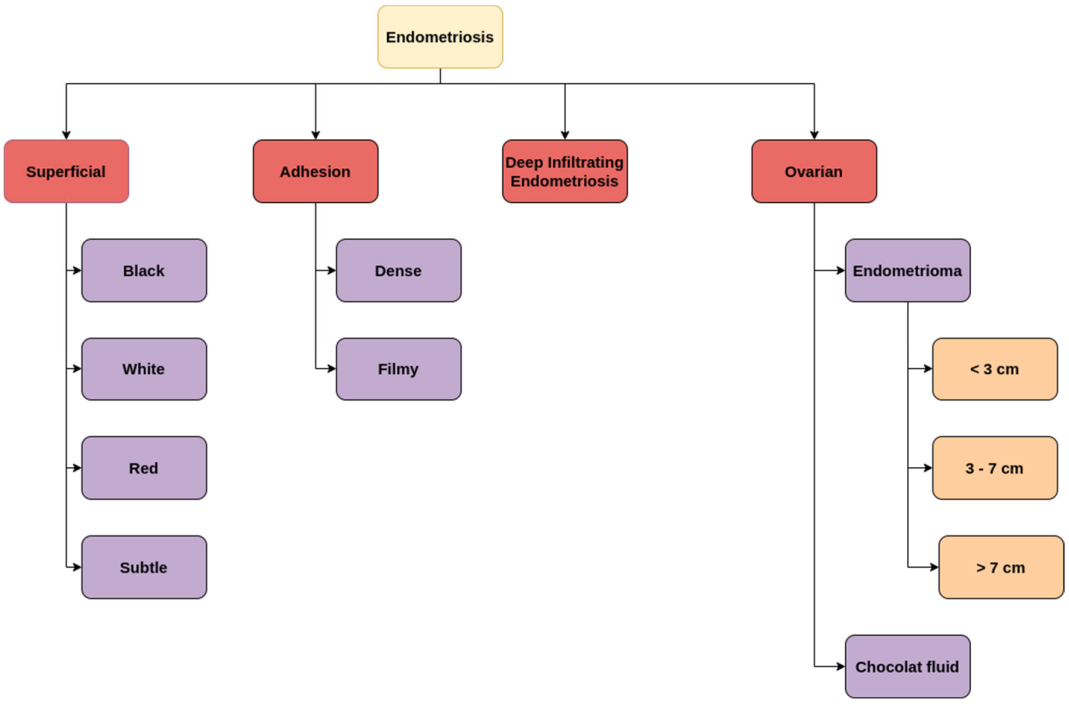


Figure 12: Endometriosis ontology.

4. APPENDIX 1: INITIAL ENDOMETRIOSIS ONTOLOGY INCLUDING VERY SPECIFIC CHARACTERISTICS

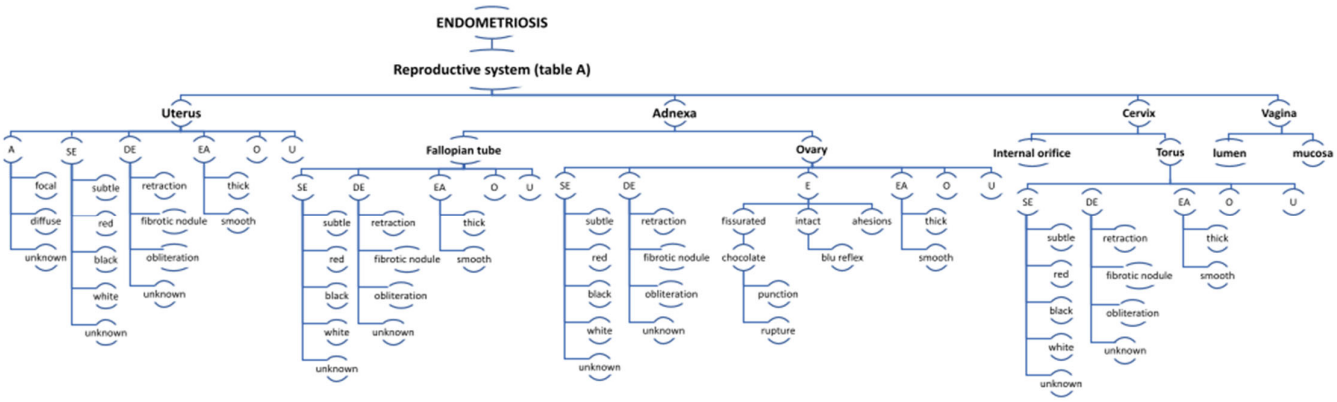


Fig.1: Endometriosis Ontology Table A: Reproductive system

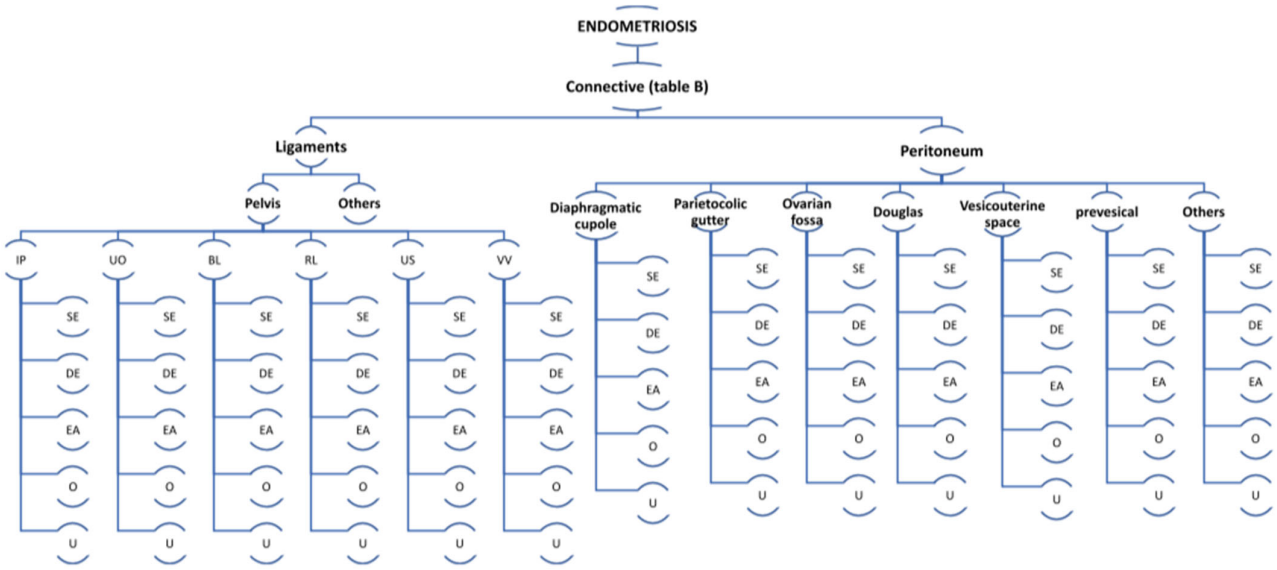


Fig.2: Endometriosis Ontology Table B : Connective

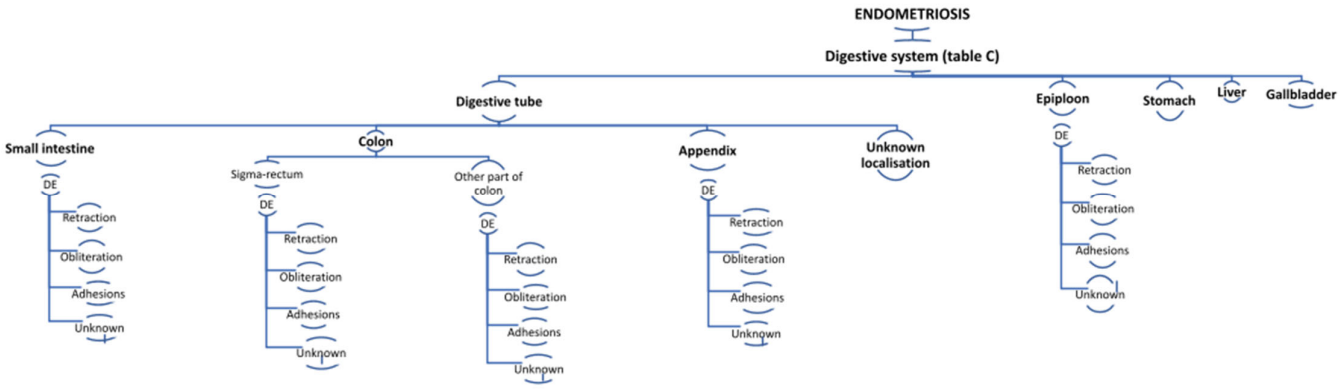


Fig.3: Endometriosis Ontology Table C : Digestive system

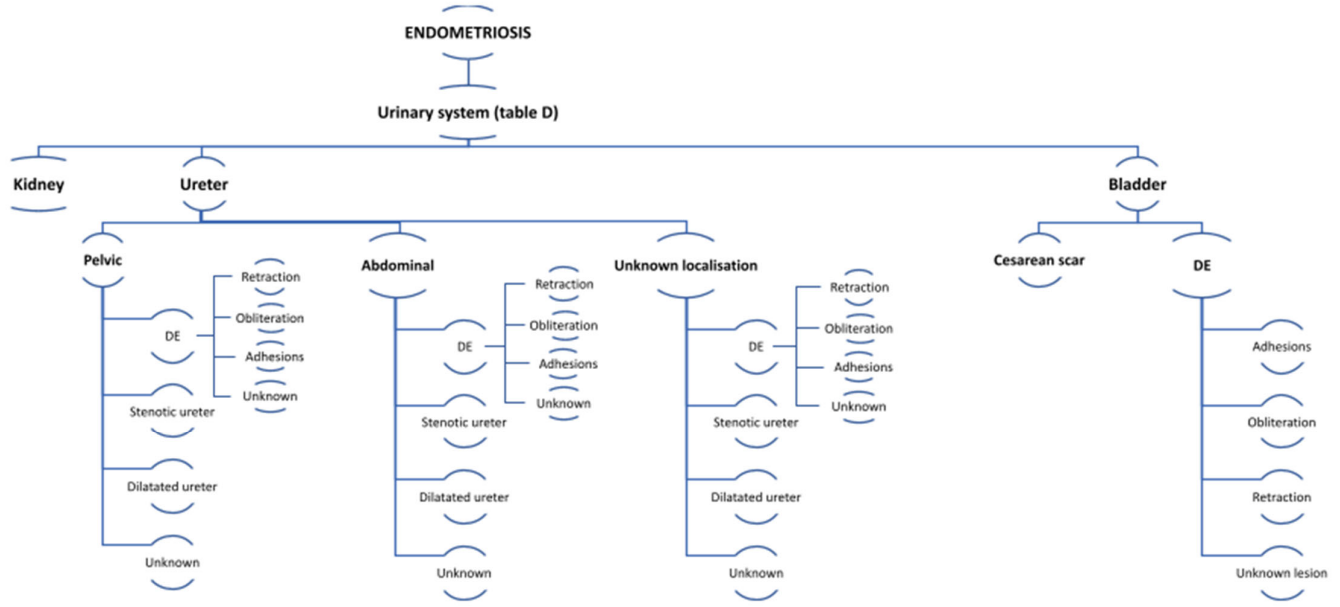


Fig.4: Endometriosis Ontology Table D : Urinary system