Novel Breast Specimen Orientation Approach through 3D Visualizations for Relocating Inadequate Margins based on the Surgical Clips: Feasibility Study.

Rob F.M. van Doremalen (✉ r.f.m.vandoremalen@utwente.nl)

University of Twente: Universiteit Twente <https://orcid.org/0000-0003-1970-3833>

Kevin B.W. Groot Lipman

Deventer Hospital: Deventer Ziekenhuis

Esther van 't Riet

Deventer Hospital: Deventer Ziekenhuis

Hans Torrenga

Deventer Hospital: Deventer Ziekenhuis

Maria M. Smits

Deventer Hospital: Deventer Ziekenhuis

Ferdinand van der Heijden

University of Twente: Universiteit Twente

Research Article

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Abstract

Purpose: The current breast specimen orientation method after breast-conserving surgery is potentially inaccurate due to deformability and mobility of the extracted breast tissue. This complicates targeted relocation during re-excision or radiation. Therefore, we propose a new 3D-visualization method to communicate the breast specimen orientation to instantly provide an intuitive overview of the resection margins in relation to the surgical clips on the wound bed.

Methods: In 15 female patients undergoing breast-conserving surgery, the surgeon labeled the surgical clips on the specimen and the wound bed. During pathologic assessment, after inking, a 3D scan was made of the specimen. Tumor tissue was annotated on the histological image and transposed to the respective location inside the 3D model. The transposed resection margins with respect to the labeled surgical clips were calculated and visualized. Intuitivity of the visualization was tested (face validity) as well as the quality of displayed resection margins and labeled clips.

Results: Average face validity score for 3D-visualization was between ‘++’ and ‘+’ for surgeons and between ‘+’ and ‘+/-’ for pathologists. Average difference between computed resection margins and reported histologic margins was 1 mm. In 8 cases not all clips could be labeled in situ. In 5 cases not all labeled clips could be retrieved by pathology.

Conclusion: The visualizations appeared valuable in interdisciplinary communications. The displayed resection margins approximated the reported margins. Consistent accurate surgical clip labelling proved challenging.

Introduction

Lifetime risk of developing breast cancer is approximately 1 in 7 for women in the Netherlands[1]. Breast-conserving surgery (BCS) has become the preferred therapy for breast cancer[2]. With BCS, tumor tissue is surgically removed with adequate margin, followed by adjuvant radiotherapy (RT). Before closing the breast, the surgeon embeds five surgical clips in the wound bed for relocation during RT. Tumor resection with inadequate margins is associated with an increased risk of disease recurrence[3, 4]. Therefore, the pathologist assesses the specimen histologically after surgery. In case of inadequate margins, the Dutch guidelines advise a re-excision or additional local RT boost[5, 6].

To limit tissue removal in re-excision or unintended radiation damage in local RT, an accurate relocation of the inadequate margins is needed for a targeted approach. Communication of the breast specimen orientation from surgical theatre to pathology is essential for accurately relocating the tumor tissue. Current best practice for communicating breast specimen orientation is to annotate the original anatomical orientation of the specimen in-vivo by first defining six sides (superficial, deep, superior, inferior, medial, and lateral) and subsequently labeling three of them, e.g. three different length stitches[7, 8]. When inadequate margins are found, pathology reports the location relating to one of these sides.

The highly deformable nature of breast tissue makes it difficult to keep track of the original anatomical orientation of the surface of both specimen and wound bed during excision, labeling, and transportation. This can result in disorientation in one in three cases [Molina2008]. Accurate communication of the breast specimen orientation between operating theatre and pathology can enable targeted therapy and reduce potential overtreatment[7, 9–11]. In literature, only a few articles present an alternative breast specimen orientation method to tackle this problem[12–14]. Intraoperative margin assessment could also prevent postoperative inadequate margins[15–17]. However, until this is 100% effective, the breast specimen orientation for relocation purposes remains relevant.

We propose a new 3D-visualization method to communicate the breast specimen orientation between the pathologist and surgeon. The aim of this visualization is to instantly provide an intuitive overview of the resection margins and their relation to the surgical clips on the wound bed. To our best knowledge, only Koivuholma et al. proposed similar 3D-visualization[18]. The resection margins are computed from histological images. The surgical clip locations are obtained by labeling them on the specimen during excision, similar to van Lanschot et al.[19]. Unlike the current breast specimen orientation approach, these surgical clips follow possible deformations of the wound bed and are thereby not affected by the deformable nature of the breast tissue. We hypothesize that this approach could improve relocation of inadequate margins during re-excision and radiotherapy. In this study, we investigated three outcomes: First, whether the 3D-visualization provides an instant intuitive overview. Second, if the displayed resection margins are realistic. Third, if surgical clip labeling is clinically feasible.

Methods

Study Design

In this single-center prospective feasibility study, we included 15 female patients planned for breast-conserving surgery at Deventer Hospital (Deventer, The Netherlands). As inclusion criteria, the patients had to be diagnosed with breast cancer, both invasive or in situ, qualified for breast-conserving surgery, above the age of 18, and without a history of surgery in the concerned breast. Patients meeting these criteria were informed about the study by their treating healthcare professional of the Deventer Hospital.

The Medical Ethical Committee “Isala clinics Zwolle” approved the study protocol (181105), and we obtained informed consent from each participant prior to the start of the study.

Study Procedure

Surgery

Standard hospital procedure was retained where possible to avoid impact on treatment outcome. However, to ensure accuracy of labeling the clips on the specimen, a couple of adaptations were made relative to the standard procedure (Fig. 1). In the study procedure, the locations of surgical clips on the

wound bed are labeled on the specimen with similar surgical clips, referred to as cliplabels in this article. The surgical clips, cliplabels, and stitches were placed during incision to ensure accurate correlation.

Pathology

Standard procedure for pathologic assessment is to ink the specimen with three different colors, indicating the original anatomical orientations in the body. The colored orientations depend on the slice direction. When slicing it left to right or vice versa, the colored orientations are dorsal (blue), ventral-cranial (red), and ventral-caudal (green). When slicing cranial to caudal, red and green indicate ventral-left and -right respectively. For this study, we added a small dot of yellow ink to indicate the location of the cliplabels (Fig. 2). After inking, the specimen is 3D scanned for the 3D-visualization method.

3D-visualization Method

Data acquisition

The 3D-visualization method requires three input variables, which were acquired during pathologic assessment (Fig. 1): (1) a 3D model of the specimen, which was acquired with a 3D camera after inking to include the colors in the 3D model; (2) an overview image of the slices including annotations where the slices were cut to fit the microscope glass; (3) a collection of digital histological images with tumor tissue annotated by the pathologist. Only tumor tissue that resides within a margin of 10mm from the edge was annotated.

For the 3D scanning setup, we used an Intel® RealSense™ D435 depth camera (Intel Corporation, Santa Clara, California, US), with RecFusion software (ImFusion GmbH, Munich, Germany). This setup was selected because it is small, portable, inexpensive, and deals well with reflective surfaces. We mounted the camera in a portable custom setup with a transparent turntable (Fig. 3). Specimens were 3D scanned by slowly rotating the turntable, always starting with the superficial side up and superior side towards the camera mount. The resulting 3D image was processed in Meshmixer (Autodesk, San Rafael, CA, USA) to remove noise and to create a solid 3D model. Subsequently, the yellow ink was intensified with the painting tool in Meshlab (Visual Computing Lab, Pisa, Italy). Slice overview images, already taken in standard procedure, were also exported. Digital histological images were annotated by the pathologist using the highlighter function in the Microsoft snipping tool. The background was removed in the slice overview image and the histological images using Photoshop CS5 (Adobe Systems, San Jose, CA) before continuing with the image processing tool.

Image processing

Our goal was to visualize the resection margin on the surface of the 3D model relative to the location of the cliplabels and thereby surgical clips on the wound bed. To acquire this visualization, the locations of the cliplabels were manually annotated on the 3D model. Moreover, the location of tumor tissue in the

histologic image must be translated to this 3D model. After this translation, the distance between the tumor tissue and the surface of the 3D model (resection margin) can be computed and visualized. The steps to accomplish this are displayed in Fig. 4 and processed using our custom program developed in MATLAB (The MathWorks, Natick, MA) [supplementary files].

Outcome Measures

1: Instant and Intuitive 3D-visualization

The 3D-visualizations were clinically assessed for face validity by pathologists and surgeons separately. Face validity was defined as its ability to clarify the orientation of tumor data in the specimen translated in a score of '++' (Greatly clarifies the orientation), '+', '+/-' (Neutral: nor clarifying, nor disorienting), '-', or '--' (Causes additional disorientation).

2: Resection Margin Evaluation

The histologic resection margins from pathologic assessment were compared to the respective resection margins computed from the 3D model. In contrast to the histologic resection margins, the resection margins from the 3D model are not restricted to the 2D plane of the histologic images. For proper comparison, the resection margins from the 3D model are computed in two ways: unrestricted considering all directions, called the 3D margin, and within the same 2D plane as pathologic margin assessment, called the 2D margin. For every resection margin, the minimal distance and anatomical orientation are documented.

Our primary objective is to validate found margins by the 3D model by comparing the 2D margins with histologic margins. Our secondary objective is to study the effects of computing the unrestricted 3D margins, as the unrestricted 3D margins should theoretically provide a more realistic representation of the resection margin.

3: Feasibility of Surgical Clip Labeling

We assessed the feasibility to accurately translate the location of the surgical clips on the wound bed to the 3D-visualization. Feasibility was determined based on observations during surgery and pathological analysis, i.e. which problems arose and where the study procedure had to be altered.

Results

Patient demographics

Characteristics of the 15 participants are shown in Table 1. Two participants (#6 and 12) had a combination of invasive ductal carcinoma (IDC) and ductal carcinoma in situ (DCIS). Pathologic assessment within two other participants (#5 and 13) showed a resection margin larger than 10mm and these participants were therefore not annotated, processed, and visualized.

Table 1
Patient demographics

#	age	tumor type	TNM classification	location	side
1	74	IDC gr. I	cT1N0	UOQ	L
2	54	DCIS gr. II		UOQ	R
3	71	DCIS gr. II		UIQ	R
4	52	IDC gr. II	cT2N0	UOQ	L
5	62	LCIS (Pleomorphic)		Central	L
6	53	IDC gr. III + DCIS gr. III	cT1N0	LIQ	R
7	59	ILC gr. II	cT2N0	LIQ	L
8	86	IDC gr. II	cT2N0	UOQ	R
9	61	IDC gr. I (Mucinous)	cT1N0	Inner half	L
10	65	IDC gr. I	cT1N0	UOQ + Upper half	R
11	71	IDC gr. II	cT2N0	UOQ	L
12	57	IDC gr I + DCIS gr. II		UOQ + LOQ	R
13	51	IDC gr. II	cT2N0	Central	L
14	69	ILC gr. II	cT2N0	UOQ	R
15	55	DCIS gr. II		LIQ	L
Note: IDC = Invasive ductal carcinoma; ILC = Invasive lobular carcinoma; DCIS = Ductal carcinoma in situ; LCIS = Lobular carcinoma in situ; UOQ = upper outer quadrant; UIQ = upper inner quadrant; LIQ = lower inner quadrant; LOQ = lower outer quadrant.					

Outcome Measure 1: Instant and Intuitive 3D-visualization

For all cases with a resection margin < 10mm, a 3D-visualization was successfully reconstructed (Fig. 5). For the best impression of the results, we refer to the version in GIF format, which can be found in the supplementary files of this article. For the 13 cases, face validity was assessed by the surgeon as ‘++’ in 4 cases, ‘+’ in 7 cases, and ‘+/-’ in 1 case, and assessed by the pathologist as ‘+’ in 6 cases and ‘+/-’ in 7 cases.

Outcome measure 2: Resection Margin Evaluation

Table 2 shows the margins found by the pathologist as compared to the margins computed from the 3D model. The mean absolute difference between the distance found by the pathologist and the distance

computed from the 2D plane in the 3D model was 1.1 mm. The maximal difference between the distance computed from the 3D model in 3D and in the 2D plane was 2.7 mm.

Table 2
Resection margins determined from the 3D model and from pathology.

Case	3D Distance [mm]	2D Distance [mm]	Pathology [mm]	Difference [mm]
1	7.5	8.1 ventral	9 ventral	-0.9
2	5.6	5.6 dorsal	8 dorsal/ventral	-2.4
3	0	0.1 ventral, medial, caudal,	0 ventral	0.1
4	6.4	6.4 dorsal	4 Dorsal	2.4
5	-	-	> 10 dorsal	-
6	0.7	3.4 ventral/ medial	< 1 ventral; 2 medial; 4 dorsal; 6 cranial; CIS 4 ventral	2.4 to 3.4
7	3.8	3.8 caudal/dorsal	2 caudal/ventral; 3 dorsal	2.4
8	1.3	1.4 cranial	2 dorsal; 4 ventral	-0.6
9	1.8	1.8 ventral	1.2 ventral	0.6
10	4.1	4.5 lateral/dorsal	4 dorsal	0.5
11	0.8	0.8 caudal/dorsal	2 dorsal	-1.2
12	0.1	0.1 cranial/ventral, 0.3 dorsal	4 ventral; CIS < 1 dorsal	0
13	-	-	> 10 caudal/ventral	-
14	2.2	2.2 dorsal	2 dorsal; 5 ventral	0.2
15	0.2	0.3 medial, 0.2 dorsal	0 medial, dorsal / ventral; <1 caudal	0

Outcome measure 3: Feasibility of Surgical Clip Labeling

Surgery

In 7 out of the 15 cases, the exact study procedure was followed. In more challenging cases, the surgeon chose to embed the clips and cliplabels after excision, outside the body, to reduce the risk of inadequate margins. In five cases (#8, 9, 10, 14, and 15) all cliplabels and clips were placed after excision and in three cases (#2,12,13) some were placed during and others after excision.

Pathology

All specimens were subsequently processed at the department of pathology according to the study procedure. The located clips were inked yellow which was well identifiable in the histologic images. However, not all cliplabels could be retrieved. In five cases (#1, 3, 7, 11, and 14) the respective lateral, lateral, caudal, medial, or dorsal cliplabel appeared missing. In cases 3 and 7, the medial cliplabels appeared double as two were situated in close proximity to each other at the medial side of the specimen. In case of a missing or double cliplabel, identifying the matching surgical clip in the wound bed was challenging.

Discussion

Summary

In this article, we present a novel breast specimen orientation approach with 3D-visualization in a small cohort. The goal was to test feasibility and evaluate to what extent the 3D-visualization supports the relocation of inadequate resection margins. In this novel approach, the surgical clips embedded in the wound bed were also labeled on the specimen. Histologic findings were subsequently reported relative to the clips, instead of relative to the original anatomical orientation in-vivo. We evaluated the feasibility through three outcome measures.

Interpretation results

Outcome measurement 1

For outcome measure 1, a pathologist (RS) and surgeon (HT) scored the face validity of the 3D-visualizations for intuitivity. These scores suggest the 3D-visualizations are predominantly of added value for the surgeons. Experienced pathologists are trained to mentally generate a 3D perspective of the resection margins similar to the 3D-visualization, termed spatial cognition[21]. It neither improves nor confuses the 3D perspective of the pathologist. Hence, the pathologist's face validity score ranges from '+/-' to '+'. On the other hand, communicating this 3D perspective of the resection margin to interdisciplinary colleagues is challenging and the visualization method might be helpful for this purpose. Therefore, pathologists might welcome the 3D-visualization for the interdisciplinary communication of their 3D perspective.

In all cases, the 3D-visualization provided the surgeon with a 3D perspective of the resection margin in the specimen on a level that couldn't be obtained from conventional reports. The scores '+/-' to '++' were primarily based on the specific case. The 3D-visualization was extremely helpful (++) in cases where the minimal resection margin was situated close to a cliplabel, or in a direct line between two cliplabels, which enables easy relocating in case of re-excision. We hypothesize that the 3D-visualization becomes less effective when the cliplabels are situated further from the resection margin, since the uncertainty of the inadequate margin location would be larger, which might be the underlying factor for the difference in scores.

Outcome measurement 2

We compared the histologic margins to both the 2D and 3D margins computed from the 3D model. The found differences can possibly be attributed to rounding errors to whole numbers by pathology, or the occurrences that the specimen is a bit squeezed during slicing, resulting in a smaller histologic resection margin ventral and dorsal and vice versa for the rest. Moreover, some cases contained tears in the histologic slice, which could not be digitally repaired, overestimating the margin. The largest difference of 3mm can be attributed to the fact that pathologic assessment was not determined in the 2D plane of the histologic slice, but perpendicular to it as it was the most outer slice of the specimen. Here, the unrestricted 3D-visualization resection margin is close to the histologic margin. This highlights the added value of the ability to determine the resection margin in all directions. A mean difference of around 1 mm for the reported resection margin between pathologic assessment and the 2D plane from the 3D-visualization is within expected range since the pathologist rounds the numbers to whole diameters. Given that the deformations during slicing could be partially responsible for the differences, the results suggest that our 3D-visualization is rather accurate.

Outcome measurement 3

For outcome measure 3, we investigated the feasibility of this clip-based approach for breast specimen orientation. The approach has the potential to directly link the histologic findings to the wound bed surface. However, for this approach to work, the locations of the cliplabels on the specimen have to correlate directly to the locations of the clips on the wound bed. Some problems were observed during the course of this study. First, in a selection of cases, the surgeon chose to place a part of the clips and cliplabels ex vivo directly after excision, which possibly distorts the correlation between both locations. We suspect that sufficient training and experience overcomes this problem, but the presence of this learning curve does complicate broad implementation. Second, we observed in two cases (#3 and 7) that two cliplabels were situated very close to each other. We suspect that in these cases the surgeon chose to increase the margin around the tumor, resulting in both the clip and the cliplabel being located on the specimen. Third, a cliplabel appeared missing in several cases. Multiple reasons can contribute to a missing cliplabel: (1) The surgeon chose to decrease the margin, meaning the cliplabel is embedded in the wound bed. (2) A cliplabel detached during excision. (3) A cliplabel gets enveloped by the specimen tissue, in which case the label was later found during slicing. Originally, anatomical orientations were assigned to each clip at pathology. This proved to be difficult when a clip (with unknown orientation) was missing or appeared double. For future research, we are looking for a more robust approach to prevent these problems[8].

Strengths and limitations

Research design

The strengths of our study design included: (1) it is a prospective study, (2) the cohort contained multiple types of cancers (DCIS, LCIS, IDC, and ILC), (3) both multiple quantitative and qualitative outcomes were

measured, and (4) multiple surgeons participated, suggesting the results are more generalizable towards other hospitals. A study design limitation was the small sample size ($n = 15$), with only one case with inadequate margins.

Research setup

The strengths of the research setup included: (1) an affordable 3D camera that handles wet and reflective surfaces well, and (2) a compact and mobile turntable setup to capture the 3D model of the specimen, which allowed coloring of the clips to mark them as well. Limitations included: (1) the relatively low detail of the camera (1 mm) leading to a smoothed 3D model, (2) the turntable setup left the bottom of the specimen uncaptured, (3) the procedure was time-consuming and laborious, (4) missing data points such as disappeared clips, or torn histologic images, (5) digital slicing was equally distributed over the specimen and not based on the real thickness of each slice, and (6) the deformable registration algorithm did not account for varying stiffness of different tissue types within the specimen.

There were two comparative studies, one about the label-based relocation approach[19], and one describing a 3D-visualization method of the specimen[18]. First, the study by van Lanschot et al. demonstrated a label-based relocation approach during oral cavity oncology surgery. The main difference with our approach was, aside from the specimen type, that they performed an intraoperative margin assessment. Therefore, they were able to number the labels and remove them before closing the wound. Second, the study by Koivulhoma et al. presented a 3D-visualization method of a tongue specimen including histology. Besides specimen type, there were several differences with our setup. First, their scanning method needed optic spray to handle wet reflective surfaces. Second, they implemented a net to capture the bottom of the specimen, where we employed a transparent turntable. Third, their method can cope with slices in multiple directions, where our method assumes parallel slicing, which is the standard at our pathology department. Fourth, they interpolated between tumor slices to create one solid tumor, where we chose not to because multiple solids (DCIS) can be present and interpolation could result in a misrepresentation of tumor tissue. Last, their method did not provide an estimation of the resection margins.

Future perspectives

Further research should be directed at improving the clip labeling technique or finding an alternative to link the location in the histologic margins to in vivo wound bed surface. Targeted treatment of inadequate margins based on this approach is only feasible when the cliplabels are an accurate representation of the surgical clips embedded in the wound bed.

An alternative strategy for follow-up research is to focus solely on the 3D-visualization benefits and disregard the cliplabels, as the 3D-visualization provides an intuitive 3D perspective in interdisciplinary communications.

A CT scan of the specimen can function as an alternative to the 3D imaging setup. Although a CT scan is more expensive, an advantage is that it provides interior information, which can be linked to histology

and enable deformation based on tissue stiffness.

When an accurate clip labeling technique is available and validated, it is interesting to extract the geodesic distance between clips and inadequate margin. The geodesic distance is the shortest distance following the curvature of the specimens' surface, which represents the maximum distance between the potential inadequate margin and the concerning clip. In addition to which clips are in the proximity of the resection margin for re-excision, the surgeon also acquires the geodesic distance from each clip with this method.

These distances could prove even more beneficial in radiotherapy, where it could indicate the area at risk for residual tumor. In radiotherapy, the geodesic distances can be interpreted as radius for a spherical area around each clip. Where these spheres overlap can be considered as the area at risk.

Although it is out of the scope of this article, the algorithm to compute the geodesic distance is developed and available in supplementary files. Although not accurate due to suboptimal clip labeling discussed in outcome measure 1, the distances were plotted on the 3D-visualizations to provide visual understanding (see supplementary files).

As mentioned in the introduction, an efficient method to avoid inadequate margins is through intraoperative margin assessment. However, for as long pathologic assessment is necessary, research for improved breast specimen orientation methods remains relevant.

Conclusion

In this article, we analyzed the relocation of resection margins after breast-conserving surgery and pathologic assessment. We aimed to solve three major challenges in communication of breast specimen orientation for in-vivo relocating inadequate margins. (1) The visualization of the pathologic assessment as a communication tool towards the surgeons: Our proposed 3D-visualization method was perceived as intuitive and valuable both surgeons and pathologists. (2) Translating the resection margin from histologic images accurately to the 3D-visualization: We found that the displayed resection margins in the visualization aligned with the reports of the pathologists. (3) Correlate the inadequate resection margins found in histologic images to the respective location on the wound bed: We found our method of labeling both the specimen and the wound bed was promising. However, the method requires improved consistency before clinical implementation is feasible. Further research should be conducted on this part.

Declarations

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Availability of data and material (data transparency): GIF results are accessible in supplementary files.

Code availability (custom code): Git link will be shared upon acceptance.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was granted exemption by the Medical Ethical Committee “Isala clinics Zwolle” (181105).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent to publish: Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rob F.M. van Doremalen, Kevin B.W. Groot Lipman, Rita Smits and Hans Torrenga. The first draft of the manuscript was written by Kevin B.W. Groot Lipman and Rob F.M. van Doremalen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest: ‘Not applicable’

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Figures

Figure 1

The adaptation of the study procedure relative to standard procedure. Dark blue boxes are overlapping instances, light blue boxes are only standard procedures and orange is an adaptation or addition in the study procedure. Yellow boxes indicate instances where data is extracted for 3D-visualization.

Figure 2

Breast specimen after inking with cliplabels inked yellow. Red represents the ventral-cranial side, blue the ventral-caudal side.

Figure 3

The 3D imaging setup. Blue circle: The 3D camera. Red circle: the transparent turntable where the specimen is placed.

Figure 4

The different steps to acquire the 3D-visualization. 1) The number of slices was determined from the slice overview image. 2) The 3D model was digitally sliced into equally sized slices. 3) The cliplabels were labeled based on the yellow inking corresponding to their anatomical orientation during surgery. 4) The tumor tissue from the histologic image is translated to the 3D model in three consecutive steps (4 a, b & c), which are repeated for every annotated histologic image. 4a) The tumor tissue is digitally delineated in

the histologic image. 4b) The delineated image is registered to the respective part in the slice overview image. 4c) The slice from this overview image is registered to the respective digital slice of the 3D model. Registration is performed through a deformable, affine, and B-spline grid-based technique [20]. 5) The smallest distance of each point on the surface of the 3D model to the registered tumor was calculated using the Hausdorff metric, generating a distance map. This distance map was visualized in color, but transparent, to show the cliptables and tumor inside the model as well.

Figure 5

Example of 3D-visualizations of case 4 (a) and 15 (b). Top two pictures show the annotated slice overview images and the bottom two a representation of the 3D-visualization of respective cases.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementalFiles.zip](#)