A European Cancer Image Platform Linked to Biological and Health Data for Next-Generation Artificial Intelligence and Precision Medicine in Oncology

Deliverable D2.1:

Clinical requirements for the EuCanImage platform and AI in cancer imaging

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Author(s)	Katrine Riklund, Maciej Bobowicz, et al
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1. Version log

Issue Date	Version	Involved	Comments
27/07/2022	0.1	Katrine Riklund & Maciej Bobowicz	First draft
29/09/2022	0.2	Katrine Riklund & Maciej Bobowicz	Revised draft
30/09/2022	1	Anais Emelie & Karim Lekadir	Revised and corrected final version.

2. Executive Summary

This task defines clinical requirements and establishes consensus, particularly for AI development and assessment. It was carried out by EuCanImage's Clinical Consensus Group (CCG, see Management Section 3.2). The clinicians (radiologists and oncologists from FCRB, UMU, UNIPI, GUMED and KAUNO) – as the users of the final AI products - provided the clinical considerations for the use of the data platform and AI solutions based on the clinical use cases in T2.3-T2.4. The AI scientists (UM, UB, ONCO, SIE) informed the working group on the developments and key aspects required to be integrated from the machine/deep learning, radiomic and radiogenomics fields, linking to the work in WP3-6 (data management and artificial intelligence WPs). The health informaticians (FCRB, GUMED) contributed with their expertise in ontologies, PACS and user interfaces. Here, TCIA's support ensured the feasibility and applicability of the assessment tools based on US experience. Medical regulators, including healthcare providers (FCRB, UNIPI and UMU), legal experts (LYN, BBMRI, UPV), AI business developers (ONCO, SIE) and medical experts (ESOI, UNIPI, GUMED), discussed thoroughly the financial, healthcare, and legal considerations of AI. Finally, in the next step we plan to include patients through patient associations (*e.g.* Spanish Group of Cancer Patients) to allow us to take into close consideration the patient perspective and needs in clinical oncology. As part of this task, the CCG had monthly teleconferences to carry out continuous discussions on the clinical requirements and clinical evaluations in this WP, while two face-to-face meetings were planned. The first meeting in UNIPI at M9 had to be cancelled due to coronavirus pandemic restrictions. The second will take place in Barcelona at M24 (October 2022). Consensus was reached using the Delphi method, resulting in a set of requirements continuously updated and communicated to the consortium. Finally, this task will also oversee feedback gathering from T2.2-T2.5 on the use of the data infrastructure, AI computational environment and benchmarking platform, and will ensure new clinical requirements and recommendations are regularly communicated to the AI and IT teams (WP3-6) to optimise EuCanImage's functionalities in further project stages.

The clinical requirements for the EuCanImage platform and AI in imaging are fundamentally described in the different use cases. During the reporting period of M1-M18, first three main WP2 Working Groups have been established, e.g., the Clinical Consensus Group (Clinical Working Group), Data Working Group and the Data Flow Working Group consisting of the clinical partners in collaboration with the data management and AI experts (on data

management, AI development and AI assessment). The clinical consensus group with the clinical partners met initially every second week to discuss the clinical needs in collaboration with the data management and AI experts, on data management, AI development and AI assessment. During the process of the clinical requirements gathering we carried out surveys on the imaging protocols, scanners and their parameters as well as the survey on the non-imaging parameters important to address clinically unmet needs in all use cases. Legal and ethical aspects of data transactions considering defined clinical requirements were reviewed and discussed with Partners from WP1 and local data owners in each site. Inputs from the medical regulators, including healthcare providers (FCRB, UNIPI, UMU, GUMED), legal experts (LYN, BBMRI, UPV), AI business developers (ONCO, SIE) and medical experts (ESOI, UNIPI, GUMED), regarding the financial, healthcare, and legal considerations of AI were also included in the consensus discussions. Consensus on the minimum required clinical information to conform with the GDPR-compliance was achieved and collated in the document with the minimum required clinico-pathological information available to all EuCanImage consortium partners. Evaluation of the legal provisions for the sharing of data in diagnostic imaging in oncology by clinical partners in collaboration with ELSI experts and Data Protection Officers on EuCanImage's legal governance were carried out and summarised in the respective deliverables (D9.1(M12), D9.4(M3), D9.6(M6)).

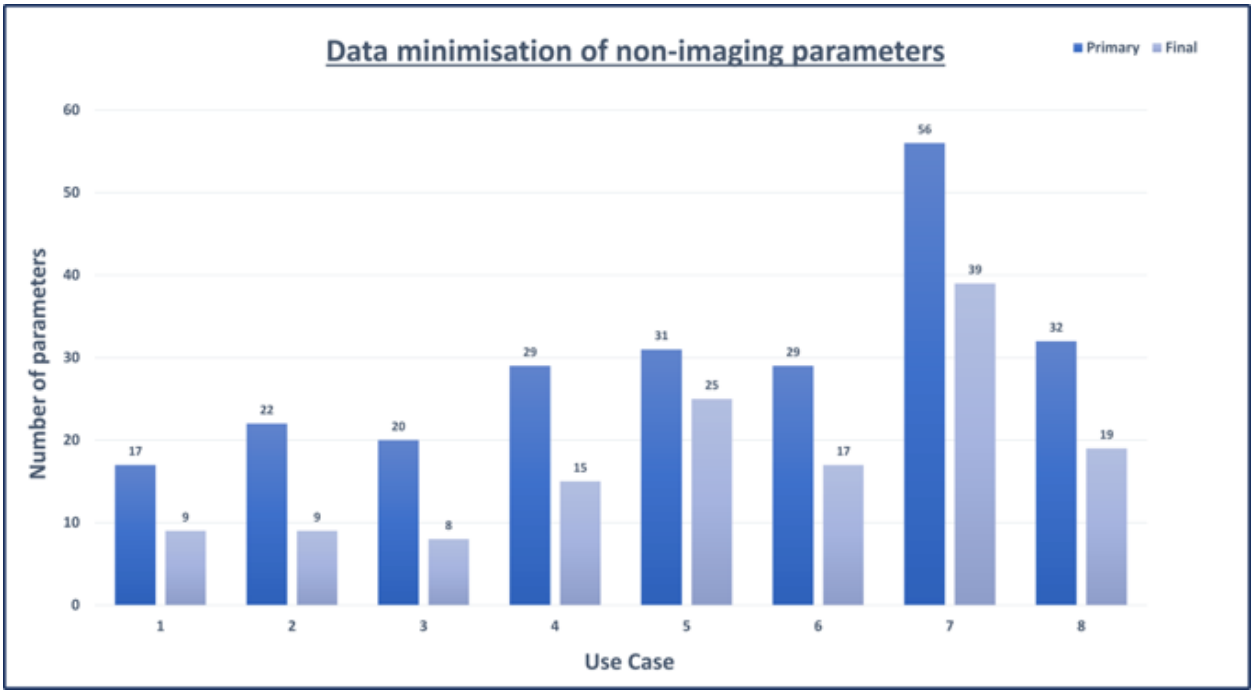

Figure 1. Number of non-imaging data parameters selected per use case.

Multidisciplinary consensus discussions on EuCanImage platform functionalities related to clinically unmet needs and clinical requirements were conducted with participation of different stakeholders including clinicians, healthcare providers, legal experts, AI developers, AI business developers, platform developers and SMEs.

For the development of AI solutions, WP2 partners performed reviews of literature and available algorithms for the specific use cases. The most recent guidelines on designing AI-driven tools in cancer imaging were reviewed and discussed. Algorithm development for the breast is most advanced and includes various algorithms for detection and segmentation of breast masses, non-massive protrusions, breast deformities, and microcalcifications.

Preliminary algorithms have been developed and trained on publicly available datasets and will be refined as new data becomes available throughout the project. For the colorectal use cases, first versions of the AI tools were developed through internal datasets by consortium partner SIE, with initial results already available. For the liver use case, the list of clinical biomarkers to include in the AI prediction models has been defined by the clinical partners and will be integrated into the AI models during the next reporting period.

Along the progress of the project, there was a need for the Clinical Working Group to subdivide to more focused organ-related Working Groups (liver, colorectal and breast) to work in parallel on the objectives of the WP. Each of the WGs met every second week starting in October 2020. The liver group was led by Jordi Rimola (FCRB), the colorectal group by Maciej Bobowicz (GUMED) and the breast group by Katrine Riklund (UMU). As a result, the document with the minimum required clinico- pathological information was created and made available to the whole consortium. To refine the clinical requirements through collaboration between the clinical partners (WP2), data experts (WP1,3-4) and AI developers (WP5-6), including on aspects related to data governance, AI development and AI assessment the needs were again discussed at the first face-to-face workshop in Barcelona in beginning of July 2022. The result, a set of required clinic-pathologic data, guided by the principle of data minimization will be presented in the specific chapters for the different use cases and is shared with the consortium. At the same time, Clinical WG defined final versions of requirements for imaging data curation, data annotation and segmentation process. Data quality assessment was also discussed. In general, only image data with diagnostic quality will be used in the project. Several suggestions were made regarding this process and it will be further developed in the respective WP. The work performed by the WP2 WGs members during M1-18 together with the outcomes of the Annotation Workshop in Barcelona resulted in the sets of standardised procedures for each use case that will be translated into eight SOPs or instructions for all involved parties taking part in tasks T2.2-5.

The annotation procedure and algorithms will first be tested in a subset of cases. The process is designed as an iterative process reviewing the results and modifying design based on them.

Along the project, some challenges have been identified. The linkage of non-imaging data to annotated data is a challenge that must be solved to make it possible to feed non-image data to the algorithms. While discussion already began to address this challenge, the Consortium made it one of the main topics to be discussed during the meeting in Barcelona at M24. Another challenge that needs to be tackled is the heterogeneity in available non-image data. This topic is already actively being addressed by the Clinical & Data Model WGs. In fact, the non-imaging data that are considered in the present deliverable is the result of a preliminary work performed by all clinical partners to determine the minimal sets of non-imaging data that are essential for each use case. However, to maintain project IP, we will not disclose in this deliverable which specific non-imaging data will be collected. This information will be publically available when the project partners achieve planned measurable outcomes and KPIs allowing disclosure of these parameters.

Furthermore, the clinical partners worked on consensus input to other WPs: WP1 especially on ethical and social implications of AI-based cancer imaging solutions, WP3 on the metadata model and EuCanImage catalogue, WP4-5 on the development of AI methods, and WP6 regarding consensus criteria and metrics for AI validation.

The clinical working group also participated in discussions on EuCanImage platform functionalities from the perspective of both data providers and clinical researchers. Different aspects of data security, data visibility and data access levels were discussed with platform developers to ensure best possible European open data sharing practices that would be GDPR compliant, privacy preserving and FAIR at the same time.

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Acronyms

Name	Abbreviation
Breast Imaging Reporting and Data System	BIRADS
Colorectal liver metastasis	CRLM
Collective Minds Radiology AB	CMRAD AB
Data Access Committee	DAC
Data Protection Agreement	DPA
Erasmus Medical Centre	EMC
European Genome Phenome Archive	EGA
General Data Protection Regulation	GDPR
Hepatocellular Cancer	HCC
Computed Tomography	CT
Magnetic Resonance Imaging	MRI

3. Expectations

3.1 Expectations on the annotation platform

Multiple discussions on the clinical requirements towards the annotation platform were carried out from the beginning of the project at M1. First, we defined the intended user groups of the tool and then involved different stakeholders and annotation platform users from different working groups e.g. clinical, data, platform, to ensure functionalities of the tool match the needs of the users and the predefined use cases in the EuCanImage project. Requirements regarding performance, security of data, reliability of the tool, availability of the web service and finally usability of the tool were discussed in detail. We divided the requirements to such aspects as functional requirements, external interface, system features and non-functional requirements. Important part of the discussion was the data management, uploads to the platform, annotation and segmentation storage format, and possibility to download RT-STRUCTS that the platform is creating. There was also a discussion on interconnectivity of RT-STRUCTS with raw DICOM files for further exploitation.

Clinicians raised important issues such as the front-end usability of the platform screen that should resemble the diagnostic screens with at least four image views (partitions of the screen) with high level of personal customisation that radiologists are familiar with from the daily workflows in their hospitals.

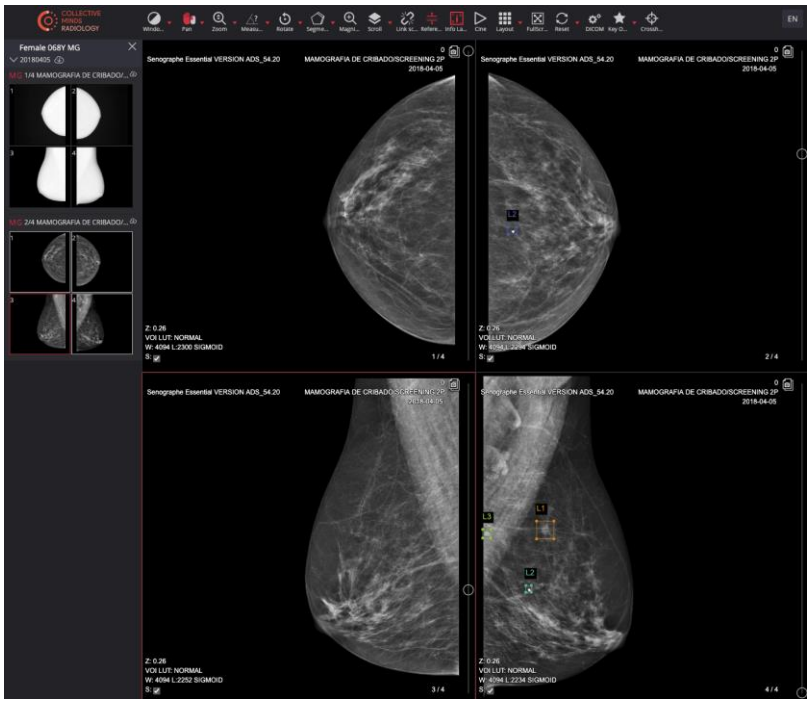

Figure 2. A view from CMRAD annotation model exemplified with a mammogram. In the lower left view point three different boundary box annotations (Li, L2 and L3) are shown.

Different segmentation tools for different uses were discussed following survey and review of available annotation and segmentation tools that the clinicians used in previous projects. Aspects of 2D and 3D images with pixel and voxel-level segmentations were discussed and chosen for different tasks depending on the use case. Different tools for manual segmentations requiring very intense human labour were reviewed with suggestions towards more semi- or fully automatic tools, especially for 3D segmentations. Specific aspects of ADC sequence, time-to-signal intensity curve, diffusion restriction, lesion morphology, PEI (positive enhancement integral), MIP (maximal intensity projection) and intensity curves in the basic layout were taken into consideration. The labelling process with the possibility of pre-selection of labels (e.g. benign confirmed, benign-likely, malignant confirmed, malignant-likely) was discussed as well. The order, the number and types of imaging sequences to load first was discussed with inputs from organ-specialised radiologists. Possibility of inclusion of RECIST 1.1 assessment tool was discussed in respect to use cases assessing response to neoadjuvant treatment (UC 5 and 7). Among non-functional requirements we discussed the ways the platform could be accessed (Web server, desktop PCs, mobile devices, tablets, or combinations), possibility of the offline mode with downloads of current imaging study and upload of segmentations - that would not be an option due to security of data issues.

Discussions were continued during the structured Data Flow WG meetings every week this year when the annotation platform reached adequate maturity level and could be fine-tuned to address needs of professional annotators, specifically radiologists and users of the annotations and segmentations, that is AI developers. CMRAD conducted an online presentation of the initial platform functionalities with a demo of annotation and segmentation process. It was followed by four weeks of beta-testing and a feedback meeting. During the meeting feedback from radiologists was presented, followed by the discussion on possible fine-tuning. At later stages, clinicians involved in the task specified requirements towards the structured radiology reports for each and every use case when the clinical requirements for all use cases were defined.

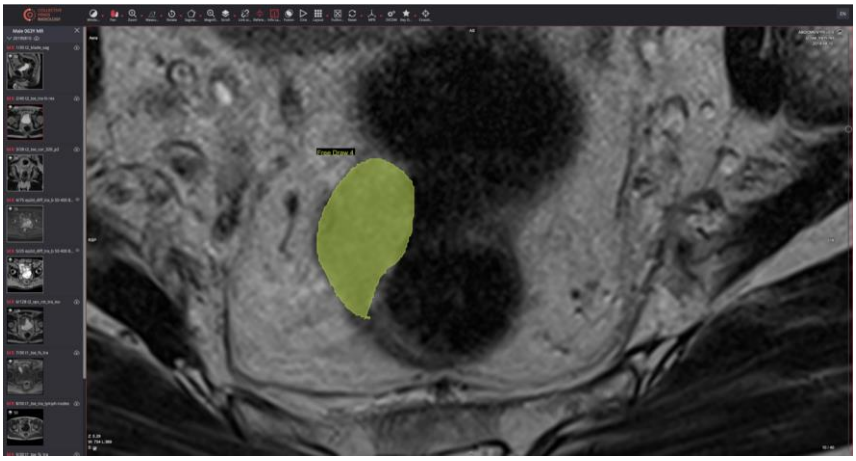

Figure 3.2. A view from CMRAD annotation model exemplified with a pelvic MRI of a patient with rectal cancer. The green area is the rectal tumour annotated with the Smart Paint 3D tool.

The major event for annotation platform functionality assessment was the workshop organised in Barcelona in July 2022. End users had a chance to participate in the live event where the platform was show-cased and there was a full 3-day immersion experience in platform functionality assessment. The annotation platform was tested on several real-life cases and all proposed and developed tools were tested in real-life conditions on variable imaging studies, from different scanners, vendors, and modalities. Based on the assessment some changes were made to the annotation strategy with slightly different choice of tools for data segmentation with more pixel-vise use cases than initially planned (described below). This approach should benefit algorithm precision and therefore should translate into better tools for all use cases and improvement in patients outcomes when the AI tools are developed. Besides the tools for image annotation the annotation platform in CMRAD has the possibility to link a customizable form to each examination where a structured report of the image findings can be stored.

3.2 Expectations on the EuCanImage Platform

Regarding clinical data (imaging and non-imaging), EuCanImage has developed following privacy preserving policies. Access to datasets is managed through a data access committee (DAC) portal. This tool will allow data owners to manage their members, attach their policies and data use conditions to their datasets, and manage access requests. The DAC portal is further discussed in the *D3.5 Data access sub-portal.* EuCanImage platform & data management are designed to be FAIR (Findable, Accessible, Interoperable, Re-usable) by adopting an harmonised/universal language that would be understood by everyone and by selecting data to minimise bias in the AI models. Furthermore, to ensure the validity and usefulness of the platform for future researchers, we meticulously selected clinical data that would not only serve our use cases but future innovative AI solutions in cancer imaging.

4. Use case no 1 - Can AI increase the diagnostic sensitivity of liver MRI, for detection of small hepatocellular carcinoma lesions with kept high specificity?

Can AI increase the diagnostic sensitivity of liver MRI, currently at 60%, for detecting small hepatocellular carcinoma lesions (less than 20mm) in cirrhotic liver, while keeping the specificity high?

Currently, the sensitivity for the radiologist to detect small HCC lesions in cirrhotic liver by MRI is about 60%. Therefore, there is a clinical unmet need to increase the sensitivity for detection with retained high specificity. In that effect, the task is to develop an algorithm for detection of small HCC on contrast enhanced liver MRI.

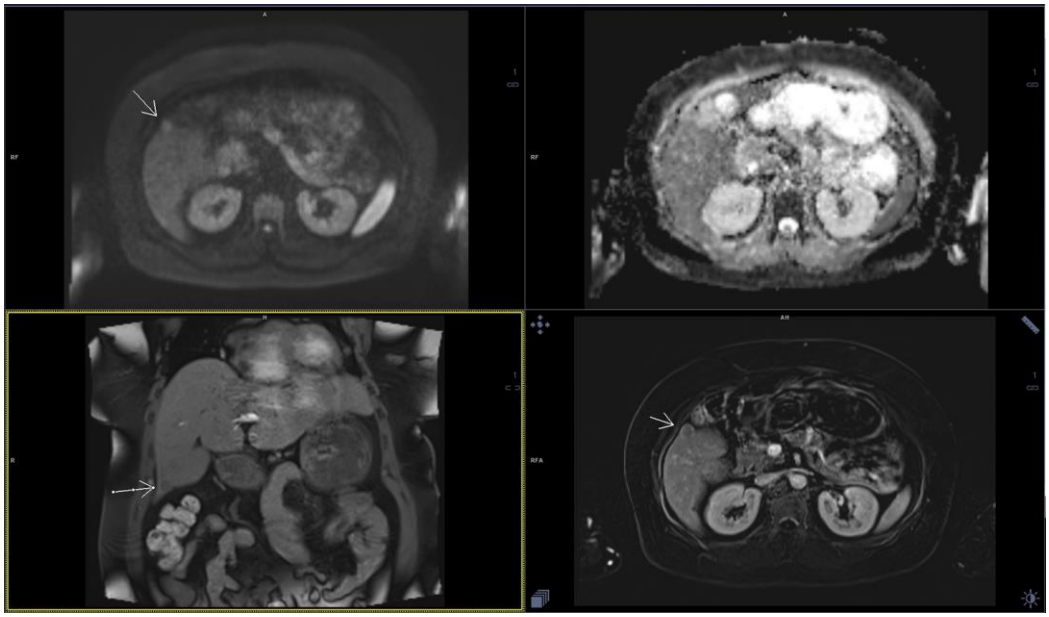

Figure 4.1 MRI examination of the abdomen. The white arrow is pointing to a metastasis.

4.1 Patient Material

A number of 2300 MRI examinations with intravascular/interstitial or hepatotropic gadolinium-based contrast medium in patients with small HCC, are available for the project (Table 4.1). No normal cases are included in use case number 1.

Table 4.1. Number and distribution between clinical partners, of use case number 1.

Liver MRI scans at the time of diagnosis	**Sample size N=1300**				
	FCRB	UNIPI	UMU	GUMED	KAUNO
	400	500	100	100	200

4.1.1 Inclusion Criteria

- Cirrhotic liver or chronic VHB hepatitis
- Untreated focal liver observation detected on liver MRI < 2cm
- Liver MRI available
- Final diagnosis by non-invasive imaging criteria of HCC EASL 2018 and/or histopathology (biopsy or cytology) if diagnosis by imaging is not possible (eg. Malignancy or atypical HCC)

- Focal liver observations with a final benign diagnosis can be included without histopathology diagnosis if stability in size can be reported after 2 years of initial diagnosis

4.1.2 Exclusion criteria

- MRI with inferior (non-diagnostic) image quality
- Cirrhosis of vascular aetiology
- Past history of HCC
- Interval time between MRI and biopsy or fine needle aspiration > 3 months
- Inability to provide the final diagnosis by imaging or histopathology of the liver observation

4.2 Segmentation and Annotation

4.2.1 Annotation process in use case no1

The initial cohort of 2300 patients will be divided into two groups. In a subset of 100 patients (group A) all lesions will be annotated and labelled. In the remaining cases (group B), one lesion will be annotated. The radiologist should choose a lesion smaller than 2 cm and with a high accuracy being HCC.

The size, and the location of the lesions should be reported in the CMRAD radiology report module.

Table 4.2 Parameters possible for selection

Parameter	**Possible options for selection**					
Arterial phase	non-rim APHE	rim APHE	Hypoenhancement	Isoenhancement	Peripheral nodular	
Portal venous phase	non-rim VPHE	rim VPHE	Hypoenhancement	Isoenhancement	Peripheral nodular	Targetoid
Delayed phase	non-rim DPHE	rim DPHE	Hypoenhancement	Isoenhancement	Peripheral nodular	Targetoid
Non-peripheral venous washout	Yes	No				
Enhancing capsule (venous phase)	Yes	No				

T2-w	Hyposignal	Mild-to-moderate hyperintensity	Marked hyperintensity			
HBP	Hypointensity	Isointensity				
LI-RADS category	LR1-LR5	LR-M				

4.2.2 Segmentation tools in use case no1

The tool Smart Paint 3D will be used to delineate the HCC visualised on MRI. The lesions are labelled as 1.HCC or 2. Non-HCC lesion. The lesions should be annotated in the phase where they are best visualised. All lesions are segmented in the same phase and thereafter automatically propagated to other series.

4.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work, a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of parameters from the patient's history and pathology report.

5. Use case no 2 - Can AI improve the classification of LI-RADS intermediate liver lesions (LR-2 to LR-4) based on multi-phasic and non-contrast enhanced CT images?

The task is to first detect the liver lesion and then to classify the lesion to correct LI-RADS score.

5.1 Patient Material

A number of 2300 liver CT scans at time of diagnosis are available for the project (Table 5.1). The aim is to develop an algorithm to automatically detect, segment and classify liver lesions according to LIRADS categories.

A multidetector CT with ≥ 8 detector rows. Images in arterial phase (late arterial phase is strongly preferred), portal phase and delayed phase are required. Multiplanar reformats are suggested and if a patient has had locoregional treatment also pre-contrast images are suggested.

Table 5.1 Number and distribution between clinical partners, of use case number 2.

Liver CT scans at the time of diagnosis	**Sample size 2200**				
	FCRB	UNIPI	UMU	GUMED	KAUNO
	700	500	200	500	300

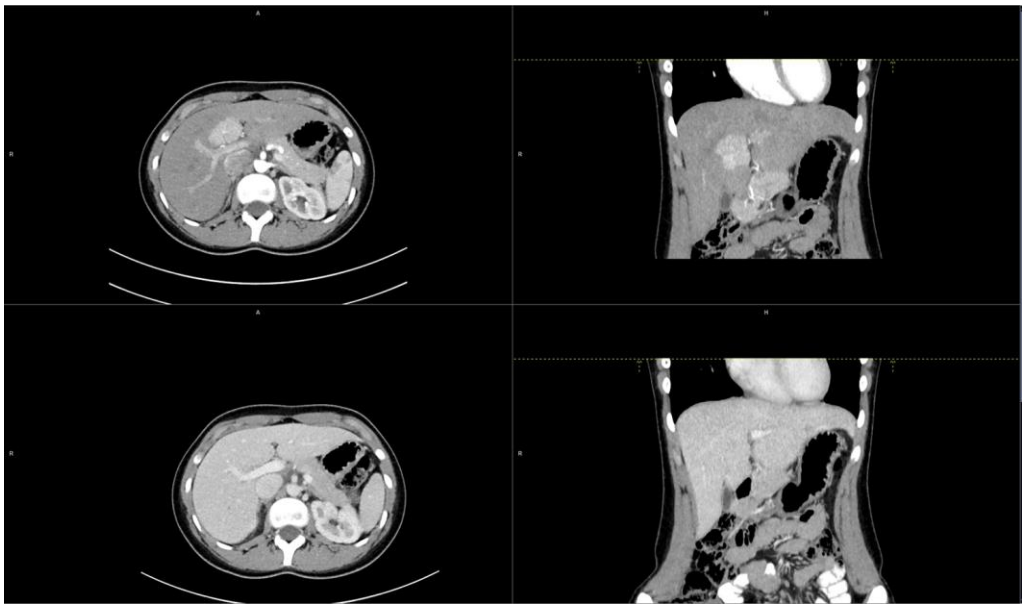

Figure 5.1 Abdominal contrast enhanced CT with two different phases. Arterial phase in the upper row and venous phase in the lower row. Axial slides to the left and coronal to the right.

5.1.1 Inclusion Criteria

- Cirrhotic liver or chronic VHB hepatitis
- Untreated focal liver observation detected on liver CT
- Liver CT should have:
  - ✓ pre-contrast injection phases,
  - ✓ post-contrast injection phases including:
    - ➢ arterial and venous portal and/or delayed venous phase
- Final diagnosis by non-invasive imaging criteria according to EASL 2018 criteria (for HCC lesions) and/or histopathology (biopsy or cytology) if diagnosis by imaging is not possible (eg. Malignancy or atypical HCC)
- Focal liver observations with final diagnosis of benignity can be included without histopathology diagnosis if stability in size can be reported after 2 years of initial diagnosis.

5.1.2 Exclusion criteria

- CT with non-diagnostic image quality
- Cirrhosis of vascular aetiology
- Interval time between CT and biopsy or fine needle aspiration > 3 months
- Inability to provide the final diagnosis of the liver observation

5.2 Segmentation and Annotation

5.2.1 Annotation process in use case no2

Lesions will be annotated and labelled in all patients. Up to ten lesions per examination should be annotated.

Table 5.1 Parameters possible for selection

Parameter	**Possible options for selection**					
Arterial phase	non-rim APHE	rim APHE	Hypoenhancement	Isoenhancement	Peripheral nodular	
Portal venous phase	non-rim VPHE	rim VPHE	Hypoenhancement	Isoenhancement	Peripheral nodular	Targetoid
Delayed phase	non-rim DPHE	rim DPHE	Hypoenhancement	Isoenhancement	Peripheral nodular	Targetoid
Non-peripheral venous washout	Yes	No				
Enhancing capsule (venous phase)	Yes	No				
LI-RADS category	LR1-LR5 and LR-M					

5.2.2 Segmentation tools in use case no2

The tool Smart Paint 3D will be used to delineate the liver lesions visualised on CT. The lesions should be annotated in the phase where it is best visualised. All lesions are segmented in the same phase and thereafter automatically propagated to other series.

5.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of parameters from the patient's history and pathology report.

6. Use case no 3 - Can AI identify liver metastases in colorectal cancer from pre- and post-operative CT?

The task in this use case is to first detect the lesion and then to do a binary classification between liver metastasis from colorectal cancer versus other types of lesions. The longest

diameter, the lesion volume, and the number of lesions in each patient should also be identified.

6.1 Patient Material

A number of 3225 CT examinations of patients with liver metastases from colorectal cancer are available for the project (Table 6.1). In this use case patients with liver metastases (50% of the patients), other focal/diffuse lesions (25%) as well as normal livers (25%) are included.

The CT examination should be done without-contrast enhancement followed by contrast enhanced phases that should include a venous, arterial and delayed phase.

Table 6.1 Number and distribution between clinical partners, of use case number 3.

		Contrast enhanced CT			
		UNIPI	**UMU**	**GUMED**	**KAUNO**
Case Distribution	CRLM	500	500	400	200
	Other lesions	250	250	200	100
	Negative studies	250	250	225	100

6.1.1 Inclusion criteria

- CRLM
- Non-CRLM liver lesions (focal or diffuse)
- Normal liver scans

6.1.2 Exclusion criteria

- No specific exclusion criteria

6.1.3 Limitations for uses

- Mucinous type of CRC
- Other liver metastases
- Patients with surgery (other local treatment) in between studies

6.2 Segmentation and Annotation

6.2.1 Annotation process in use case no3

Similarly to Use Case 1, the patients' cohort will be split in two groups. First, a subset of 100 patients (group A) with liver lesions will be annotated and all lesions will be labelled. The algorithm testing on this first evaluated subset of patients will give an indication of the usefulness to detect and classify liver lesions on CT. If the result is sufficient the automated annotation of the rest of the cases (group B) will be done, otherwise another group of 100 cases will be annotated in the same way as Group A. In Group B, up to three lesions should be annotated. The radiologist should choose lesions with a proven diagnosis.

The labelling, size, and the location of the lesions should be reported in the CMRAD radiology report module.

6.2.2 Segmentation tools in use case no3

The tool Smart Paint 3D will be used to delineate the liver lesions visualised on CT. The CRLM lesions are labelled as L1-3, other pathologies will be marked with label 'O', while normal/negative studies will be labelled as 'N'. The lesions should be annotated in the phase where it is best visualised. All lesions are segmented in the same phase and thereafter automatically propagated to other series.

6.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of parameters from the patient's history and pathology report.

7. Use case no 4 - Can AI identify mesorectal lymph node metastases in pelvic MRI?

Today, the accuracy for detection of lymph node metastasis patience with MRI is 78%. The sensitivity is reported to be 69% and the specificity 81%. The task for this use case is to increase the sensitivity and specificity of detection of lymph-node metastasis by using an algorithm that detects mesorectal lymph nodes in pelvis MRI. After detection the lymph nodes are classified as malignant or non-metastatic (benign). The probability of malignancy should be displayed for each node.

In clinical reporting the following is suggested to be included according to ESGARs consensus guidelines:

- Total number of mesorectal lymph nodes
- Number of metastatic lymph nodes
- Size & number of morphological suspicious criteria:
  <5 mm - three criteria to be graded as malignant
  5-8 mm - two criteria to be graded as malignant
  >9 mm with either irregular outer border or heterogeneous signal – graded as malignant
- Morphologically suspicious criteria:
  - Round shape
  - Irregular border

- Heterogeneous signal

7.1 Patient Material

A number of 1800 pelvic MRI examinations, T2-weighted images and DWI, in patients with rectal cancer are available for the project (Table 7.1). The examinations are acquired before the start of treatment. No normal cases are included in use case number 4.

Table 7.1 Number and distribution between clinical partners, of use case number 4.

Pelvic MRI	Sample size N=1800			
	UNIPI	UMU	GUMED	KAUNO
	1000	400	100	300

7.1.1 Inclusion criteria

- patients with rectal cancer
- MRI scan before rectal surgery

7.1.2 Exclusion criteria

- Surgical treatment of rectal cancer prior to neoadjuvant treatment (it has to be primary rectal cancer with no surgical treatment before neoadjuvant)

7.1.3 Limitations for uses

- Other operations on the rectum (e.g. fistulectomies)
- Urinary incontinence/endoscopic treatment - TEM excision
- Other cancers in the lesser pelvis - prostate cancer

7.2 Segmentation and Annotation

7.2.1 Annotation process in use case no4

In a subset of 100 patients all lymph node-like lesions will be annotated and labelled. In the remaining cases at least four lesions should be annotated according to the ESGARs consensus guidelines. The lymph nodes closest to the rectal tumour should be chosen.

The size, and the location of the lesions should be reported in the CMRAD radiology report module.

7.2.2 Segmentation tools in use case no4

The tool Smart Paint 3D will preferably be used to delineate the lymph node like lesions visualised on MRI. The lesions are labelled as follows:

1. Metatatic
2. Non-metastatic

Automatic lymph node count as well as size calculation will be carried out based on pixel-wise segmentations.

The lesions should be annotated in T2-weighted images where it is best visualised. All lesions are segmented in the same phase and thereafter automatically propagated to other series.

7.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of parameters from the patient's history and pathology report.

8. Use case no 5 - Can AI predict the level of response to neoadjuvant radio(chemo)therapy based on primary MRI in rectal cancer for local staging and restaging?

The task in this use case is divided into several levels. First, the lesion should be detected and automatically segmented. Following that an assessment should be done of the cT-stage, i.e. detection of the longest diameter. Thirdly, a prediction of the probability of success of neoadjuvant treatment in terms of complete response, partial response or no response should be done.

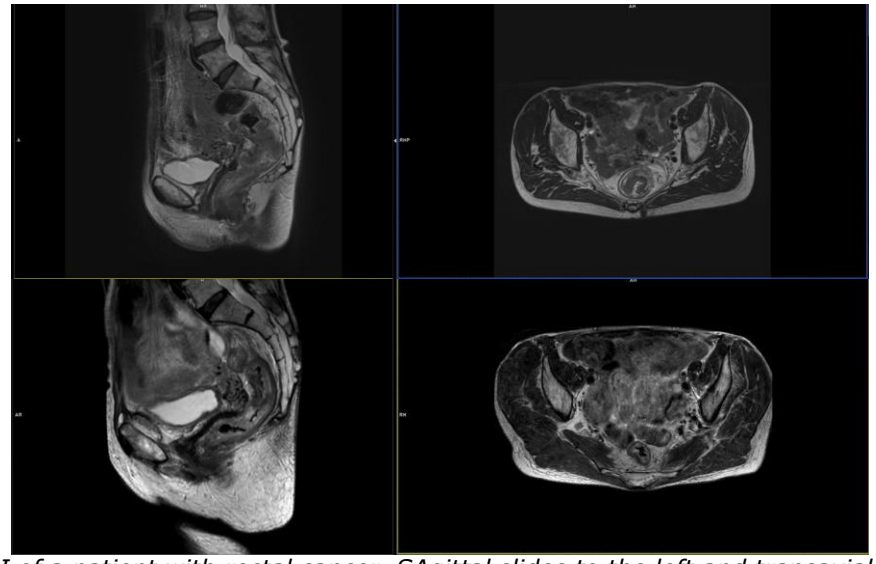

Figure 8.1 MRI of a patient with rectal cancer. SAgittal slides to the left and transaxial to the right.

8.1 Patient Material

The patient material in use case number 5 is the same as in use case number 4. A number of 1800 pelvic MRI examinations, T2-weighted images and DWI, in patients with rectal cancer are available for the project (Table 8.1). The MRI examinations are acquired before the start of neoadjuvant treatment. No normal cases are included in use case number 5. Cases will be as evenly distributed across classes of responses (complete, partial or no response) as possible.

Table 8.1. Number and distribution between clinical partners, of use case number 5.

Pelvic MRI	Sample size N=1800			
	UNIPI	UMU	GUMED	KAUNO
	1000	400	100	300

Suggested phase order during the MRI assessment:

1. High-spatial-resolution sagittal, coronal, axial T2-weighted MR images
2. Axial T2 – weighted MR images for 3D reconstructions
3. Apparent diffusion coefficient (ADC) map
4. T1-weighted MR images with fat suppression
5. Axial T1-weighted MR images
6. Diffusion-weighted imaging (DWI)

8.1.1 Inclusion criteria

- Patients with primary rectal cancer
- MRI before neoadjuvant treatment
- Neoadjuvant treatment

8.1.2 Exclusion criteria

- Previous surgical treatment of rectal cancer prior to neoadjuvant treatment (it has to be primary rectal cancer with no surgical treatment before neoadjuvant)

8.1.3 Limitations for uses

- Other operations on the rectum (e.g. fistulectomies)
- Urinary incontinence/endoscopic treatment - TEM excision
- Other cancers in the lesser pelvis - prostate cancer

8.2 Segmentation and Annotation

8.2.1 Annotation process in use case no5

The rectal cancer will be annotated and labelled in all patients.

The size, and other parameters of the lesions should be reported in the CMRAD radiology report module.

8.2.2 Segmentation tools in use case no5

The tool Smart Paint 3D will preferably be used to delineate the rectal cancers visualised on MRI.

8.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of parameters from the patient's history and pathology report.

9. Use case no 6 - Can AI distinguish five molecular subtypes of invasive ductal breast carcinoma on mammograms?

The task is to classify the lesions, detected and annotated in use case 8, into five different molecular subtypes:

- ✓ Luminal A
- ✓ Luminal B- HER2 negative
- ✓ Luminal B - HER2 positive/HR positive
- ✓ HER2 positive(enriched)/HR negative (non-luminal)
- ✓ Basal-like/Triple negative

An additional task is to give the probability/certainty score in percentage.

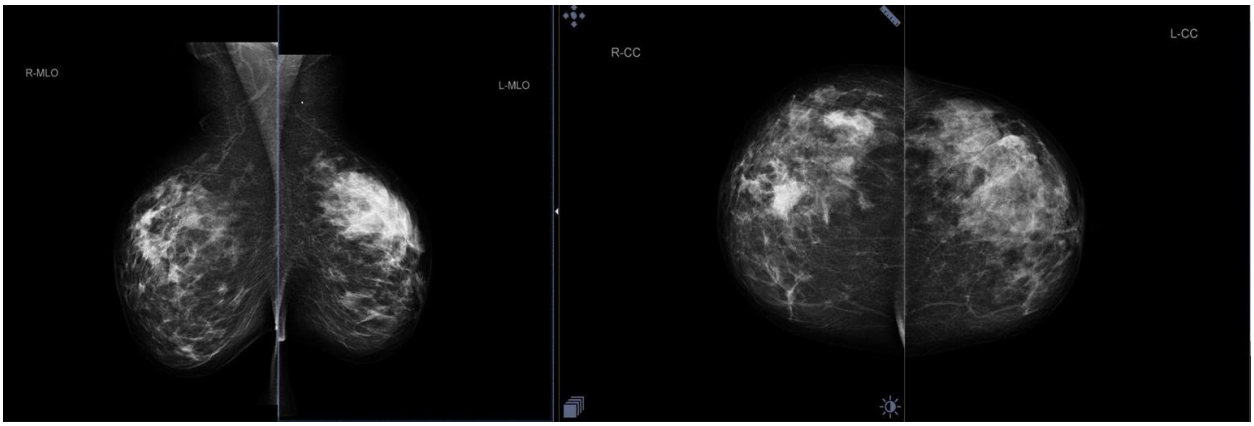

Figure 9.1 Four projections of a mammogram of a patient with breast cancer.

9.1 Patient Material

Use case 6 and 8 share the same patient material. A number of 8 600 screening or clinical full field digital mammograms are available for the project (Table 9.1). CC and MLO projections are provided by all centres with materials available in a smaller subset of patients. The distribution between cases will be approximately 50% malignant, 25% benign lesions and 25% normal images. For use case 6 only the patients with breast cancer are included.

Table 9.1. Number and distribution between clinical partners, of use case number 6. The 4100 malignant cases are used in use case number 6.

UC6 and 8		**Sample size**				
		FCRB	UNIPI	UMU	GUMED	UB
Screening and clinical mammography images	Malignant	500	500	1500	600	1000
	Benign	250	250	750	300	500
	Normal	250	250	750	300	500

For use case 6 a real-life distribution of molecular subtypes is needed for testing although all clinical centres will make efforts to provide enriched and more balanced numbers of subclases for training

9.1.1 Inclusion criteria

- Biopsy-proven breast cancer
- Full field digital mammograms (FFDM)
- Both screening and clinical/symptomatic subjects

9.1.2 Exclusion criteria

- Carcinomas other than ductal
- Only benign lesions
- Negative studies

9.2 Segmentation and Annotation

9.2.1 Annotation process in use case no6

As use cases 6 & 8 share the same dataset and annotation strategy, the annotation of all cases is done in the same workflow on the CMRAD annotation platform. The lesion-level analysis will be the main strategy in use case 6.

9.2.2 Segmentation tools in use case no6

The tool Smart Paint 3D will be used to provide pixel-vise delineation of breast cancer in mammograms. Special emphasis would be placed on consistent labelling of the same lesions in two different projections especially in multi-lesion cases. One malignant lesion will be annotated per patient.

9.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of parameters from the patient's history and pathology report.

10. Use case no 7 - Could AI tools enable to de-escalate neoadjuvant systemic therapy (NST) in patients highly likely to achieve a pathological complete response (pCR)?

The task is both to segment the tumour and to predict the response to treatment based on breast MRI and non-imaging data before treatment. The prediction should be classed as:

- complete response (pCR)
- partial response
- no response
- progressive disease (PD)

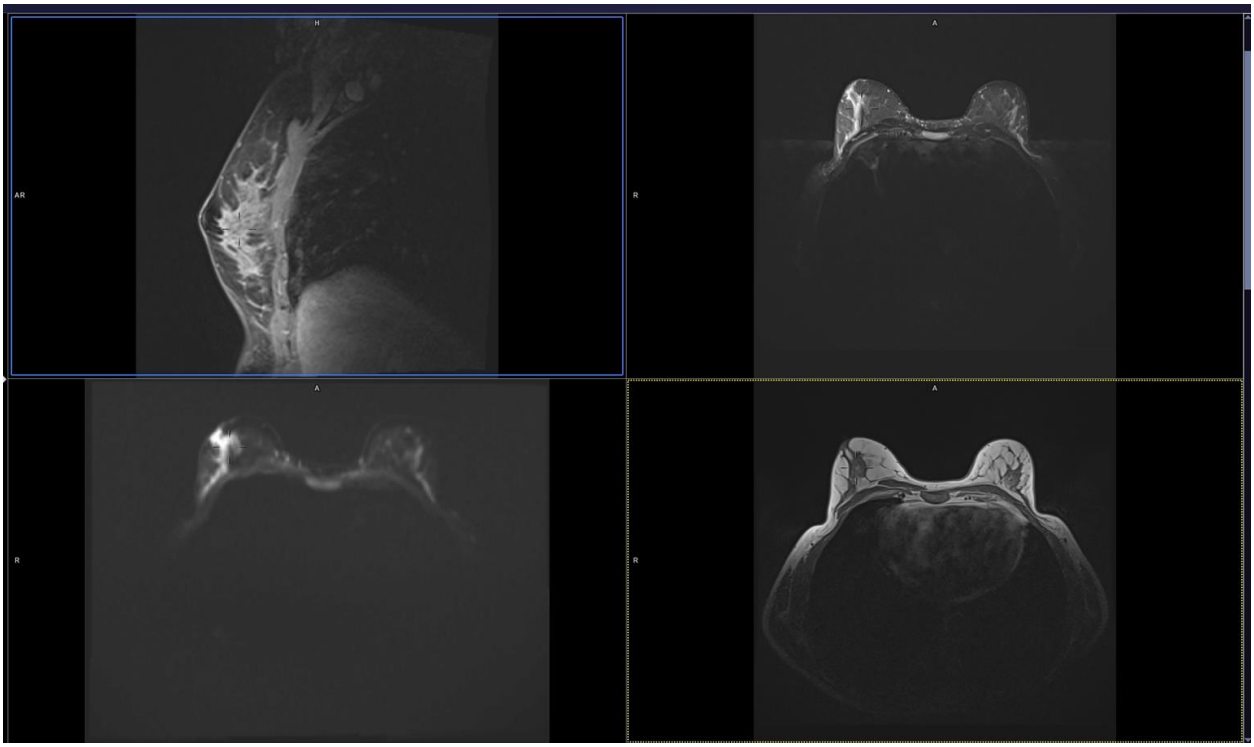

Figure 10.1 Breast MRI examination.

10.1 Patient Material

A number of 2 018 breast MRIs are available for the project (Table 10.1).

Table 10.1. Number and distribution between clinical partners, of use case number 7.

Breast MRI images before NST	**Sample size**				
	FCRB	UNIPI	UMU	GUMED	UB
	500	1000	120	45	353

The phase order during the MRI acquisition:

1. T1W sequence native: breast composition, hyperintensity (ex.blood)
2. T2W sequence: lesion signal intensity ex. high for fluid, presence of oedema
3. T1W post contrast sequences + subtraction: I acquisition after 90s – background enhancement, lesion type: focus/mass/NME,time/intensity curve assessment – initial enhancement/ delayed phase
4. DWI (at least b-value 0 and 700) with ADC map

10.1.1 Inclusion criteria

- MRI obtained before the beginning of the systemic therapy (ChT / HT)
- Patients with primary, locally advanced breast cancer - all subtypes (limitation - uneven distribution of subtypes that benefit from neoadjuvant systemic therapy might insert selection bias)
- Full pathology reports (pre and post NST)
- Breast MRI 1,5 T or 3T
- MRI obtained according to the established protocols

10.1.2 Exclusion criteria

- MRI with non-diagnostic image quality (for example significant hematoma hindering the assessment of the lesion - biopsy > 6 weeks)
- Deficiencies in non-imaging data
- Patients with ongoing systemic treatment (for previous breast or other cancer)
- Breastfeeding patients (breast swelling)
- Pregnant patients

10.2 Segmentation and Annotation

10.2.1 Annotation process in use case no7

One major malignant lesion with matching pathological confirmation should be annotated. Use default for labelling. The label "I" should be used for all foreign bodies (implants, tissue markers, pacemakers, ports) similar to other use cases.

The lesion level and the subject level according to BIRADS criteria should be reported in the CMRAD radiology report module.

10.2.2 Segmentation tools in use case no7

The tool Smart Paint 3D will preferably be used to delineate the breast cancer visualised on MRI.

The lesions should preferably be annotated in the second sequence after CM (gadolinium). Another sequence should be used if the tumour is better visible in another sequence. All lesions are segmented in the same phase and thereafter automatically propagated to other series.

10.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. The final list consists of xx parameters from the patient's history and pathology report.

11. Use case no 8 - Can AI improve the assessment of screening and non-screening mammograms by automatically differentiating benign from malignant tumours?

The task is to detect breast lesions in digital mammograms, to automatically segment the lesions and then to classify the lesion to malignant or non-malignant. The classification should be done on both lesion level and on image level. The density in the mammograms should also be scored with the ACR density score and classified to groups A-D. Finally, the cT stage should be determined based on the longest diameter measured from the annotation obtained in postprocessing.

An additional task is to give a malignancy probability score in percent.

11.1 Patient Material

Use case 6 and 8 share the same patient material. A number of 8 600 screening or clinical mammograms are available for the project (Table 11.1). All examinations are digital with minimum CC and MLO projections. Laterals are available in a subset of cases. The distribution between classes is 50% malignant, 25% benign lesions and 25% normal images.

Table 11.1. Number and distribution between clinical partners, of use case number 8.

		Sample size 8 600				
		FCRB	UNIPI	UMU	GUMED	UB
Screening	**Malignant**	500	500	1500	600	1000

and non-screening mammography images	**Benign**	250	250	750	300	500
	Normal	250	250	750	300	500

11.1.1 Inclusion_criteria

- Female patients
- Screening and non-screening patients
- FFDM with min. CC and MLO projections
- All types of malignant and nonmalignant lesions
- Negative screening cases

11.1.2 Exclusion criteria

- Male breast cancer cases due to selection bias (much lower prevalence with poor data availability)
- Patients <18 years of age

11.2 Segmentation and Annotation

11.2.1 Annotation process in use case no8

The three major pathologies in each examination will be annotated and labelled. The lesions are labelled as L1, L2 and L3. L1 is the first order label for malignant lesions. Labels must be inserted in both CC and MLO for the same lesion (matched lesion labels). The label "I" should be used for all foreign bodies (implants, tissue markers, pacemakers, ports).

The lesion level and the subject level according to BIRADS criteria should be reported in the CMRAD radiology report module.

11.2.2 Segmentation tools in use case no8

The tool Smart Paint 3D will be used to delineate the three major breast lesions in the mammograms. All other visible pathologies should be segmented with boundary box or Smart Paint 3D. A boundary box should be used to segment groups of similar types of calcifications.

11.3 Clinical (Non-image) data

From an initial list with non-image data used in the clinical work a minimization process was done via discussions between clinical partners and AI-researchers. As use cases 6 & 8 share the same dataset, the final list discussed in Use Case 6 chapter applies to use case 8.