RESEARCH PROPOSAL

Title: *A 3D Patient-Specific and Posture-Specific Cancer Lesion Model integrated into Augmented Reality to Improve Breast Lumpectomy*

Project coordinator: *Assaf Hoogi, PhD*

1. Abstract

Breast cancer is the most common cancer among women worldwide. For these women, breast conservative surgery combined with radiotherapy has become the standard treatment. However, up to 25% of the cases may have a positive pathologic margin, which results in high rate of re-operations with their accompanied morbidity and risks. On the other hand, sometimes surgeons may excise considerable amounts of healthy tissue, thus limiting the ability to achieve adequate cosmesis. A method to precisely identify the location and geometry of cancer lesions, considering the specific posture and the image statistics of each individual patient, will provide a much greater probability of a well-planned and successful surgery. This proposal presents an end-to-end framework that includes MRI-Mammogram registration (imaging- and sensor-based), as well as 3D lesion modeling and integration into an Augmented Reality platform. Using internal learning and single image analysis, the proposed framework delivers a patient-specific analysis. Through this type of approach, we are able to address key challenges of medical imaging, such as the limited amount of labeled data and significant variations in image statistics between patients. Preliminary promising results were already obtained. We expect that the impact of such a project will be extremely significant, including less re-operative procedures, minimizing costs, hospitalization days, and surgery complications.

2. Scientific background and state of the art

In 2018, 2.1 million breast cancer cases were diagnosed worldwide with 600K deaths. It is the most-commonly diagnosed cancer among American women and became the most common cancer globally as of 2021, accounting for 12% of all new annual cancer cases worldwide, according to the World Health Organization. Breast conservative surgeries for cancer lesion removal, also called lumpectomy or partial mastectomy, combined with radiotherapy have become the common treatment for diagnosed women. However, accurately locating and removing the lesion during a lumpectomy, especially when the lesion is small and nonpalpable, is a major challenge [1]. In that case, since many breast malignancies are caught in their early stages and are not palpable, breast surgeons must rely completely on pre-localization done by radiologists using imaging – mammograms, ultrasound, magnetic resonance (MRI) – to locate the cancer lesions. However, according to the type of imaging, patients can be either standing or lying down in different positions – and the breast may even have to be compressed or will simply be stretched by gravity. It is time-consuming and takes an experienced surgeon and radiologist to interpret the images and to infer, as precisely as possible, the actual location of the lesion from these non-overlapping, deformed views, in order to pre-localize the lesion for the surgeon. Except for lesion localization, accurate analysis of the lesion shape and geometry is critical to the surgery success. Without these two key-elements, the surgeon may supply either incomplete lesion removal or on the other hand - excessive normal tissue removal, which result in high re-operation rates (~25%) and increased surgical costs. The re-excision rate gets up to 70% in US, 56% in Canada and 30% in UK [2-6]. In addition, the location and shape of the lesion are important prior to surgery in order to better plan the procedure. The current gold standard of clinical practice for locating lesions is invasive - guide wire localization (GWL) prior to surgery (usually the patient has to come a day before the lumpectomy itself), in which a thin wire is inserted into the lesion mass under image guidance with its terminal tip within the lesion [7].

However, the location of the guide wire tip inside the breast tissue only provides a rough estimation of the lesion location, without its accurate shape and boundaries. Aside from this, it is also an invasive procedure (with all its complications/risks) and even with this GWL method, the reoperation rate remains high [8-9]. Furthermore, with continued improvement in imaging technology, smaller lesions are being diagnosed, which increases the demand for high-precision localization [10]. ***These limitations highlight an unmet need for a noninvasive precise tool that identifies and segments 3D breast lesions with high accuracy and minimal interruption to the surgical process.***

3. Research Hypothesis and specific aims

Hypothesis - we hypothesize that by developing a 3D computational model for comprehensive analysis of breast cancer lesions, which will be patient and posture dependent and will be integrated into an augmented reality application, we will be able to significantly improve the performance of teams in operating rooms by improving pre-operation planning and by enabling more accurate performance during the operation itself. Consequently, we will decrease reoperation rates, invasive procedure risks, pains, and hospitalization periods.

Team experience - The research team includes experts in computer vision, machine learning, breast imaging, and breast surgery. *Dr. Assaf Hoogi (primary PI and Project coordinator)* previously showed innovative works

in Computer Vision and Machine Learning for identifying and analyzing highly heterogenous cohort of cancer lesions, developing automatic and adaptive approaches [11-14]. Dr. Hoogi received the Outstanding Young Researcher Award from the American NIH--NCI, recognizing his many contributions to the development of innovative imaging image processing methods. The Sheba 3D Medical Solutions Center (_Dr. Dina Orkin, primary PI_) deals with accurate diagnosis, planning and surgical accompaniment. The 3D Medical Solutions center has also an experience in developing AR framework for hard and soft tissues (see Preliminary Results). _Prof. Sklair_ (secondary PI) is the director of breast imaging unit in Sheba Medical Center, who has a lot of experience with studies that aim to develop novel techniques for better breast imaging [15-21]. _Dr Zippel_ (secondary PI) is a breast surgeon that will help to validate our method by exploring the operations accuracy, the re-operation rate and the improvement of these aspects with and without our proposed methodology.
The specific AIMs of this proposal are presented in Figure 1 and are detailed below.

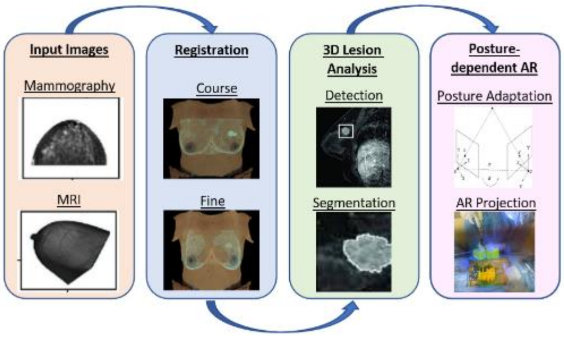


Figure 1. The main steps of the proposed technique

AIM1 – Extract 3D key-points for posture-dependent non-rigid breast and lesion registrations
The first step of our proposal is registration. To do that, we will apply a multiscale coarse-to-fine image registration; _1) Coarse_ registration to deal with a significant posture variability caused by different modalities and their screening protocols, _2) Fine_ registration for more accurate and local non-rigid lesion registration. For the _coarse_ registration, we will use image biomarkers and external sensor-based features. The latter will be supplied by using a 1) laser sensor to provide 3D depth and distance information and 2) RGB camera. Both will be located in the operating room. We will use an _internal learning approach_ and a _single image analysis_ to make the coarse registration. First, a posture estimation module will be applied for the natural domain images (i.e., sensor-based analysis), using a single image PoseNet. Then, the network output will be fed into a registration module. The weights of this network will be passed through a 3rd module, where medical images (e.g., MRI, mammograms) will be processed. Once the best-matched 2D MRI-Mammogram pair has been identified (out of the whole volumetric MRI), the 2D MRI slice will be registered (to the paired Mammogram) and will be the final framework output. _Fine_ registration will then be applied to improve the local registration of the non-rigid lesions, optimizing and finetuning the initial coarse registration. The fine registration will be based on image biomarkers alone.

AIM2 – Develop 3D computational model to fully characterize a cancer lesion
We will supply a fully automated and comprehensive lesion analysis by developing adaptive localization and segmentation methodologies that will be able to deal with a significant diversity of image statistics. This will be accomplished by extending our previous methods [11-14] to 3D models and by incorporating an internal learning approach. Incorporating the latter will enable the training procedure to be much more patient-specific, without "external" image statistics of other patients and as a result – it will dramatically improve the lesion analysis.

AIM3 – Incorporate the developed 3D lesion model into an AR application to improve lumpectomy
We will use the whole information extracted in previous AIMs to improve lumpectomy procedures. The analyzed cancer lesion (and its surrounding) will be projected on top of the patient's body via augmented reality (AR), adapted to the new patient's posture during surgery. The surgery results are expected to be improved significantly since surgeons will be able to 1) pre-plan the lumpectomy better than before, and to 2) identify the exact tissue to be removed (during real-time surgery). By doing so, the surgeons will avoid accidentally removing too much healthy tissue or removing only a part of the cancerous tissue.

In our first step, we will analyze 100 women who have both 2D Mammograms and 3D volumetric MRIs. We will validate our method by exploring the re-operation rate of patients' groups – with / without AR assistance. IRB approval will be obtained and will be ready to the start time point of the research. Clinical data will be anonymized according to Sheba Medical Center protocols.

4. Detailed description of the proposed research

- ***AIM1 – Extract 3D key-points for posture-dependent non-rigid breast and lesion registrations***

Clinical Background and Motivation

To extend our knowledge about the "scene", we will fuse the whole image information that we will have on hand (e.g., Mammography and MRI), enjoying the best from both worlds while overcoming their weaknesses. For example, one distinct advantage of MRI is its ability to better detect small breast lesions that are sometimes missed on mammograms. MRIs are also more effective in detecting breast cancer in women with dense breasts or breast implants. On the other hand, MRI prones to more false positive detections than mammograms. Mammograms are important source of information because they can show calcifications in breast tissue, thus can help in determining whether a specific object is cancer or not. Therefore, establishing spatial correspondence between 2D mammograms and volumetric breast MRI scans can help to evaluate and assess different types of breast findings. However, identifying such correspondence is far from being a trivial problem – not only that the images have different contrasts and dimensionality, but they are also acquired under vastly different physical conditions. Moreover, the expected difference between the images is further exacerbated by the effect of mechanical compression of the breast during mammography examination along with the fact that, as opposed to MRI scans, mammograms are projective.

The challenge of MRI and mammogram registration have been addressed in several studies using a range of different approaches. Biomechanical Finite Element Models (FEMs) are popular and are used to predict the deformation of breast tissue due to compression [22-24]. However, the main disadvantages of using FEM-based methods relate to their computational complexity, high sensitivity to the results of image segmentation as well as their dependency on third-party numerical solvers. A fully automated method has been proposed in [25] which performs a complete registration of MRI volumes and mammograms in both directions, i.e., from MRI to mammogram and from mammogram to MRI. In [26], in contrary to other FEM-approaches, the authors performed registration on the density maps extracted from both MRI and mammogram scans. In [27], the same group of authors proposed to define the similarity measure using intensity gradients, which was shown to be much less sensitive to the difference in imaging contrasts between MRI and mammography. Soleimani and Michailovich introduced a two-stage computational scheme for 2D Mammogram and 3D MRI registration that estimates the global (compression dependent) part of the spatial transformation first, followed by estimating the residual (tissue dependent) part of the transformation of much smaller magnitude [28].

The Proposed Method

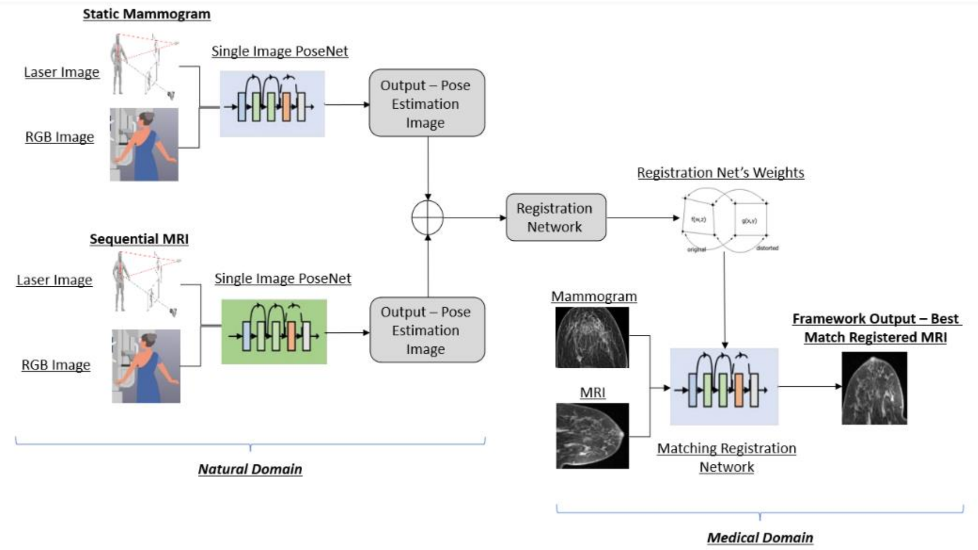


Figure 2. The proposed coarse P2P registration approach

A multiscale coarse-to-fine image registration will be developed; *1) Coarse – Posture to Posture (P2P) registration* – to deal with the significant patient's MRI-Mammogram postures variability, *2) Fine – Lesion to Lesion (L2L) registration* - for more accurate and local non-rigid lesion registration, finetuning the coarse one.

Our coarse registration will be divided into two phases (see Figure 2).

- *Posture Estimation module (left side of the scheme)*– the input relies solely on sensor-based information (e.g., laser sensor, RGB camera). There are no imaging scans involved in this learning phase. When sensor-based information is used, estimating the coarse posture is easier than using medical images - where the image statistics may be more complex, and the analysis depends also on tissue compression (these aspects will be addressed in the Fine registration scale). In order to achieve this, we will apply a single image PoseNet (for each imaging modality type) [29], which will make the posture estimation more patient-specific. Each PoseNet will output an image with a 3D patient's posture estimation.
- *Final Posture Registration (right side of the scheme)* – both output PoseNet images will be fed into a 2nd module – registration network. The optimal weights of this network will be determined to achieve the most accurate transformation between these two PoseNet output images. Then, 2D mammogram and 2D MRI slices of the same patient will be then fed into a last module - matching registration network. Since these medical images are directly related to the sensor-based ones, the shared weights from the 2nd module should do a good job registering these medical images as well. The output of this module (and, in fact, of the whole framework) is a registered 2D MRI slice that will best match the specific 2D mammogram, out of all MRI slices of the 3D volume.

The fine registration scale will be achieved via a 2-input deep learning architecture, which will not incorporate any sensor-based information. The architecture will use one input channel for the 2D mammogram and another channel for the best-matched 2D MRI slice that was previously selected during coarse registration. Fine registration will be applied to improve the local non-rigid lesion registration in soft tissue; each patch in the matched MRI image will be registered to its best matched Mammogram patch (within a surrounding window – to be safe). Hence, every patch can be transformed independently.
Having identified the optimal registrations (Coarse and Fine together), we will apply these transformations to all 2D slices from the volumetric MRI in order to create a registered MRI volume.

<u>*Pitfalls and alternative approach*</u>
Depending on the results of registration, we may choose an alternative strategy. Rather than registering the two images, mammogram/MRI will be viewed as a specific form of multi-view image fusion with a pure <u>*joint representation*</u>. Multiview image fusion, which has been extensively studied in both medical and natural domains, is similar to our multimodality case in that the images are obtained from different angles and may include different image details or image statistics. Multi-view fusion can also cause some object distortion due to the perspectives/angles from which the images are captured, which is part of the distortion we want to eliminate when fusing mammograms and MRIs. There are several highly relevant medical works that involve information fusion when ultrasound (US) imaging is one of the sources [30-32]. The use case is similar to ours in that 1) US is a technician-dependent imaging technique, as a result, it can have different tissue compression levels, similar to mammogram vs. MRI. 2) US imaging views can differ considerably. In this case, we are illustrating a situation where there is a large disparity between the screened images. To apply this alternative approach, we will use two separate networks and eventually fuse the data at a later feature level.

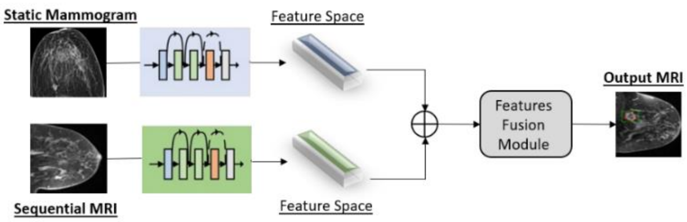


Figure 3. The alternative approach for MR/Mammogram Fusion

<u>*AIM2 – Develop 3D computational model to fully characterize a cancer lesion*</u>

<u>*Clinical Background and Motivation*</u>
An understanding of a patient's breast micro-anatomy is crucial prior to surgery in order to identify lesions' location and their exact boundaries and to plan the surgical corridor in advance. The relationship between cross-sectional 2D Mammograms, MRI images, and patient anatomy can be challenging. It requires surgeons to transfer two-dimensional images into complex three-dimensional structures that lack anatomical landmarks (apart from a limited guide wire) [33-34]. Therefore, having a 3D model of the breast and the cancer lesion will enable surgeons to pre-plan the surgery more accurately and to provide much better operation results.

While developing the 3D model, this proposal tackles two main challenges of medical imaging; 1) limited labeled data, 2) high data diversity. To do that we will propose a solution based on internal learning, which has gained a significant exposure in the natural image domain over the recent years. This research field focuses on learning techniques for complex visual inference tasks where the training cohort and test cohort are identical, with zero additional "external" examples to train on. The cohort may contain a single image, a single video or a single patient. The main strength of internal learning approach relates to its ability to train the learning architecture on a limited labeled data only and take advantage of the overfitting characteristic (which is usually a weakness, but not when using internal learning). Another advantage relates to the fact that internal learning is patient-specific, thus we do not use any "noisy" irrelevant image statistics from other patients. In medical imaging, these key-ideas can have a significant contribution because data labeling is an expensive and time-consuming task and as a result, there is only a limited available labeled data. Additionally, since a specific type of cancer can be seen differently for different patients, and especially for breast cancer - when women's breasts can be fatty or dense - it is particularly crucial to reduce the variability of statistics. Selecting a patient-specific learning approach is the way to do that. **Surprisingly, and despite the strengths of internal learning and its huge potential, especially in the medical imaging domain, as far as we know internal learning approach has never been incorporated in the medical field until now.**

- *Proposed Methodology*

Here we will extend the methods that we previously developed [11-14] to significantly improve their performance. We will do that by

- Extending these 2D techniques to 3D versions.
- Using Internal learning to improve patient-specific analysis.

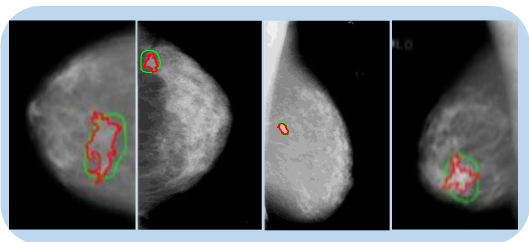
With general details, the DALS (Deep Active Lesion Segmentation) technique that we already presented in [14], consists of 1) U-Net architecture to automatically detect and roughly segment the cancer lesion and 2) a level set methodology to finetune the rough segmentation. The U-Net helps to learn the adaptive level set parameters, depending on the image statistics and the distance of the Zero Level Set contour from the cancer lesion. Here we will extend both parts, U-Net and Level Set, to their 3D versions.

In addition, the DALS technique is based on external learning. In this work, we will use an internal learning instead. In our case, the internal cohort will contain a single patient, so that the learning architecture will be adapted to the image statistics of a specific patient only. This approach has a key contribution especially in breast cancer because each woman has different breast imaging patterns (i.e., dense tissue, fatty tissue).

- *Preliminary results*

As was mentioned above, Dr. Hoogi academic career focuses on medical imaging and specifically on the full diagnosis of cancer lesions, thus his resume is highly relevant to this research grant. Cancer lesions have a significant diversity of their spatial image characteristics, which is mainly a result of the screened organ, the imaging modality, and the acquisition method. This lesion diversity includes low contrast lesions, noisy lesions, lesions with unclear boundaries, and high-heterogeneous lesion surrounding that should not be considered as part of it. Hence, the task of lesion detection and segmentation is extremely challenging. Dr. Hoogi previously developed adaptive generalizable frameworks for cross-modality lesion detection and segmentation, applying exactly the same frameworks on different lesion datasets with results that are superior to the baseline method. The adaptive methods automatically estimate the weighting parameters of the level set cost function and the adaptive size of the local window surrounding each contour point [11-14]. While in previous methods the weighting parameters and the window size were manually tuned and stayed fixed over the whole process, in Dr. Hoogi works these parameters are automatically re-estimated over iterations of the segmentation process and for every lesion separately. His works are the first demonstration of a fully adaptive framework for deformable models that supplies more general, robust, and accurate lesion segmentation.

In this research grant Dr. Hoogi's lab was already able to supply an accurate breast lesion segmentation. Figure 4 illustrates the automatic detection and segmentation results for high diversity of breast cancer images in both MRI and Mammograms.



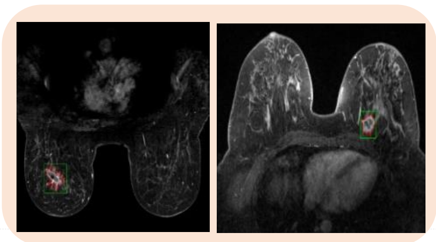


Figure 4. Automatic lesion localization and segmentation. Blue - initial results for Mammogram images. Orange – MRI images. Green – Ground-Truth for general localization that was made by the radiologist. Red – the obtained accurate lesion segmentation made by our automatic algorithm.

- *Validation*

  The lesion analysis phase will be validated by comparing the automated results (i.e., detection, segmentation) with the manual annotations made by two experts and experienced radiologists. We anticipate that the variability between our results and the results provided by each radiologist will be comparable or smaller than the variability between the two radiologists.

- *Pitfalls and alternative approaches*

  As we mentioned above, we will implement an internal learning approach. It is possible that a particular patient's data may be too heterogeneous or too limited over time, which makes the learning process harder. Therefore, we will use a weighted-patient approach, wherein the training will rely more on instances that will be obtained from the same patient and will rely less on (but will still consider) images that will be obtained from other patients. This approach is between external training (i.e., relying on "external" instances from other patients) and internal learning (i.e., each learning procedure will be based on internal examples from the same patient only). That way, we ensure that a new patient image will be analyzed mostly according to her typical image statistics.

- ***AIM3 – Incorporate the developed 3D lesion model into an AR application to improve lumpectomy***

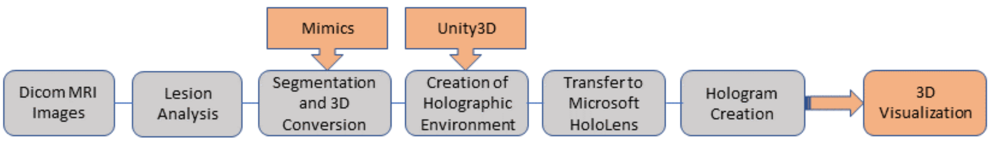
- *Clinical Background and Motivation*

  Recent innovations in 3D spatial technology and augmented reality (AR) have accelerated exploratory research in breast cancer imaging. Merging digital and physical anatomic structures of the breast with lesion included in a digital 3D breast model, can be visualized through AR in the operating theater. Virtual and augmented reality technology can be more effective at conveying information that requires a three-dimensional understanding of an environment. This novel technology is starting to be used in various fields in medicine [35], including medical research [36], surgical planning [37], medical training [38], patient therapy [39], and patient education [40]. It has also been shown that these immersive virtual experiences can promote improved recall [41].

  However, to the best of our knowledge, only two recent papers authored by a similar group of researchers presented a non-invasive method for breast cancer localization, using augmented reality to guide and improve breast surgery [42-43]. There is an important role for these papers in opening the door to this fascinating field. However, the authors of [42] mainly focus on localization (without an accurate shape analysis) and they used only three physical breast markers on the patient's breasts to identify the lesion. Localization without an accurate characterization and shape analysis is sub-optimal, and using a limited number of markers, especially when the screened tissue is non-rigid, has a limited performance as well. In [43], the authors presented an extended breast and lesion analysis, however their method requires specific patient posture for 3D surface analysis. In addition, the annotations are done with a black permanent marker before surface data acquisition and after 3D surface scan, cod liver oil pills are fixed upon these marks for MRI acquisition**.** This shows that the methods are highly strict and non-robust and that any deviation from the required patient posture or from the procedure protocol will decrease the technique accuracy.

- *Proposed Methodology*

  Researchers at Sheba Medical Center will be in charge of the augmented reality (AR) phase, which will involve several commercial devices and softwares. As a first step, we will use Mimics (Materialise NV, Belgium) to create 3D surface models (from 2D MRI slices) of the desired environment surrounding the patient's breasts. Unity3D (Unity Software Inc., CA, USA) will then be used to create the holographic environment from the Mimics output. We will input hologram properties in advance (color and transparency), while basic functionality (e.g., lock in position and scale) will be available on the main menu. Then, we will export the



  reconstructed 3D environment as FBX files for use with the Microsoft HoloLens (Microsoft Corporation, Redmond, WA, USA). The HoloLens is wireless, so gestures can be used in sterile environments like operating rooms without ever touching. Figure 5 summarizes all main steps of the AR phase.

Figure 5. Main steps for implementing the lesion analysis information (and its environment) in the AR application

- *Preliminary results*
  The proposal deals with soft t  e in an AR application is much more challenging than that of hard/r non-optimal holographic environment. Despite the challenging task, F y results of projecting the holographic environment (transparent gray body are promising and impressive. Furthermore, looking at the loc (the left one of the two, marked by an arrow) confirms that the AR les spot on the patient's breast.

Figure 6. Preliminary AR results. The cancer lesion is green colored. The breast environment is presented in transparent gray color (AR) on the patient body.

- *Validation*
  Our AR approach will be compared to the standard pre-operative localization with guide wire localization (GWL). We will divide our 100 patients into two subgroups – the proposed AR-based and the standard wire-based. The validation will focus on 1) the number of successful operations with minimal false positives (histopathology will be used as ground truth), and 2) the amount of healthy tissue left behind (should be maximal if the lesion shape was accurately estimated). In the long run, validation will also quantify the number of re-operations.

5. Significance, innovation, and potential benefits of the proposed research

Several key-contributions have been made to two different research fields - medicine and computer science;
Computer science – we present adaptive methods for comprehensive analysis of 3D cancer lesions with maximum adaptability to a specific patient and to a specific body posture. Moreover, we incorporate internal learning and single image analysis approaches, which are emerging fields in the natural domain but as far as we know - have never been applied in the medical domain. Our approach presents novel solutions for core challenges in computer vision (CV) and machine learning that are highly associated with medical imaging (e.g., limited labeled data and different image statistics for different individuals).
Medicine – the clinical need is obvious, and the key-contribution of the proposed methodology is significant. We introduce a comprehensive 3D modeling of cancer lesion in *soft tissue* that is then incorporated into AR. This improves 1) preoperative planning and 2) performance accuracy during the surgery itself. As a result, suffering, hospitalization period, costs related to invasive procedures, infection risks, and re-operation rates will be reduced.

6. Applicability

The proposed study will have a significant impact on personalized healthcare, the direction the clinical world is heading. Once a model has been validated, any operating room can use it to increase the accuracy of surgeries and decrease the risk of postoperative complications - infections, extended hospital stays, re-operation rates, etc.

Breast tissue is soft and flexible. Therefore, its adaptation to the patient's posture is more complicated and challenging than in the case of hard tissues. Hence, despite the focus of the proposed study on breast cancer, there is no doubt that an algorithm that is designed to address the variety of challenges of breast tissue can also be used in surgical procedures of other tissues of lesser visual complexity. Lastly, the AR application is friendly and easy to use, so it is likely to be adopted by surgeons.

7. Work plan and Gantt

Each collaborator sub-group that participates in this proposal has its unique contribution and impact.
- Assaf Hoogi, PhD – the group is highly experienced with Computer Vision and Machine Learning fields. Thus, it will be charged on developing the algorithm and the technique for the image analysis.
- Dina Orkin, PhD – the lab has a lot of experience in Augmented Reality applications in Clinic and will be charged of the Augmented Reality incorporation in this proposal.
- Miri Sklair, Prof. – she will consult about the imaging techniques, the clinical protocol for imaging breast cancer patients and will supply the clinical data
- Dov Zippel, MD – he is a breast surgeon that will help to evaluate the method (e.g., its accuracy and convenience) during the surgery itself.

Task	**Sub - Task**	**Group**	**6 mo**	**12 mo**	**18 mo**	**24 mo**	**30 mo**	**36 mo**
AIM1	Modality and Lesion Registration	Hoogi's lab - 1st Graduate Student						
	Validation - registration	Hoogi's lab & Prof. Sklair						
AIM2	Lesion Analysis – detection and segmentation	Hoogi's lab – 2nd Graduate Student						
	Validation – lesion analysis	Hoogi's lab & Prof. Sklair						
AIM3	Integration in AR (with improvements)	Orkin's lab – expert AR researcher						
	Validation – AR implementation	Orkin's lab & Prof Zippel						
Initial Clinical trial	Exploring the technique maturity to be part of the clinical protocol. At this point – as an auxiliary tool,							
Publications	Conferences and Journals	Hoogi, Orkin, Sklair and Zippel						

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