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Radiopaque Fiducials Guiding Laparoscopic Resection of Liver Tumors

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Background: Minimal invasive laparoscopic resection of liver tumors is less traumatic compared with open surgical resection and may be a better option for many patients. However, localization of intrahepatic tumors remains a challenge. Availability of hybrid operating rooms, equipped for high performance radiologic imaging, allows for new methods of surgical navigation.

Methods: Twelve patients planned for laparoscopic resection of liver tumors were included. Before resection started, tumors were marked with radiopaque fiducials. Four fiducials were positioned with ultrasound within 1 cm of the tumor. Tumor and fiducials were localized with contrast enhanced cone beam computed tomography. Fluoroscopy with an overlay of cone beam computed tomography markings was projected side-by-side on the same screen as the laparoscopic view to visualize tumor location. The fiducials were eventually removed. Laparoscopic ultrasound, the standard method of localizing a tumor, was also used. The benefits of the 2 visualization methods were estimated by the operator. Procedure times, radiation doses and resection margins were recorded.

Results: Fluoroscopy with radiopaque fiducials provided valuable information, complementing the laparoscopic ultrasound, particularly during the early phase of resection. In the later phase, mobilization of the tumor-containing liver segment caused significant displacement of the fluoroscopic overlay. The technique evolved during course of the study, with decreasing procedure times and radiation doses. Radical resection was achieved for all patients.

Conclusions: Radiopaque fiducials and fluoroscopy can complement laparoscopic ultrasound for guiding resection of liver tumors. Combining radiologic and optical imaging in a hybrid operating suit may facilitate development of augmented reality techniques for surgical navigation.

Key Words: liver surgery, laparoscopy, fiducials, cone beam computed tomography, image guided surgery

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BACKGROUND

Liver resection is a potentially curative treatment for patients with malignant liver tumors.[1] Laparoscopy minimizes the surgical trauma and is generally beneficial, given that it can be carried out with precision.[2,3] However, intraoperative localization of tumors and other vital intrahepatic structures may be challenging. Tumors are not visible in the laparoscopic camera unless located at the surface, or accidentally incised. Intermittent ultrasound, currently used to localize tumors during laparoscopic liver surgery, is a valuable tool, but has limitations. When resecting deep parenchymal tumors, keeping the 3-dimensional (3D) direction of the probe and translating it into an optimal resection line is difficult when the liver is moved and deformed during surgery. In addition, when air enters the resection line after starting the parenchymal partition, the ultrasound image may be blurred with loss of tumor demarcation.[4]

Hypothetically, laparoscopic resection of liver tumors would be facilitated if the optical vision provided by the laparoscopic camera could be augmented with 3D information on the location of tumors and other vital structures, beyond the liver surface. Such augmentation would require use of high definition diagnostic imaging together with an advanced navigation system.

Similar approaches have been developed for neuro-surgery and spine-surgery,[5,6] where rigid bone structures provide accurate landmarks for registration. But for soft tissue abdominal surgery, severe deformations and movements of tissue during the surgical procedure pose additional challenges. One potential way to overcome this is to combine and integrate the optical laparoscopic vision with a real-time see-thru modality such as fluoroscopy. However, neither tumors nor other intrahepatic structures are directly discernable on fluoroscopy; they need to be enhanced, or marked.

In this study we explored a new strategy to visualize the location of intrahepatic tumors during laparoscopic resection by marking the tumor with nearby radiopaque fiducials and combining the laparoscopic and the radiographic techniques in a hybrid operating environment. The overall aim was to develop a workflow where the position of the tumor can be traced during the procedure as a complement to the use of ultrasound.

METHODS

Patients

Twelve patients with liver tumors planned for laparoscopic resection between May 2016 and November 2019 were included. Three were diagnosed with hepatocellular

TABLE 1. Patients, Diagnoses and Procedures

Patients No.	Age (y)	Diagnosis	Fiducials	CBCT Tumor Enhancment	Liver Segment	Tumor Size (mm)	Radical Excision (Minimum Marginal) (mm)	Procedure Time
1	52	Benign*	Coils	Arterial	4	30	Yes (10)	6 h
2	72	CRLM	Coils	Arterial	6	22	Yes (3)	4 h 21 min
3	61	CRLM	Coils	Arterial	8	13	Yes (7)	3 h 3 min
4	76	CRLM	Coils	Arterial	8	12	Yes (1)	6 h 30 min
5	44	CRLM	Gold rods	Arterial	5	27	Yes (7)	6 h 5 min
6	59	CRLM	Gold rods	None†	8	12	Yes (13)	7 h 10 min
7	70	CRLM	Gold rods	Arterial	4b	20	Yes (6)	4 h 30 min
8	69	CRLM	Gold rods	Arterial	4b	32	Yes (1)	8 h 30 min
9	67	BDC	Gold rods	Venous	5, 6, 7	20	Yes (7)	7 h
10	61	HCC	Gold rods	Venous	8	43	Yes (13)	6 h 10 min
11	52	HCC	Gold rods	Venous	5, 6	80	Yes (5)	4 h 10 min
12	74	CRLM	Gold rods	Venous	6, 7	32	Yes (10)	4 h 29 min

*HCC was suspected based on radiologic imaging but microscopy of resected sample showed no malignancy.
†Patient 6 had a hypovascular tumor that could not be reliably outlined with arteriography.
BDC indicates bile duct cancer; CBCT, cone beam computed tomography; CRLM, colorectal liver metastasis; HCC, hepatocellular carcinoma.

carcinoma, 8 had colorectal metastasis and 1 had bile duct cancer. In all cases the planned resection volume was < 2 liver segments. Demographics and details on patients are listed in Table 1. All patients were informed by a liver surgeon and signed an informed consent to participate. The study was approved by the regional ethic review board (Dnr 592-16).

Preoperative Computed Tomography (CT)

A multidetector CT with arterial and portal phase contrast enhancement was acquired preoperatively for diagnosis and planning of the invasive treatment.

Venue and Peroperative Procedures

The procedures were done in a hybrid operating room equipped for both laparoscopic surgery and interventional radiology. For the laparoscopic procedure, a standard equipment was used including cavitron ultrasonic surgical aspiration for parenchymal transection and a laparoscopic ultrasound transducer (B K Medical, Herlew, Denmark). Due to updating of radiologic imaging apparatus in our institution, and to the exploratory nature of the project, equipment and certain procedural details changed over time to improve the workflow. The radiologic equipment for the first 4 procedures was an Artis zeego robotic angiographic system and for the remaining 8 procedures an Artis pheno robotic angiographic system (both Siemens Healthineers, Forchheim, Germany).

Fiducial Marking of Tumors

Four radiopaque markers (fiducials), were percutaneously implanted in close proximity, within 1 cm, from the tumor and within the planned resection volume, without touching the tumor. Two different methods of implantation and 2 types of fiducials were used. In the early phase of the study, the implantation was done before final positioning and draping of the patient, guided by percutaneous ultrasound and fluoroscopy. In the later phase, the implantation was done after CO_2 insufflation of the abdomen, guided by laparoscopy and laparoscopic ultrasound. In the first 4 patients, endovascular coils were used as fiducials, delivered through a 21 G needle using an 0.18-inch guidewire as coil pusher. In the remaining 8 patients, gold rod markers of 1×5 mm, primarily developed for guiding radiation therapy (CyberMark, Civco Radiotherapy, Iowa) were used as fiducials. The gold markers are pre-mounted in dedicated delivery needles with integrated push-wires for release.

Peroperative Cone Beam Computed Tomography (CBCT)

After implanting the fiducials, a peroperative contrast enhanced CBCT was acquired to locate the tumor in the coordinates of the angiographic system and in relation to the fiducials. Again, 2 different CBCT protocols were used over the time span of the study. In the first 8 patients, the tumor was visualized with arterial contrast enhancement (Fig. 1). An angiographic microcatheter was placed in the hepatic artery or one of its branches. Contrast concentration was 100 mg iodine/mL, volume 32 mL, injection rate 4 mL/s and x-ray delay 3 seconds. However, in one of these patients the tumor was avascular and could not be reliably defined. In the last 4 patients the tumor was visualized with parenchymal phase contrast enhancement. The benefit of this approach was that selective catheterization of a liver artery was not necessary. Contrast was injected in the cubital vein, 350 mg iodine/ml, and the volume was adjusted for a total dose of 500 mg iodine/kg body weight. In all cases CBCT was done using a 5 second C-arm rotation in landscape mode (5s Dynamic CT Body).
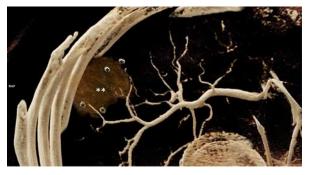

FIGURE 1. Volume rendering depiction of a cone beam computed tomography with contrast enhancement from a catheter positioned in the hepatic artery. The tumor (two white asterisks, **) is discernible due to its arterial blood supply. The 4 gold fiducial markers in the immediate vicinity of the tumor (black asterisk, *) are highly radiopaque.
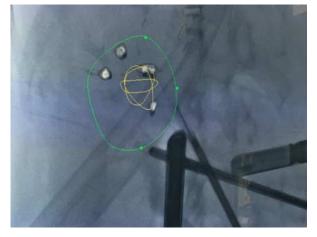
FIGURE 2. Fluoroscopic view with overlay from perioperative cone beam computed tomography (CBCT) during laparoscopic resection. The tumor is highlighted with yellow ellipsoid markings, manually made in the CBCT volume. The planned resection line on the surface of the liver is marked with a green circle. Four coil fiducials are highlighted as white patches, created by processing the CBCT image, and visible also as dark patches, due to their high radiodensity. In this image the white and the dark patches are nearly perfectly aligned, confirming good position of the overlay in this projection. The laparoscopic instruments are visible in the lower right quadrant of the image.

Overlay on Fluoroscopy Screen

Fiducials and tumors were manually marked in the CBCT volume by outlining them with lines or ellipses in 1 or 2 projections, using the Syngo software tools. In some cases, the planned resection border on the liver surface was also marked. The line markings were displayed as a dynamic overlay on the fluoroscopy screen (Fig. 2).

Localizing Tumor During Resection

During the resection, the C-arm of the angiographic robot was positioned to project the laparoscopic instruments and the fiducials on real-time fluoroscopy without disturbing

FIGURE 3. Positioning of patient, angiographic C-arm, and laparoscopic instruments. The C-arm of the angiographic robot traverse the operating area from the patients left cranial quadrant. The operators are positioned in the left caudal quadrant, looking at the screen on the right side of the patients (Fig. 4).

FIGURE 4. The large combined screen in the hybrid operating suite projects the optic laparoscopic image (top right) side-by-side with the fluoroscopic image (top left, on this image without the markings from the cone beam computed tomography). The cone beam computed tomography volume is visible in the bottom left section of the screen.

the operators (Fig. 3). Most of the time, this projection coincided approximately with the optical view of the laparoscopic camera, giving the operators guidance on the location of the tumor in 2D. To assess how deep into the liver the tumor was located in relation to the dissection plane, the C-arm was occasionally adjusted to a projection perpendicular to the optical view. The fluoroscopy image (with line markings from the CBCT) was shown side-by-side with the laparoscopic camera view on the same large screen (Fig. 4). The accuracy of the overlay was estimated by the sideway displacement between the real-time-fiducials on fluoroscopy and the overlaid fiducial markings from the CBCT. Whenever a significant displacement between the 2 occurred, the overlay was adjusted by realigning the fiducial-markings-on-overlay with the fiducials on fluoroscopy, yielding a correct 2D tumor location in that projection. To correct for displacement in 3D, realignment was done in 2 separate, and > 60 degrees divergent, C-arm projections.

Workflow During Laparoscopic Resection, After Adjustments

After experience-based adjustments of the procedure protocol, the resulting workflow was: (1) Induction of general anesthesia. (2) Laparoscopic insufflation of abdomen and mobilization of the liver, if necessary. (3) Percutaneous placement of fiducials (gold markers) guided by laparoscopy and laparoscopic ultrasound. (4) CBCT with intravenous contrast enhancement. (5) CBCT image preparation on the in-site work station. Manual markings of tumor, fiducials and intended resection line on the liver surface and creation of a live overlay on fluoroscopy screen. (6) Laparoscopic resection of the tumor with fluoroscopy guidance (and intermittent laparoscopic ultrasound for confirmation).

Evaluation of Image Guidance

Evaluation of imaging modalities (laparoscopic ultrasound and fluoroscopy with markers) was done using a 0 to 10 scale of value during the procedure (0 = method added no value, 10 = method added excellent value). Benefits and problems experienced by the operator were noted in a case report (CRF) form after each procedure.

RESULTS

The operator-perceived value of the guiding techniques for localizing the tumor during the resection, as estimated by the surgeon, scored higher for ultrasound, mean 7.8, compared with fluoroscopy, mean 5.8. Fluoroscopy was however often considered useful in the initial phase of the resection, when the overlay was not yet offset by motions and deformation of the liver. Fluoroscopy was also considered useful for marking the intended dissection plane on the liver surface with electrocautery.

Changes in the workflow resulted in a gradual decrease in procedure preparation times. Mean preparation time before the resection could start, including induction of anesthesia, draping of patient, placement of radiopaque markers and localizing the tumor with CBCT, decreased from 5 hours and 12 minutes in the first 4 patients to 2 hours and 15 minutes in the last 4 patients. Mean radiation dose area product was $9668\,\mu Gym^2$ (range: 1694 to 19,486 μGym^2). The presence of the C-arm of the angiographic robot in the working area of the surgeons was of relatively little consequence for their working ergonomic and vision of the laparoscopic image screen as long as the C-arm was in the standard anterior-posterior projection.

Limitations of fluoroscopy and fiducials for localizing the tumor included overlay misalignment caused by liver motions and deformations. Respiration movements caused the overlay to be offset by ~0.5 to 1.5 cm with each breath. Deformations due to mobilization of the segment to be resected increased during the procedure at several centimeters at the end. Furthermore, estimating the depth of the tumor in relation to the liver surface required oblique fluoroscopy projections, causing the C-arm to disturb the laparoscopic workflow. Other concerns with the technique included increased duration of the procedure and the inconvenience of wearing radiation protective clothing. In one early patient when percutaneous ultrasound was used to position the marking coils, the tumor was difficult to visualize and the first coils were placed in another segment, too far from the tumor to be useful for guidance. This was discovered on the enhanced CBCT and new coils were placed near the tumor, using the CBCT for guidance. In one patient, when gold rods were used as fiducials, one of the rods was partially placed in a liver vein and subsequently, during the procedure, migrated to the left lung where it remained, also at follow-up CT. After this incidence, all subsequent patients were preoperatively screened for cardiac arteriovenous shunts to preclude the possibility of paradoxical arterial embolization and additional care was taken not to place the fiducials close to vessels.

All tumors were radically resected during procedures. Two patients had extended postoperative care in the intensive care unit. One developed transient organ failure (patient 1) and one had a deep postoperative infection and transient renal failure (patient 6). One patient with a singular colorectal cancer metastasis at the time of the procedure died during follow-up due to generalization of the colorectal cancer (patient 2). Remaining patients were free from local or distant recurrence during a mean follow-up of 18 months (range: 2 to 31 mo). Microscopy evaluation of specimens confirmed the preoperative diagnosis in all patients but one, where no malignant cells were found (patient 1).

DISCUSSION

In this exploratory feasibility study we demonstrate (1) that it is possible to mark liver tumors with radiopaque fiducial markers using percutaneous or laparoscopic ultrasound, (2) that contrast enhanced CBCT can be used to localize and outline liver tumors and establish their spatial relation to implanted fiducials, (3) that fluoroscopy can be used simultaneously with laparoscopy in a hybrid operating suit, (4) that an overlay outlining a liver tumor can be projected on the fluoroscopy image, side-by-side with the laparoscopic image of the liver surface, and (5) that this combination of imaging methods can aid the surgeon in localizing the tumor during resection.

Augmented reality; digital enhancement of a real-life image, has tremendous potential in surgery. Digital constructs from 3D radiologic images can be used not only for diagnosis and preoperative planning, but also for navigation during procedures.[7,8] But for intra-abdominal, parenchymal, laparoscopic procedures, several challenges remain. Tumors are hidden inside organs and are difficult to visualize peroperatively. Movements and deformations caused by breathing and surgical manipulation continuously change the anatomy.

We believe our suggested method has a certain value already as used in this series of patients. This was concluded in the assessment score. Particularly, value was noted for marking the resection line on the liver surface with electrocautery and for navigation during the early phase of the resection, before the anatomy became more distorted. In a later phase of the procedure, when the segment to resect was mobilized and retracted to allow laparoscopic view into the tissue, the accuracy and the value of the overlay decreased. Similarly, a decreased supportive value of laparoscopic ultrasound is also often experienced in the later phase of the parenchymal partition, due to distorted anatomy and air/CO_2 in the field of resection.[9] However, it was concluded by the surgeon's assessment that laparoscopic ultrasound remained the most valuable peroperative tool for tumor localization and its use was not reduced by the introduction of the fiducial-based method.

During the study period, the workflow was optimized and procedure times could be gradually reduced. Fiducial placement before start of surgery, guided by percutaneous ultrasound as done in the early phase of the study, delayed start of the resection and was occasionally difficult to perform if the tumor was located in a less accessible part of the liver. Fiducial placement later in the procedure, when the patient was draped and positioned, using laparoscopic vision and ultrasound, was both easier and quicker. The adoption of dedicated gold rod markers also facilitated fiducial placement. However, the inadvertent migration of one rod to the lung raised concerns of possible paradoxical arterial embolization and prompted yet another amendment to our protocol, preoperative ultrasonography of the heart to exclude transseptal shunting.[10]

The method has shortcomings. Preparations increase total procedure times. Fluoroscopic and laparoscopic views are not yet integrated on the same image. Movements and organ distortions, particularly when the liver and the segment to be resected have been mobilized from surrounding tissues, gradually makes the outline of the tumor less accurate and relevant, although the fiducial markers, placed close to the tumor and remaining in the segment to be resected, are still visible on fluoroscopy, giving the operator a useful perception of where the tumor is located. To estimate how deep into the liver the tumor and the fiducials are located, impractical C-arm projections are necessary, obstructing the operators and interrupting the resection. But

it should be noted that the established method of localizing tumors, laparoscopic ultrasound, also interrupts the resection. Finally, the method adds ionizing radiation to a procedure that otherwise is performed without any radiation. However, the radiation dose was relatively small, approximately one third of what is used for a standard endovascular aortic repair in our center.[11]

The main potential of the presented method may eventually be as a bridge between a see-on-technology (laparoscopy) and a see-throu-technology (fluoroscopy) to enable new inventions in surgical navigation. Navigation (Latin Navis = Ship) is the science of finding a way from one place to another[12] and requires (1) determination of the "self" position and (2) a reliable map of the surroundings. Interventional radiology, a medical discipline based on interventions with see-thru-technologies, utilizes image fusion between preoperative 3D and peroperative imaging as navigation tools during a wide spectrum of procedures, such as fluid drainage, biopsy, ablation therapy and placement of implants. For interventional radiology procedures, both the self-position and the map are determined with see-thru-methods. Navigation during open, laparoscopic and endoscopic procedures is a rapidly developing field with many potential clinical applications.[13,14] However, in current applications, it is theoretically and practically limited by the fact that the self-position is determined by optical methods while the map is created by radiologic see-thru-methods (such as CT and magnetic resonance). Another limitation with current methods for surgical, and in certain aspects also radiologic navigation, is that the map is static while the real world (the patient's anatomy during procedures) is not. Hence, contrary to marine or terrestrial navigation, in surgical and interventional navigation the map must be continuously updated and realigned to remain reliable. Our method, with fluoroscopic tracking of fiducials marking a tumor in the depth of the liver during laparoscopic resections, can potentially generate information and data useful for calculations of movements, deformations and spatial relations between surgical instruments and optically hidden anatomic structures, providing a new interface between imaging methods and promoting development of new integrated techniques for augmented reality in surgery.

CONCLUSIONS

Radiopaque fiducials visualized with fluoroscopy can be used to guide laparoscopic resection of liver tumors. Combining radiologic and optical imaging methods may facilitate development of augmented reality techniques for surgical navigation.

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