Clinical relevance of model based computer-assisted diagnosis and therapy

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ABSTRACT

The ability to acquire and store radiological images digitally has made this data available to mathematical and scientific methods. With the step from subjective interpretation to reproducible measurements and knowledge, it is also possible to develop and apply models that give additional information which is not directly visible in the data. In this context, it is important to know the characteristics and limitations of each model. Four characteristics assure the clinical relevance of models for computer-assisted diagnosis and therapy: ability of patient individual adaptation, treatment of errors and uncertainty, dynamic behavior, and in-depth evaluation. We demonstrate the development and clinical application of a model in the context of liver surgery. Here, a model for intrahepatic vascular structures is combined with individual, but in the degree of vascular details limited anatomical information from radiological images. As a result, the model allows for a dedicated risk analysis and preoperative planning of oncologic resections as well as for living donor liver transplantations. The clinical relevance of the method was approved in several evaluation studies of our medical partners and more than 2900 complex surgical cases have been analyzed since 2002.

Keywords: Medical image computing, Models, Risk analysis, Computer-assisted diagnosis, Liver surgery

1. INTRODUCTION

The prerequisite of computer aided diagnosis is the silent digital revolution in image based medical diagnosis and therapy. As a result we witness the major new historical phase in the development of radiology as field of science and medicine. The early phase extends from the discovery of X-rays in 1895 to approximately the early 1970s. The second phase begins with the introduction of CT and MRI and certainly continues. The third phase begins some time in the middle 1990s is a on the onset of a complete digitization of all image based and image related processes and aims at software assistants for diagnosis and therapy. Looking back at the first phase it appears almost miraculous at which pace diagnostic breakthrough applications followed one another:

1896:	first angiogram	1902:	first image of brain lesion
	first dental image	1905:	first image of kidney
	first image of in vivo heart	1910:	first contrast agent (Bariumsulfate)
	first image of headan dpelvis	1923:	first image of gall bladder
	first image of thorax	1929:	first heart catheter (Fossmann)
		1956:	Ultra sound

Let's remember that the development of the modern natural and engineering sciences beginning with the heroes such as Galileo, Brahe, Kepler, and Newton have made their steps and jumps based on a critical advancement of measurements. Historically from the point of view of the practitioners, radiology by and large has been an interpreting discipline in which measurements in a controlled scientific manner did not have a place.

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The complete digitization of all processes now permits us to introduce measurements in obvious and more subtle ways based on image information. And already we witness that image acquisition aims both at providing images for human interpretation and as well as information to be exploited for measurements. In some sense interpretation is replaced by arguable and reproducible knowledge. CAD in the narrow sense but also computer assisted diagnosis in a broader sense start right here and quite like the natural and engineering sciences have shown as in their progress modeling and models become possible and necessary to fully exploit the given information or generate model based new information which exceeds and extends the image information.

It is the position of this invited lecture that along this development we need to rethink the issues of clinical relevance of our contributions and the impact that follows on how we manufacture and provide solutions in the domain of software assistants. Here are our major points and concern that we believe should have a stronger emphasis and which be addressed in our case study:

- Models and modeling in CAD will become increasingly important. Models require a patient individual fit. This in turn requires at times innovative measurements.
- What are the systematic and random errors and uncertainties which pollute the patient individual data and may question the integrity of a model. How sensitive does a model react against the variability and errors in the data? How does one monitor the gain or loss of the suitability of a model?
- Models have to be flexible and must allow for some user interaction and correction. For example extraordinary pathologies may occur or intra-operative findings may be discovered which have to be adequately integrated. Ideally, a model will indicate its limitations and monitor its own integrity.
- Evaluation of models is a particular problem. Classically medicine is accustomed to rely on clinical studies. It appears that here methodologies from the natural sciences have to introduced for supporting validity and evidence, which may result in a cultural clash.

2. THE SENSITIVITY OF RISK

In our case study, we will discuss the risk analysis for tumor resections in the liver. An optimal resection in terms of surgical technique is the so-called R0-resection that guarantees the complete excision of the lesion and a microscopically tumor-free resection margin. On the other hand as much healthy parenchyma as possible should be preserved. Considering the anatomy of the liver, we have to take into account vascular structures in the neighborhood of the tumor. Removing the tumor together with the safety margin from the liver, local vascular structures have to be transected that are supplying or draining a dedicated liver region and thus defining a territory at risk (Fig. 1).

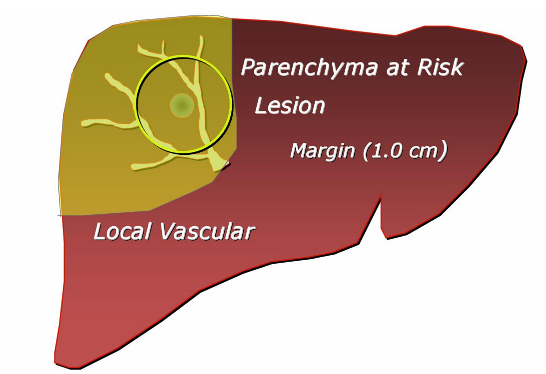

Fig. 1 Schematic drawing of a lesion in the liver surrounded by local vessels. Together with a safety margin of 1cm (circle) vessels have to be transected supplying a part of the liver (yellow), which will have an impaired inflow and are therefore considered as the parenchyma at risk.

The risk distribution can be considered as a function of the vascular systems and the two parameters tumor location and safety margin. Regarding an individual vascular structure as a fixed parameter, then position and margin influence in particular two attributes of the risk territory: First, the size of that region depends on the influence of the transected vessels in terms of supplied or drained parenchyma. Second and much more important for the surgical intervention is the sensitivity of the territory to small changes of the parameters position and margin. There exist parameter settings with a 'robust' risk where changes that are e.g. in the magnitude of the achievable surgical precision alter the risk territories only to a limited extend. But more interesting and even more difficult to estimate are risk territories with parameters, where small modifications change the risk significantly and thus demand a different resection strategy. Fig. 2 shows two adjacent positions of an artificial tumor in a single vascular system extracted from a corrosion cast of a human liver. The parenchyma at risk is much smaller for the position of the tumor shown in the left while the second position compromises for the largest safety margin the complete right hemiliver. The more sensitive the risk distribution appears at a specific position of a tumor the more important is a risk analysis for this region.

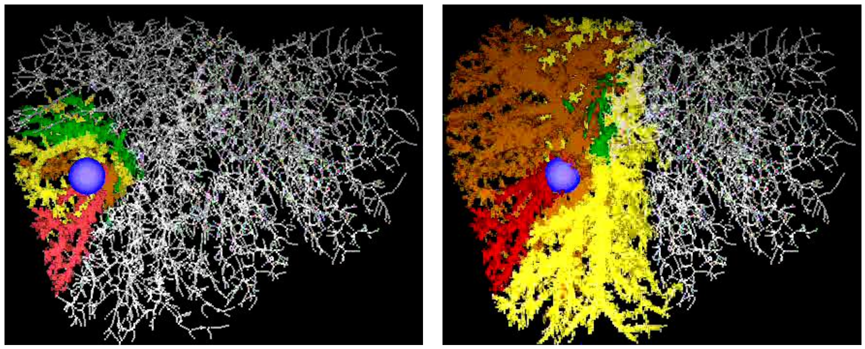

Fig. 2 A sphere as a model for tumor has been placed in the 3D model of a corrosion cast. The different colors of the thick branches indicate which part of the portal venous system would be affected by a resection of the tumor with different safety margins. The position of the tumor influences significantly size and location of the parenchyma at risk and is thus an example for a very sensitive tumor location.

Taking into account the fact that the liver is supplied or drained by four vascular systems, the risk distribution is even more complex. For the final aim of supporting the physician in identifying an optimal resection strategy, also aspects of surgical feasibility have to be considered.

3. LIVER SEGMENTS AND TERRITORIES

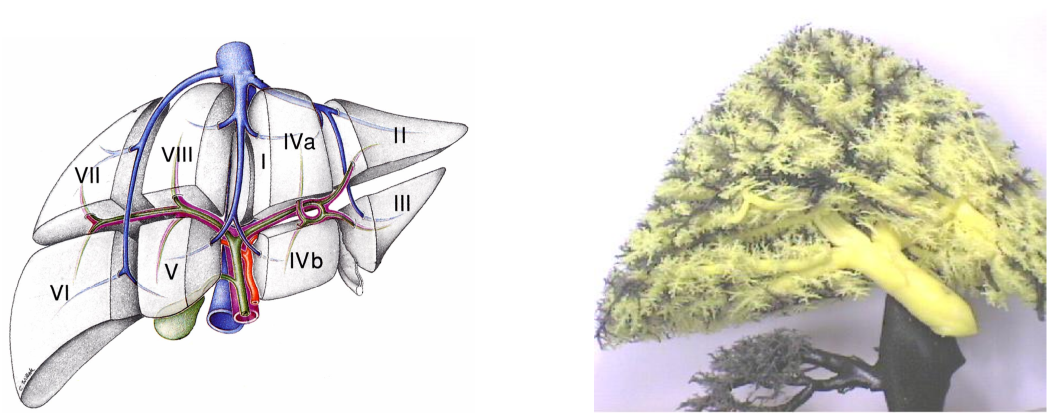

Fig. 3 Liver anatomy. Left: Four vascular systems supply or drain the liver, hepatic artery (red), portal vein (magenta), hepatic vein (blue), and bile ducts (green). Right: Corrosion cast of a human liver with portal vein (yellow) and hepatic vein (black), prepared by Prof. J. Fasel, Geneva, Switzerland.

The vascular anatomy of the liver is complex since four different vascular systems supply and drain the liver: hepatic veins, portal vein, hepatic arteries, and bile ducts (Fig. 3). The latter three vascular systems run almost parallel peripherally and are called the portal triad. Although in the liver hilum where these vessels enter into the liver parenchyma, a great inter-individual variability is present and fixed spatial resolutions of major vascular branches do not exist. In case of high resolution data and sufficient contrast, a separate risk analysis for all systems is possible. For data where the image quality is not sufficient e.g. for extracting smaller but relevant branches of hepatic artery and bile ducts, the analysis should be performed only for the portal vein as the leading system of the triad while keeping in mind that vascular anomalies have to be assessed separately.

Risk analysis and preoperative planning for liver surgery is based on multi-phase computer tomography (CT) or magnetic resonance imaging (MRI) data with contrast enhanced vascular structures (examples in Fig. 4). The contrast agent passes through hepatic artery, portal vein and hepatic vein and during this time two or three datasets (phases) are acquired showing one or two vascular systems each. The imaging of bile ducts requires a different contrast agent at least for CT images.

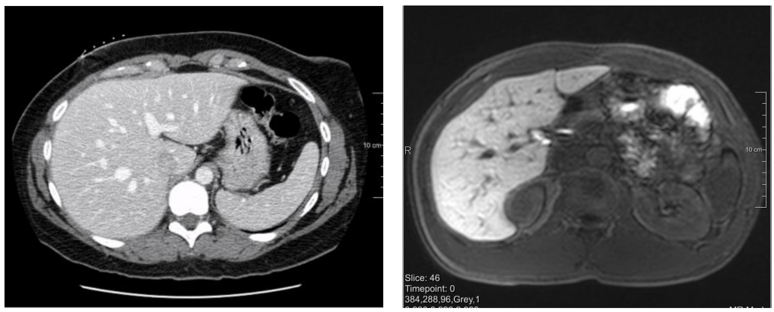

Fig. 4 Cross-sectional slice of a 3D dataset of the abdomen. In the CT image (left) vessels appear bright due to application of contrast agent, while a liver-specific contrast agent in the MRI data brightens the parenchyma (right), thus showing the vessels as dark tubular structures.

3.1 The Couinaud scheme

For a surgeon, it is difficult to mentally construct the 3D structure of vascular systems based on cross-sectional slices of radiological data and to estimate which part of a vessel system would be damaged as a consequence of a surgical intervention. In order to enable surgeons to perform liver resections respecting the vascular anatomy, a schematic model of the liver is employed that was introduced by Couinaud in 1957 long before CT technology was introduced[1]. At this time, a preoperative evaluation of the individual vascular liver anatomy was not possible. Following the Couinaud model, the human liver can be divided into eight segments which are determined according to the main branches of the portal vein and the hepatic veins. A liver segment is supposed to be defined by the supplied territory of a third-order branch of the portal vein with intermediate hepatic veins (Fig. 3). Applying the widespread scheme of Couinaud directly is questionable, since the liver segments do not correspond well to the individual territories (Fig. 5) and do not reflect common anatomical variants, e.g. trifurcations of the portal veins or inferior hepatic right veins draining directly into the inferior caval vein[2-4].

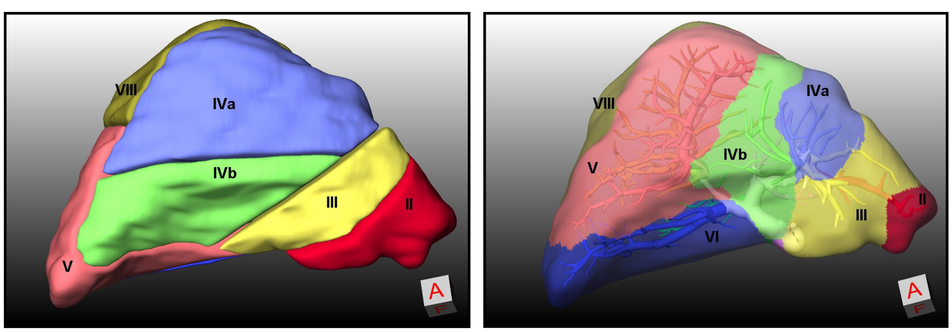

Fig. 5 Comparison of Couinaud segments and approximation of portal venous territories. Segments and territories differ significantly in position and size for this corrosion cast of a human liver.

3.2 Analysis of individual anatomy

The patient-individual risk analysis for a specific surgical intervention is based on the information that can be extracted from abdominal CT or MRI data. Relevant for liver surgery are the intrahepatic vascular systems, the shape and volume of the liver, and for oncologic surgery, the size and position of tumors. The MeVis group started in 1992, as the first group world-wide, with the computer-assisted analysis of branching patterns of hepatic vascular systems and functional vascular units which finally led to software assistants for liver surgery planning[5-9]. For the analysis of radiological data we perform the following image processing steps: Liver segmentation is achieved with a modified live-wire algorithm, a semi-automatic edge-oriented algorithm as described in Schenk[10,11]. The analysis of vascular systems is described in detail in Selle[12,13] and consists of 1) an image preprocessing step to eliminate in homogeneities within the liver[14,15], 2) segmentation of the vascular structures with a modified region growing algorithm[16,17], 3) determination of the centerlines (skletonization) of this segmentation result, and 4) the hierarchical analysis of the vascular trees[12,18]. From the skeletonized vessels the different vascular systems are separated semi-automatically, and analysis for each of these systems can be performed. The analysis includes identification of the major branches of the portal vein, thus giving an individual classification similar to Couinaud's scheme (Fig. 5 and 6) and a subsequent risk analysis.

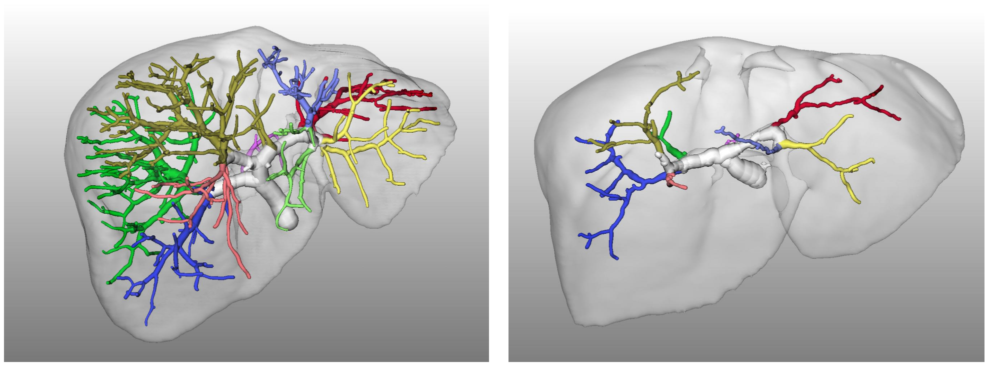

Fig. 6 Portal vein classification and example for different data quality. Analysis of the vascular system with a subdivision similar to Couinaud's scheme. Results for good high-resolution data (left) and low contrast images (right).

Being aware of image quality problems, e.g. anisotropic resolution, low contrast or high image noise, and displacement or compression of vessels by tumors, we focus on robust methods that meet the demands of short runtime and sufficient level of automation. For difficult cases, an additional mode for manual corrections is available.

Assuming that the image data has an excellent quality and spatial resolution comparable to that of a corrosion cast, then a tumor could be directly assigned to a single territory and a risk analysis could be performed directly from the vascular structures. This assumption of optimal data cannot be fulfilled due to the need to avoid excessive radiation exposure in case of CT or with the currently available scanner technique for MRI. As a consequence, there is a demand for an approximation of vascular substructures or liver territories that can be met with model based approaches.

4. LIVER MODELS

Perhaps the most salient contribution of mathematics to medical image analysis consists of models as a basis for extraction of meaningful parameters from the data for speculations about information which is not directly visible in the image data. For risk analysis in liver surgery, we require a model to estimate the assignment of a given position, most notably of a given lesion part, within the liver to a certain subbranch of each vascular system. This can be achieved in two ways, which will be further detailed below: firstly, by modeling the vascular system to the required level of detail, and, secondly, by identifying a suitable assignment function. Under specific assumptions, these two approaches are equivalent in a certain mathematical sense that will not be discussed here.

4.1 Modeling vascular systems

Inspired by the theorems of Hess and Murray on the principle of minimum work in vascular systems[19,20], by the simulations of Meinhardt[21], who derived complex structures, such as trees or networks, from basic cellular mechanisms, i.e., activation, inhibition, and elongation, and based on our own observations[22], we developed a method for constructing realistic vascular systems[23].

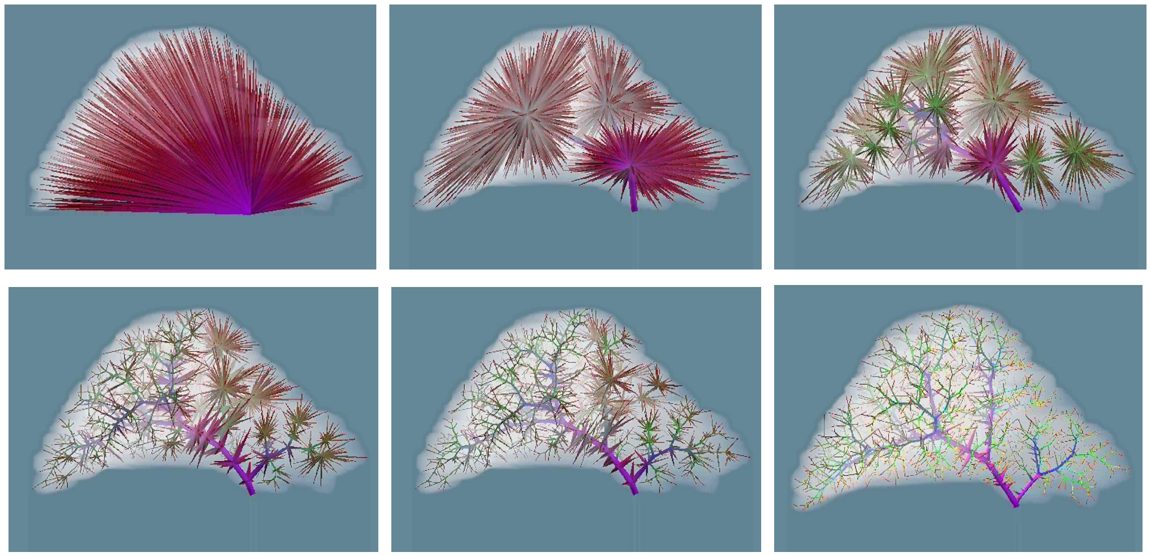

Fig. 7 Result of the constructive optimization model for a portal vein within a predefined liver hull. Starting with a simple configuration where each liver cell is supplied by a straight vessel from the hilum, the vascular system is modified step by step following a mathematical minimization principle for the physical work of blood transport.

Our model is initialized by a complete but overly simple and suboptimal tree that fills an organ at a given resolution using straight tubes. This initial tree is then subject to positional and topological local optimization techniques, as shown in Fig. 7. The boundary conditions for the optimization procedure are given by the position and flow distribution for all vascular end points corresponding to the leaves of the tree, by the position of the vascular hilum corresponding to the tree root, and by the maximum blood pressure available for organ perfusion. Then, according to the Hess-Murray law, optimization can be driven by intravascular volume minimization. Our algorithm is novel in that it implements topological changes corresponding to the subsequent merging and splitting of bifurcations, which have proven essential for the optimization process. For global optimization, we additionally employ a multi-level approach based on iterative pruning[23]. The generated models are found to be similar to real data acquired from corrosion casts of a human liver (cf. Fig. 8).

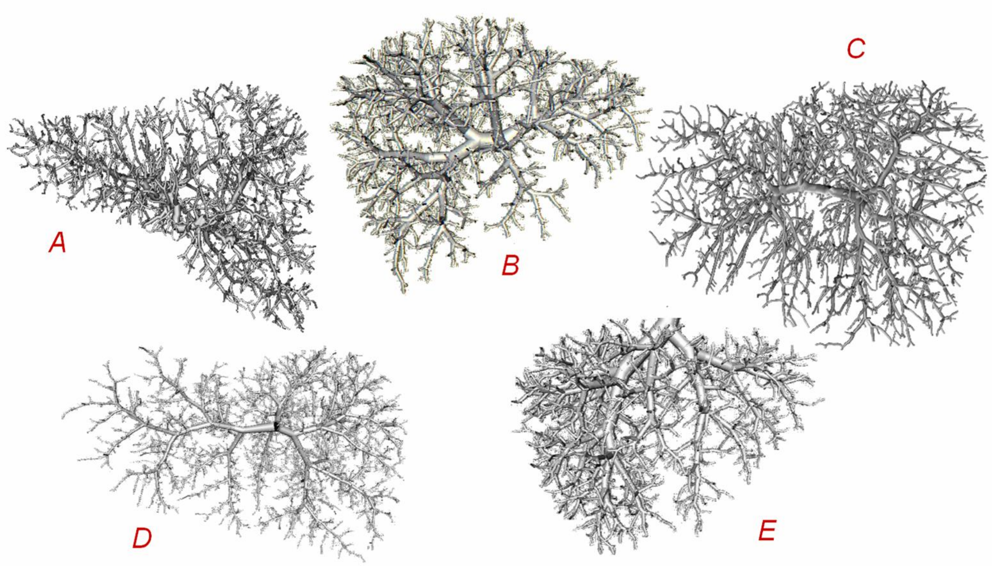

Fig. 8 Vascular systems from corrosion cast of real humans livers (A,C) and from the optimization process of our model within a given liver hull (B,D,E).

4.2 Laplace Model

In this model approach, we are searching for a function assigning each liver cell to one of the branches of a vascular tree. The definition of a realistic function must reflect the probability that the ends of the various incomplete subtrees reach and supply a liver cell. Measures for this "reachability" can be expressed by a metric. A cell then is assigned to that branch which has the shortest distance with respect to a suitable metric. The choice of a metric is difficult since the blood supply is realized by complex branching structures, whose formation process is not fully understood (see Hahn[22] for a discussion).

The use of potential functions was inspired by recent advances in statistical physics dealing with growth models for branching structures known as Laplacian fractals (lightning, viscous fingering, electrochemical deposits, and other deposits driven by diffusion) [24-26]. The Laplace model (cf. Fig. 9) is based on a fundamental equation of physics and offers interesting venues for a scientific understanding of the prediction method. Details of this model and its implementation can be found in Selle[12].

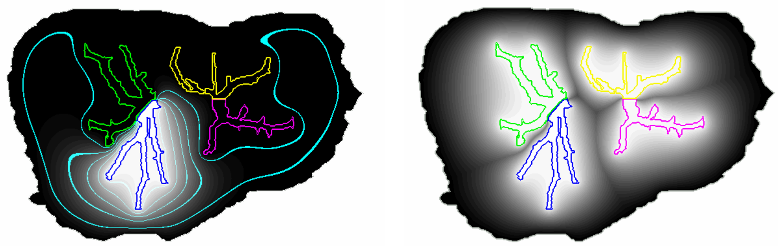

Fig. 9 Laplace Model using a metric based on potentials. Left: The potential for the single branch (blue) is set to 1 (white) and to 0 (black) for the other branches and the region outside the liver. The gray values for the other cells indicate the potential ranging between 0 and 1. Lines indicate surfaces of equal potential. Right: The maximum of the potential functions for all branches reveals the segment boundaries.

4.3 Nearest Neighbor Model

Assuming the most popular distance measure, the Euclidean distance, as metric for the "reachability" measure, we get another model for our assignment problem. The Nearest Neighbor method is conceptually simple and has rather low computational complexity. When comparing the results of the two assignment functions for the eight corrosion casts (cf. section 4.4), the differences for the liver territories are quite small[12,13]. Regarding our problem of liver subdivision, the territories are relatively rough shapes and the deviations are more prominent for smaller structures. Having in mind the medical problem of liver surgery, it is obvious that the differences for the territories are smaller than the achievable surgical precision. Therefore, the computational fast algorithm is utilized for clinical routine.

4.4 Model Evaluation

As an example we will show the anatomical evaluation for the quality of approximated territories. The validation of the methods is based on a study on eight vascular corrosion casts of the human liver[2,12]. High-resolution CT scans of the corrosion casts allow for extracting the portal branches with an accumulated length of about 10–18 m (contrary to in vivo data with a length of only 1–1.5 m). This yields sufficient branching generations for the determination of location and geometry of portal liver territories. For this work, we choose branches that define the segments according to the scheme of Couinaud (Fig. 10, upper left). The gaps between the branches were closed with morphological dilation and erosion operations. Due to the large number of branching generations extracted, the resulting solid portal segments provide a precise approximation of the true anatomical segments.

The derived segments have been compared with liver segments manually specified by anatomists[2]. To simulate the incomplete portal trees obtained from in vivo radiological data, we systematically pruned the trees obtained from the casts (Fig. 10, upper row). Finally, the predictions made for the pruned casts and the exact segment anatomy of the cast were compared to validate the approximation methods. For the validation study, we distinguish three degrees of pruning, covering the different "quality levels" of the portal vein, which are expected to be found in clinical CT data of different quality.

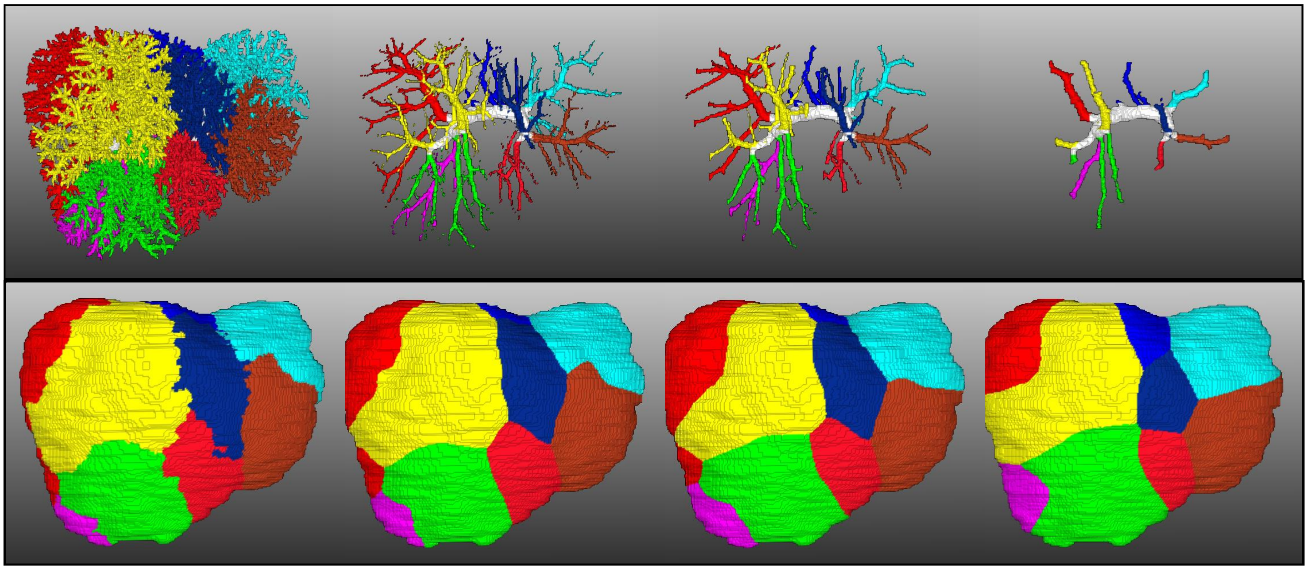

Fig. 10 Rendering of the portal vein obtained from a CT scan of a human liver cast. The main subtrees in the corrosion cast (upper left) are labeled by colors representing the liver segments. The pruned vessels (upper row) simulate the rather incomplete trees obtained from in vivo CT scans. Based on these pruning levels, the liver segments (lower row) are predicted with the Laplace model and compared with the authentic anatomical segments (lower left).

A quantitative evaluation of the accuracy of the approximation methods was carried out by computing the volumetric overlap between the approximated and the authentic segments. The Laplace method predicts the portal segment volumes with accuracy between 80% for the third order branches (Fig. 10, upper right) and 94% for branches that can be extracted in currently optimal multi-detector CT data[12,13].

5. APPLICATION OF MODELS

In the previous chapter we have utilized our model for a subdivision into territories of common supply or drainage. For the application to our initial problem of risk analysis for tumor resections we closer examine the vessels extracted from the images and label all branches and dependent subbranches that are located within a specific safety margin around the lesion. Every labeled branch supplies or drains a dedicated liver region that defines the corresponding risk territory for this vessel, lesion, and safety margin, respectively (Fig. 11). These risk territories provide the basis for subsequent analysis steps and for the final resection proposal. Before proceeding with the actual surgical planning, we will analyze more closely the complex interrelationship of tumor position, safety margin and affected volumes.

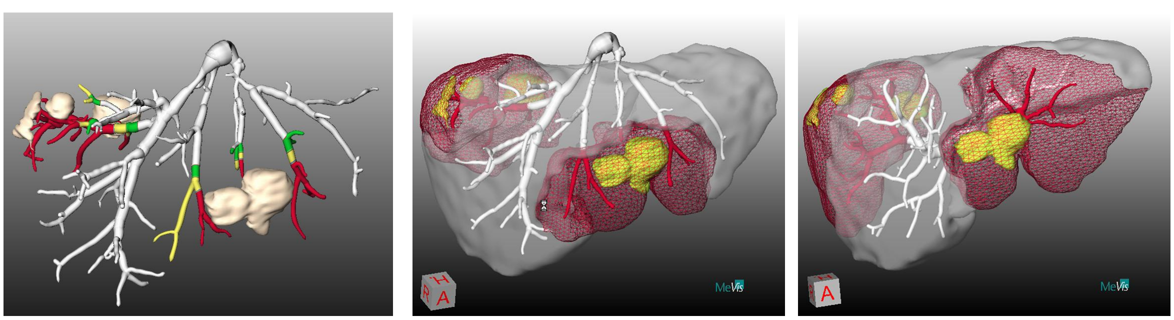

Fig. 11 Risk analysis with multiple metastases. The colored subbranches of the hepatic vein would be affected if the metastasis was resected with a safety margin of 5mm (red), 10mm (yellow) or 15mm (green).Based on the vascular analysis (left) the risk territories are computed for the hepatic veins and a safety margin of 1cm (middle). Risk analysis for the portal vein of the same patient is shown in the right image.

5.1 Combine Risks

The next step would be to combine the risks from each individual vascular system. Before this, we will take a more general view to the relation of safety margin and liver volumes at risk. Following the nearest neighbor model (section 4.3), a Voronoi tessellation of the liver volume according to the centerline voxels of the segmented vascular structure approximates the perfusion or drainage areas. Combining this information with a distance transformation with respect to the tumor boundary and taking the hierarchical dependencies of the vascular tree into account, a "safety map" of the liver can be calculated. This map then encodes the safety margin at which each particular volume will be affected by the tumor. The combined risk of different vascular systems can then be simply computed by assigning each voxel the minimum value of the individual safety maps. The quantification of compromised volume as a function of the safety margin is extracted from these maps by histogram analysis. Fig. 12 exemplifies the interrelation of safety margin and territories at risk for a given tumor position. The discontinuities in the compromised volume curves (Fig. 12 bootom right) correspond to the transection of major vessels, setting the dependent territories at risk. Hence, these curve discontinuities directly correspond to sensitive parameters for the surgical planning: Given that the corresponding safety margin is required to guarantee the R0-resection, the surgeon has to decide, whether the loss of functional volume in this magnitude can be tolerated.

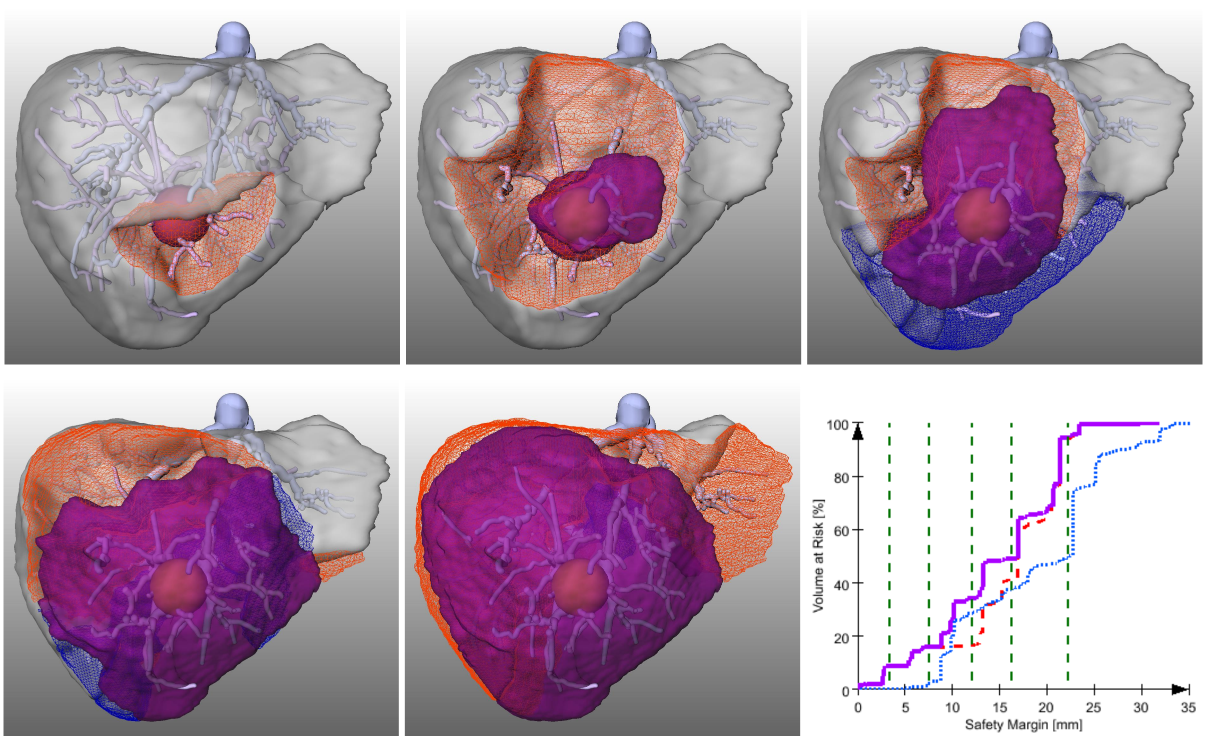

Fig. 12 Risk volumes as function of the safety margin. An artificial spherical tumor and the impaired volumes for hepatic veins only (dark blue), portal veins only (light red) and for both vascular system (purple) with safety margins of 3.4mm, 7.6mm, 12.1mm, 16.3mm, and 22.2mm are visualized. The diagram in the lower left shows the risk volume as a function of the safety margin (dotted: hepatic vein, dashed: portal vein, solid: combined).

5.2 Cascading Risks

Due to the entanglement of the different vascular systems within the liver, it is in general not possible to remove reasonable parts of the liver in such a way that the supply as well as the drainage will completely be ensured for all parts of the remnant. As the risk territories for the different vascular systems do not overlap with each other exactly, the removal of any of these territories will cut off some primarily not affected parts of the other vascular systems, respectively (cf. Fig. 13). Hence, the removal of a primary territory at risk from one vascular tree will in general enlarge the affected volumes induced by the other vascular systems and vice versa. The resulting cascading of risk areas is most prominent for centrally located lesions, but will appear in the peripheral regions as well, where the vascular systems are more unidirectional. As a consequence, surgical resection planes must be adopted such that as many as possible major vessels are saved. In case of the liver, this is of particular importance for the arterial vessels and bile ducts.

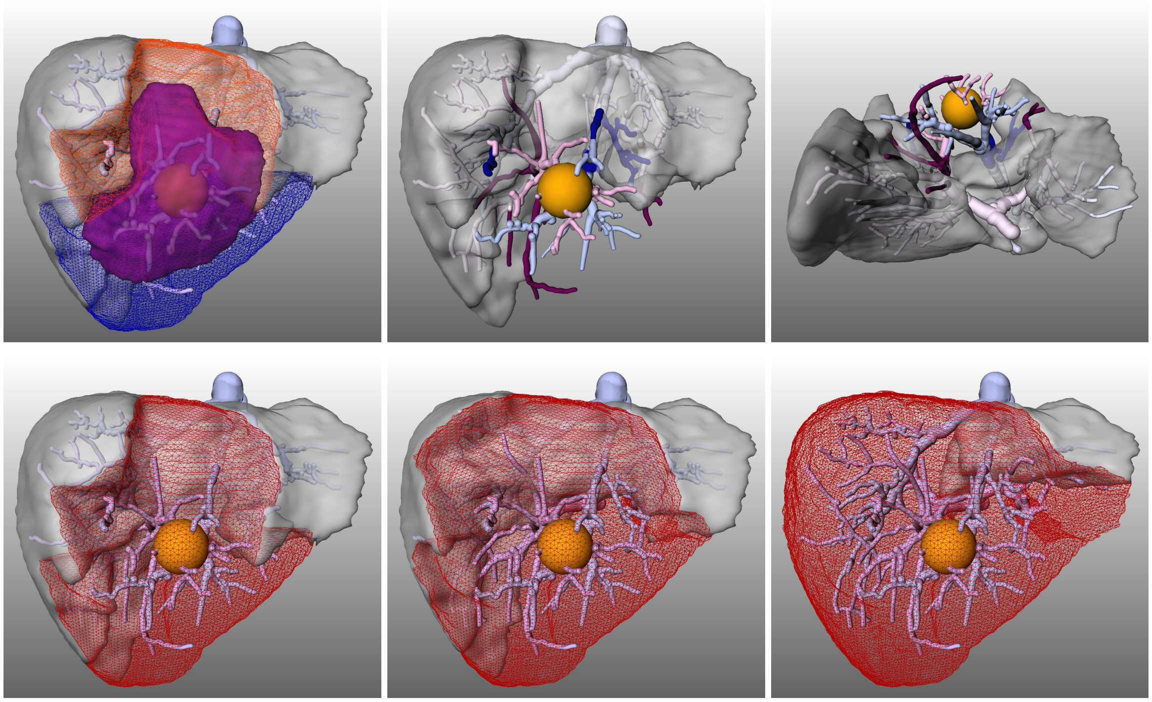

Fig. 13 Cascading of risk territories for an artificial tumor. Upper left: Primary territories at risk for hepatic vein only (dark blue), portal vein only (light red) and for both vascular systems (purple). Upper middle and right: Impairment of vascular systems (light colors: impaired by safety margin, full colors: impaired by collateral risk territory).Lower row: Cascading of risk territories (left to right: primary territories at risk, 1st extension, and 2nd extension).

5.3 Risk maps

As we have discussed in the beginning, the sensitivity of the risk distribution to inaccuracies in tumor localization or intended safety margin reflects the criticality of the succeeding surgical procedure. To give a first guess of the distribution of sensitive and of robust tumor locations in the liver, we conduct a statistical experiment: By placing artificial tumors with an assumed distribution of radii at different locations within the liver, we calculate the probability that a given safety margin will just coincide with the distance to a larger vessel.

For these situations, a small inaccuracy in the resulting surgical procedure will either save or endanger the volume supplied or drained by the vessel in question. Assuming a Poisson distribution with mean size of 3cm for the tumor diameter and a safety margin of 1cm, we get the resulting assessment of sensitivity for a tumor position as shown in Fig. 14. Here 'robust' represents a mean value of less than two substantial clashes for a distribution of tumors located at that specific position and 'very sensitive' represents more than four substantial clashes. We assume a substantial clash, if more than 5% of the liver volume is in question. These risk distributions are evaluated for portal vein and hepatic veins.

In terms of this new definition, the robust positions are located at the outer regions of the organ with no major vessels, but interestingly also in the very central part of the liver (Fig. 14). In this central region, the nearest affected vessel often leads to a loss of the total liver or of a complete liver lobe, hence the mean number of critical clashes is low – even though a tumor at this position might be inoperable. The most critical positions in terms of uncertainty or inaccuracy are located half way out from the central vessels. In these regions, the segmental structures of both vascular systems interweave each other. The resulting risk maps give a first guess about the locations of tumors, for which a precise planning of the surgical strategy promises the most benefit.

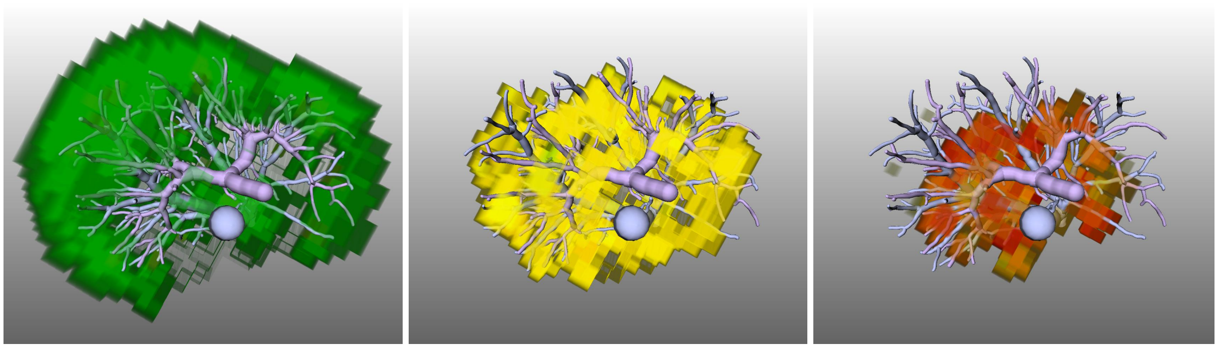

Fig. 14 Sensitivity distribution for tumor positions concerning the stability of risk territories: Each cube represents the statistical mean value of sensitivity of the respective position. The images show positions with different levels of sensitivity, from robust to very sensitive (left to right).

6. RESECTION PLANNING AND ADAPTION

We have analyzed the risk distribution and the influence of the parameters location, margin and vascular system in detail. Now the question arises how can we create an adequate resection proposal for a specific individual patient?

6.1 From risk territories to resection proposals

Based on the risk analysis for a given safety margin that is defined by the surgeon or derived from the margin-volume function (cf. section 5.1) we can compute the risk territories for the portal vein and the hepatic veins (Fig. 15). It is obvious, that the intersection of these territories should be part of the resection proposal as it includes the tumor and represents a region without supply or drainage.

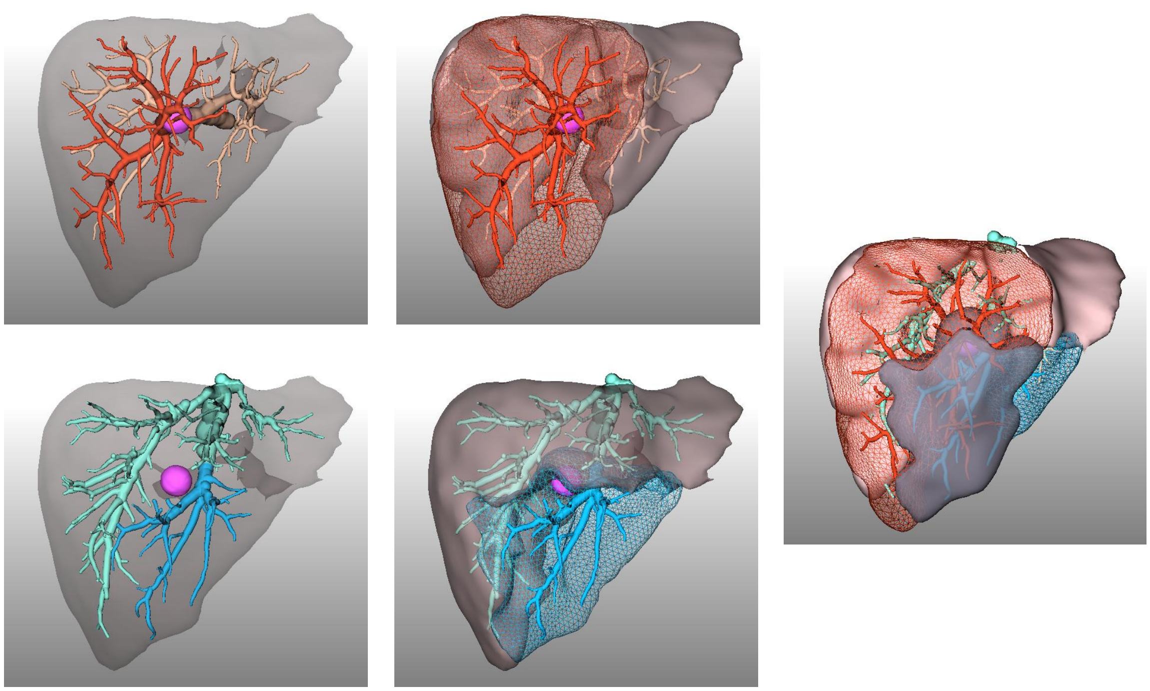

Fig. 15 Risk analysis and territories. A hypothetical spherical tumor has been placed in a clinical dataset. Vessels transected with a given safety margin are marked as darker structures (left) and risk territories are visualized with a mesh surface (middle). Combining the risk analysis for portal vein (upper row) and for hepatic vein (lower row) we get the joint risk territory (right) derived as the union of the two risk territories. The intersection of the portal and the hepatic risk territories contains the tumor and should be part of the resected parenchyma (right, continuous surface).

The first resection proposal that would come into one's mind is the union of the two risk territories. But, as the discussion in section 5.2 has shown, a resection of this area would result in additional impaired liver regions without perfusion or drainage and, thus, the resection proposal should rather be smaller (Fig. 16). In general, the optimal resection plane lies between the intersection and the union of all risk territories.

Our experience and the discussion with our surgical partners have shown that besides the results of the risk analysis several other factors have to be considered for an adequate resection proposal. Some of these factors are 1) maintenance of import supplying vessel branches (hepatic artery and portal vein), 2) access to the tumor 3) minimal resection surface 4) consideration of typical, well experienced resection types (e.g. hemihepatectomy), 5) remaining volume, 6) possibility of anastomoses and reconstruction of vessels, 7) typical surgical approaches for multiple metastases and 8) the option of alternatives such as radiofrequency ablation. Fig. 17 shows a resection proposal that was defined interactively with our software,[27,28] and preserves the large branch of the right hepatic vein that was transected with the automated resection proposal based on the union of risk territories (cf. Fig. 15). In conclusion, it is an ambitious task to create feasible automated resection proposals and unclear if it is even possible for all cases.

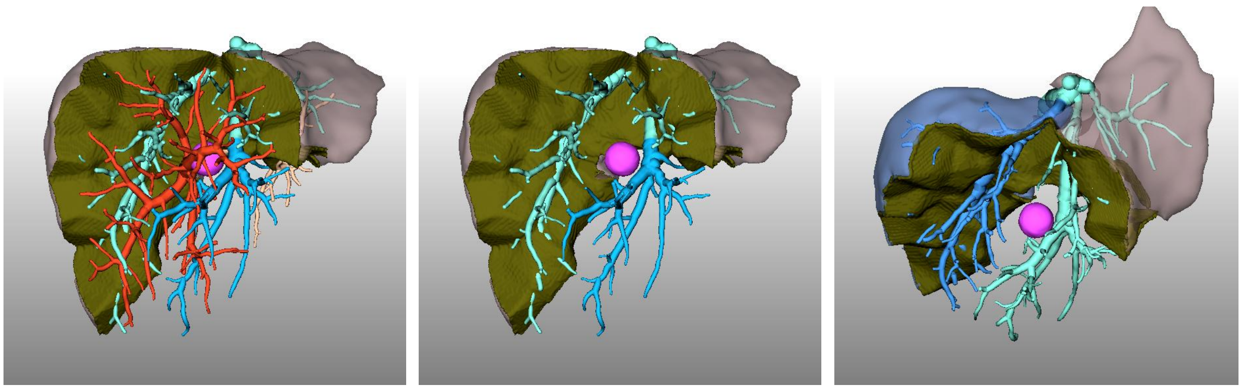

Fig. 16 Automated resection proposal. Using the union of portal vein and hepatic vein risk territories as a resection proposal, would lead to interference of additional vessels. Here, the right hepatic vein would be transected and the rest of the right hemiliver would be without drainage (dark).

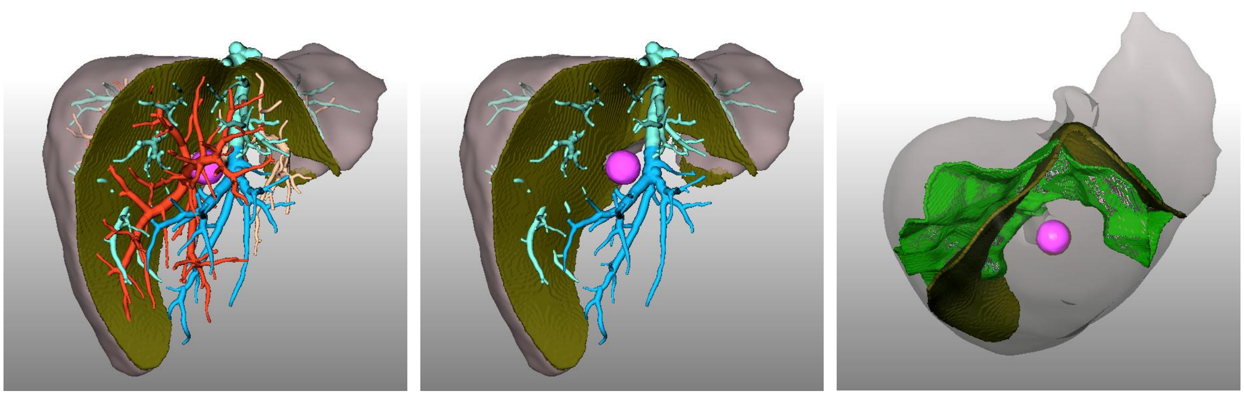

Fig. 17 Interactive resection proposal and comparison. The manually defined resection proposal preserves the main branch of the right hepatic vein (middle) and reflects with its smoothness the surgical practicability. A comparison of the two resection proposals in the cranio-caudal view (right).

6.2 Resection proposals for living donor liver transplantation

In living donor liver transplantation (LDLT) the liver of a voluntary healthy donor is divided into the graft for the recipient and the remnant liver that remains in the donor. In contrast to the donation of the relatively independent left lateral lobe graft for a pediatric recipient, the adult living donor liver transplantation (ALDLT) requires a subdivision of the right liver lobe near the middle hepatic vein (MHV) (Fig. 18). Due to the complex vascular liver anatomy and the restricted liver volume that has to be sufficient for both the healthy donor and the diseased recipient, a detailed risk analysis is mandatory for this intervention[29].

Each resection proposal in ALDLT is based on the main bifurcation of the portal vein and a subdivision of the liver into right and left portal vein territories. This is caused by the fact that, e.g. for right lobe grafts, the right branch of the portal vein will be anastomosed to the stump of the central portal vein in the recipient. The subdivision still leaves a large degree of freedom for the resection line. Since there are usually no other relevant branches of the portal vein in the central area, the risk analysis is concentrated on the draining MHV. As stated above, one major problem in LDLT is a sufficient volume and more precisely a sufficient 'functional' volume. The required volume for donor and recipient is dependent on size and weight of the person and therefore critically in particular with small donor livers. Territories that depend on transected subbranches of the MHV are at risk of insufficient drainage and postoperative function. Therefore, this volume is subtracted from the graft or respectively from the remnant volume. The resection proposal is not only depending on the functional volume in donor and recipient, but also on the individual surgical strategy of each LDLT center and surgeon. Regarding this strategy, a typical resection can be located directly near the MHV, in a distance of 1-2cm and depending on the assignment of the MHV to graft or recipient on the left or right side of the MHV. Recently, left liver lobes are also considered as grafts in LDLT, changing the resection proposal due to the subdivision of the portal vein at the other, the right side of the bifurcation.

In conclusion, resection proposals for ALDLT are based on a rough subdivision of the portal vein into left and right branch but the final decision if the liver volume is sufficient for donor and recipient and the exact resection proposal is mainly influenced by the risk analysis for the MHV.

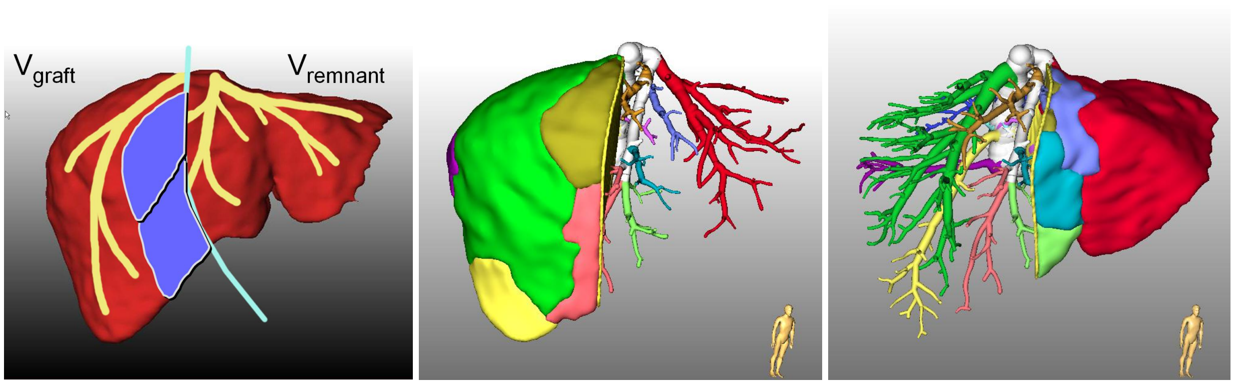

Fig. 18 Risk analysis for adult living donor liver transplantation. Left: With the planned resection two larger branches of the middle hepatic vein (MHV) will be transected. The dependent territories (blue) are at risk of insufficient drainage and postoperative function. The risk analysis for a graft without MHV shows drainage territories that are at risk and therefore potentially reduce the functional graft volume (middle). A risk analysis with a resection proposal procuring the MHV for the graft shows the regions with potential outflow obstruction in the donor (right).

6.3 Intraoperative adaptation of risk assessment

In oncologic liver surgery, additional tumors that were not visible in the preoperative images are often found during the intervention. With such findings, the resection strategy must be updated or completely revised. To provide surgeons with an efficient tool for the quantitative assessment of planning, which is integrated in the workflow of oncologic liver interventions, the planning system is combined with an ultrasound-based navigation system.[30-32] Beside providing means to transfer the preoperative planning onto the patient's situs, the combination of planning and navigation systems allows to determine exact position and size of a new found tumor and transfer these information to the planning system.

For this purpose a registration technique for intraoperative ultrasound images and preoperative planning data is required. We implemented a progressive registration method that is robust, executable in real-time and interactive adaptable. Therefore the surgeon defines a small set of corresponding markers in the preoperative radiologic data and the intraoperative ultrasound images (usually at ramifications). In a first step, an affine transformation is computed in real-time and is applied to the preoperative data. If needed, the surgeon can refine the result in a second step by applying a non-linear registration method.

Fig. 19 Intraoperative adaptation of planning. Top left: GUI of the planning system showing the risk analysis for a pig's liver with artificial tumors after applying a risk analysis adaptation. Top right: Preliminary evaluations in the operating room using the planning system (left monitor) and the ultrasound-based navigation system (right monitor) for laparoscopic liver surgery. Bottom: Scheme of data exchange between planning system and navigation system for the intraoperative incorporation of a newly detected tumor.

Tumor size and position are determined by the surgeon who defines the new found tumor directly on the ultrasound image by drawing a circle around the tumor. For simplification, tumors are assumed to be approximately spherical in shape. Once the tumor is added to the planning model a new risk analysis is performed and the results are transferred back to the ultrasound-based navigation system. After a computation time of less than 30 seconds the planning update is visible on the ultrasound screen. Furthermore, it is possible to delete added tumor or change their attributes. Fig. 19 illustrates the XML-based exchange protocol, defined between the planning software and the navigation system.

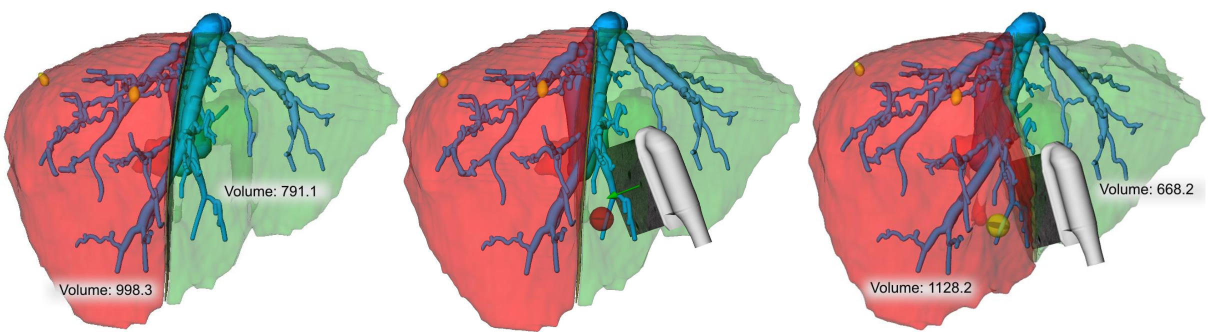

Fig. 20 Left: Preoperatively planned right hepatectomy. The right part of the liver model (red) shows the parenchyma to be resected, while the left part is intended to remain. The yellow nodules represent segmented metastases. Middle: A new resection plane is defined with the ultrasound-based navigation system. The red sphere represents an intraoperative detected tumor. Right: The preoperative resection plane is merged with the resection plane defined intraoperatively and the volume calculation is updated.

Based on the new risk situation the surgeon can define an adapted resection surface interactively by using the navigated ultrasound probe as input device: In order to sculpt an arbitrary shape around newly detected tumors (e.g., a wedge-shaped resection) the surgeon can define a set of planes using the ultrasound plane as reference (cf. Fig. 20). First tests in the operating room confirmed that in case of newly discovered tumors an adaptation of a preoperative risk analysis is a beneficial support for precise liver surgery. The combination of planning system and navigated ultrasound offers a crucial decision support, is easy to use and integrates smoothly into the clinical workflow. The new system provides major support for evidence-based decision making in the surgical theatre and thus improves the safety of the surgical interventions.

Moreover, the availability of planning data directly at operation table calls for the development of special visualization methods supporting the cognitive needs of the surgeons in the surgical workflow. E.g. in case of parallel visualization of ultrasound plane and the 3D planning model, occlusion of the ultrasound by the planning model is an inevitable problem.To address these problems, we define three guiding requirements to ensure clinical applicability[31]:

1. **Diagnostic Usability**: While the whole visualization is presented in a single view, ultrasound information should always be visible, even if it would be occluded by planning data or parts thereof.
2. **Orientation Aid**: Spatial relations between ultrasound plane and planning data should be clearly perceivable without rotating or translating the camera.
3. **Error Identification**: Since recent intraoperative registration methods make a compromise between real-time and error-prone computation, a clear hint to perceive registration errors should be provided.

The main objective of our visualization approach is to provide the surgeon with a focus view on the ultrasound plane and a context view on the planning model in order to ensure diagnostic usability.

To optimize the intraoperative guidance furthermore, the use of non realistic rendering techniques for the condensation of information is of major interest. E.g. the distance to critical structures can be color-coded on planned resection surface to attract the alertness of the surgeon.

7. CLINICAL EVALUATION

A typical clinical evaluation requires a study with a randomized decision of utilizing the results of the risk analysis or not and the subsequent evaluation of clinical criteria, i.e. patient outcome in terms of 5-year-survival, complication rate, tumor recurrence, blood loss and others. There are two reasons why this standard evaluation procedure is not suitable for the software-assisted risk analysis. First, it is ethically not justified to leave out information that helps the physician in decision making and operation planning and second, the clinical criteria of the study depend on multiple factors, e.g. medical history of the patient, degree of liver steatosis, experience of the surgeon, surgical technique that would require from the statistical point of view an enormous, not achievable number of cases for reliable conclusions.

Nevertheless, it is possible to analyze a dedicated aspect for application of the model-based risk analysis. Lang et al showed that with 15 oncologic resections, the surgical strategy was changed in one third of the cases when taking the results of the risk analysis into account[33]. In another study, results of the resection of hilar cholangiocarcinoma with the preoperative analysis were compared to older interventions where the software was not available. Here, the sensitivity, specificity and accuracy of the new methods proved to be significantly higher and even increased the R0-rate from 62.3% before 2002 to 92.9% with our software[34,35]. In a recent case of liver metastases that were treated preoperatively by chemotherapy, one lesion was no longer visible in CT data and not palpable during surgery. Therefore, the resection was performed as one of the first world-wide as navigated surgery and on basis of the risk analysis and planning that was made on a combination of the two CT data sets before and after chemotherapy.[36] In living donor living transplantation, an algorithm for the surgical operability was developed that is based on the results of our risk analysis for the middle hepatic vein[43].

Several other clinical partners have approved the usefulness of the risk analysis and preoperative planning for oncologic surgery[37-42] as well as for living donor liver transplantations[43-55].

8. CONCLUSION

We have presented an example how mathematical models can be applied to a medical problem: the analysis of vascular structures and the approximation of liver territories supplied or drained by them. The evaluation with corrosion casts showed how the quality of image data influences the correctness of the segment approximation and helps to estimate errors and indicates the robustness of the model. Based on the model, we developed a risk analysis for liver surgery. Discussing miscellaneous aspects of combined risk territories and the difficult transfer from the risk analysis to a clinically useful resection proposal, we showed what problems have to be overcome before a model could be applied in clinical reality.

Our approach provides a new, measurable and objective basis for the assessment of risks in liver surgery and the development of new surgical standards. Since 2002 we have analyzed more than 2900 data sets from more than 95 clinical sites world-wide and transferred our research results into a commercially available service[56]. More than half of the processed cases are related to living donor liver transplantations and more than 1000 data sets were analyzed for oncologic resections. About 250 analyses were performed for surgical interventions of other organs e.g. kidney and lung, and show that our approach is not restricted to the liver but can also be applied to other organs characterized by hierarchical vessel systems.

The application of models to radiological data gives an example how medical image computing can provide a basis for new developments and values for diagnosis and therapy. Essential in this context is the step from subjective interpretation to reproducible quantification. Computer-assistance in medicine is an interesting and valuable field for mathematical and scientific approaches and can be achieved in an intensive interdisciplinary cooperation of mathematicians, scientists and medical experts.

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