Surg Endosc (2001) 15: 135–140
DOI: 10.1007/s004640080066

Surgical Endoscopy
Ultrasound and
Interventional Techniques

Accuracy and effectiveness of laparoscopic vs open hepatic radiofrequency ablation

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Received: 1 March 2000/Accepted in final form: 13 May 2000/Online publication: 21 December 2000

Abstract

Background: The purpose of this study was to compare the accuracy (in terms of ultrasound-guided probe placement) and the effectiveness (in terms of pathologic tumor–free margin) of laparoscopic vs open radiofrequency (RF) ablation.

Methods: Using a previously validated tissue-mimic model, 1-cm simulated hepatic tumors were ablated in 10 pigs randomized to open or laparoscopic techniques. Energy was applied until tissue temperature reached 100°C (warm-up) and thereafter for 8 min. A pathologist blinded to technique examined all specimens immediately after treatment. Analysis was by Fisher's exact test and the Mann-Whitney U test; $p < 0.05$ was considered significant.

Results: Off-center distance (3.5 ± 1.6 vs 4.2 ± 1.4 mm), size (24.7 ± 3.1 vs 25.6 ± 3.8 mm), symmetry (40% vs 73%), margin positivity (33% vs 9%), and margin distance (1.1 ± 1.2 vs 2.2 ± 1.6 mm) were not significantly different between laparoscopic ($n = 15$) and open ($n = 11$) ablations, respectively. The proportion of round/ovoid lesions (20% vs 64%) was lower ($p = 0.043$), and warm-up time (20.2 ± 14.0 vs 10.7 ± 7.5) was longer ($p = 0.049$) for the laparoscopic than for the open groups, respectively.

Conclusion: Accurate probe placement can be achieved using laparoscopic and open RF ablation techniques. The physiologic effects of laparoscopy may alter ablation shape and warm-up time. Additional studies are needed to establish effective ways of achieving complete tumor destruction.

Key words: Radiofrequency ablation — Tumor-mimic — Ultrasound — Laparoscopy — Liver surgery — Porcine model

Radiofrequency (RF) ablation is a focal ablative therapy for primary and metastatic liver tumors. A high-frequency current is delivered through an electrode (the RF probe), which is placed into the tumor under ultrasound guidance. The current causes ionic agitation within the tissue, generating heat and causing cell death. Preliminary reports have shown that RF ablation may be effective [4, 10, 15, 20, 22, 23]; furthermore, it may be safer than other focal ablative therapies, such as cryotherapy [14].

RF ablation may be performed via the percutaneous [15, 23], laparoscopic [3, 22], or open approach [4, 10]. For any of these methods, successful ablation depends on precise targeting of the lesion and the destruction of the entire tumor. To date, the accuracy of laparoscopic probe placement has not been evaluated. Similarly, the effectiveness (in terms of ability to achieve pathologic tumor-free margins) of the laparoscopic approach has not been established. The purpose of this study was to compare the accuracy and effectiveness of laparoscopic vs open RF ablation.

Materials and methods

RF ablation using a tumor-mimic model

Using a previously validated tumor-mimic model [19] (Fig. 1) and a 50 W, 480 kHz generator (RITA Medical, Mountain View, CA, USA), we performed RF ablation in 10 pigs. Approval for this study was granted by the University of Texas Institutional Animal Review Committee.

The animals were fasted overnight and premedicated with an intramuscular injection of Telazol (tiletamine/zolazepam) 4 mg/kg, ketamine 2 mg/kg, and atropine 0.4 mg/kg. Anesthesia was maintained with 1–3% of isoflurane. An endotracheal tube was inserted and connected to a ventilator with a tidal volume of 15–20 ml/kg at a rate of 12–18 breaths/min. Inspired O_2 was maintained at 100%. Pulse oximetry, end-tidal CO_2, blood pressure, and three-lead electrocardiogram were monitored throughout the operation. Respiratory rate and tidal volume were adjusted to maintain an

Presented in part at the annual meeting of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), Atlanta, Georgia, 31 March 2000

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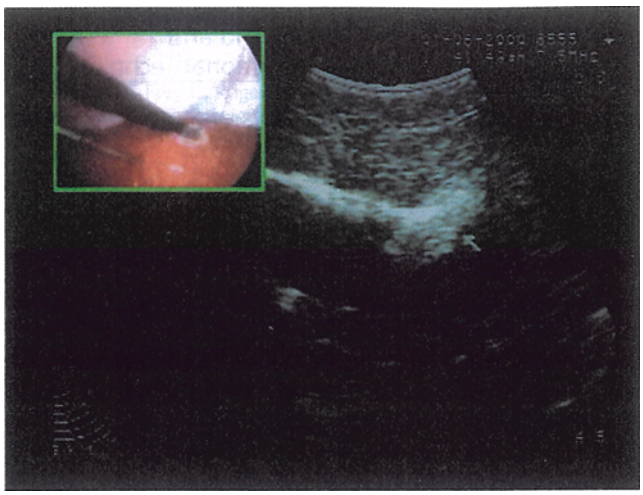

Fig. 1. Laparoscopic and sonographic views of RF ablation probe placement in the longitudinal plane (arrow indicates tumor-mimic).

end-tidal CO_2 of 25–30 mmHg. Intravenous fluids (normal saline) were maintained at 4 ml/kg/h.

The tumor-mimics (3% agarose, 3% cellulose, 7% glycerol, and 0.05% methylene blue) were created using a laparoscopic technique. A CO_2 pneumoperitoneum was established to a pressure of 10–12 mmHg using a Veress needle. Three to four 12-mm ports were used. A 13-cm, 18-gauge needle was flushed with sterile water and placed through the abdominal wall in an area directly overlying the targeted liver tissue. The needle entered the peritoneal cavity under laparoscopic visualization. Using ultrasound guidance, the needle tip was advanced into the liver to a depth of 1.5–2.0 cm, taking care to avoid vascular and biliary structures. A 0.7-cc bolus of the agarose mixture heated to 65°C was injected through the needle into the hepatic parenchyma. The needle was withdrawn and the puncture site cauterized. Additional tumor-mimics were created by placing the needle through the abdominal wall at separate sites. Three tumor-mimics were created in each animal at standardized anatomical locations within the liver. Each tumor-mimic was measured sonographically in three dimensions (longitudinal, transverse, and anterior-posterior) immediately after creation; the measurements were averaged to calculate tumor-mimic diameter.

The animals were connected to a dispersion electrode and randomized to either laparoscopic ($n = 5$) or open ($n = 5$) RF ablation. Randomization was performed using sealed envelopes that were opened after the tumor-mimics were established. The port configuration used for creation of the tumor-mimic was left in place and used for laparoscopic ablations. For the open approach, the ports were removed and a bilateral subcostal incision was made. A 25-cm, 15-gauge RF probe with four semicircular deployable electrodes (3-cm expanded diameter) (Fig. 2) was placed into the center of tumor-mimics using a freehand technique and 7 MHz ultrasound probes (Lynx Ultrasound Unit, B & K Medical, North Billerica, MA, USA).

For the laparoscopic approach, the RF probe was guided into the center of the tumor-mimic by initially placing the probe parallel (Fig. 1) to the ultrasound transducer so that the longitudinal plane was visualized. RF probe placement was performed by a surgeon and radiologist working together. The surgeon (D.J.S.) advanced the shaft of the probe and simultaneously guided the probe tip into the tumor-mimic using a grasper. The radiologist (L.M.W.) provided real-time ultrasound guidance. Once the probe was positioned in the longitudinal plane, a transverse image was obtained and the electrodes were deployed.

For the open approach, a single surgeon (D.J.S.) performed both ultrasound scanning and RF probe placement simultaneously. As in the laparoscopic approach, the RF probe was initially placed parallel to the ultrasound transducer. After the probe was guided to the tumor-mimic center in the longitudinal plane, the transducer was turned 90°, placement was verified in the transverse plane, and the electrodes were deployed.

For each laparoscopic or open probe placement, a difficulty level was assigned according to a four-point Likert scale [6] that was anchored by explicit descriptors, which included "easy," "mildly difficult," "moderately difficult," and "very difficult." The rating was based on the subjective assessment of the surgeon immediately following probe placement for each tumor-mimic.

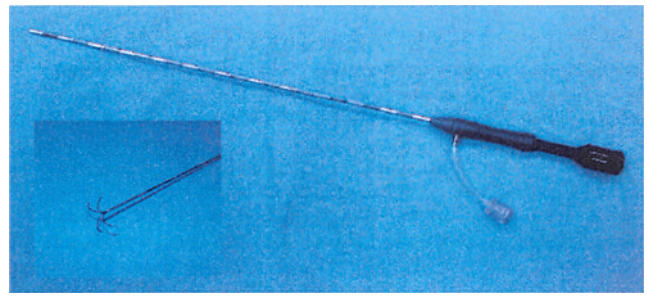

Fig. 2. RF probe with four deployable electrodes (inset).

Tumor-mimics were ablated using a standard protocol [15]. The four deployed electrodes continuously monitored temperature, impedance, and power; parameters were recorded at 30-sec intervals. Maximum power (50 W) was applied until all electrodes reported temperatures >90°C and the average temperature was ≥100°C; this was defined as the "warm-up" phase of ablation. The generator then delivered enough power to main an average tissue temperature of 100°C for 8 minutes.

Pathologic examination

A single pathologist (G.L.) who was blinded to ablation technique reviewed all specimens immediately postoperatively. The livers were serially sectioned parallel to the axis of the RF probe tract (defined as the longitudinal plane) in 4-mm slices. Representative portions of treated tissue were frozen, sectioned in a cryostat at 5 μ in thickness, and stained using routine hematoxylin-and-eosin (H&E) methods and a histochemical technique for tissue oxidative enzymes using nicotinamide adenine dinucleotide (NADH) [20]. Ablation shape, size, symmetry, off-center distance, and margins were determined. Longitudinal, transverse, and anterior-posterior measurements of the ablated tissue were averaged to calculate ablation diameter. "Off-center distance" was defined as the distance between the center of ablated tissue and the center of the tumor-mimic, as measured on gross examination.

Data analysis

SigmaStat software (SPSS Inc., San Rafael, CA, USA) was used for data analyses. Summary data are presented as mean ± standard deviation (SD). Comparisons between the laparoscopic and open groups were made using Fischer's exact test and a two-tailed Mann-Whitney U test. Statistically significant differences were defined as $p < 0.05$.

Results

Ten consecutive pigs with a mean weight of 46 ± 4 kg underwent tumor-mimic creation and RF ablation. Pigs 2,4, 8, 9, and 10 were randomized to laparoscopic ablation; pigs 1,3,5,6, and 7 were randomized to open ablation. Three tumor-mimics were created and ablated in each animal. Pig 3 (open) died during tumor-mimic creation, so the data were excluded. One tumor-mimic creation in the open group (pig 1) was unsuccessful. Data were available for 15 laparoscopic ablations and 11 open ablations.

Tumor-mimic size (9.6 ± 2.1 vs 10.0 ± 2.0 mm) was not different for the laparoscopic and open groups, respectively ($p = 0.599$). Probe placement difficulty ratings were higher (more difficult) for the laparoscopic approach (3.0 ± 0.8) than for the open approach (1.5 ± 0.7) ($p = 0.001$). Opera-

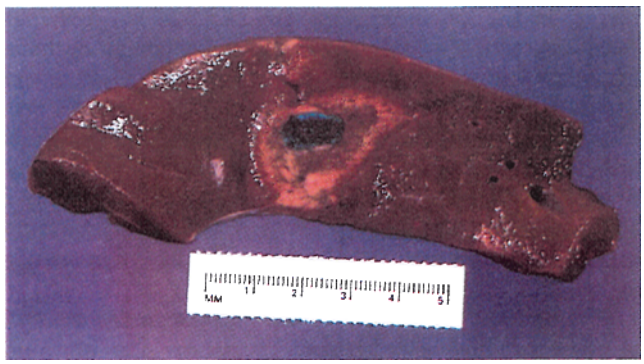

Fig. 3. Gross pathology section of a tumor-mimic ablation. The simulated tumor (blue) is surrounded by ablated tissue (white), hyperemic liver tissue (bright red), and normal liver (red).

tive time was longer in the laparoscopic group (5.4 ± 1.3 h) than in the open group (4.2 ± 0.3 h) ($p = 0.016$).

The pathologist (G.L.) was blinded to ablation technique. On gross examination, the boundary between viable and nonviable tissue was sharply demarcated; there was no overlap between any ablations. Tumor-mimic (blue) was surrounded by ablated tissue (white), an area of hyperemia (bright red), and normal liver (red) (Fig. 3). Ablation shapes ranged from cloverleaf patterns to almost spherical. Irregularities in ablation shape were often seen in close proximity to blood vessels. Ablated tissue could not be distinguished from nonablated tissue on H&E sections. NADH staining (Fig. 4) demonstrated nonviable cells in the area that corresponded to the white charring on gross examination. NADH sections sometimes showed extension of the kill zone into hyperemic tissue, but foci of viable cells were often seen as well.

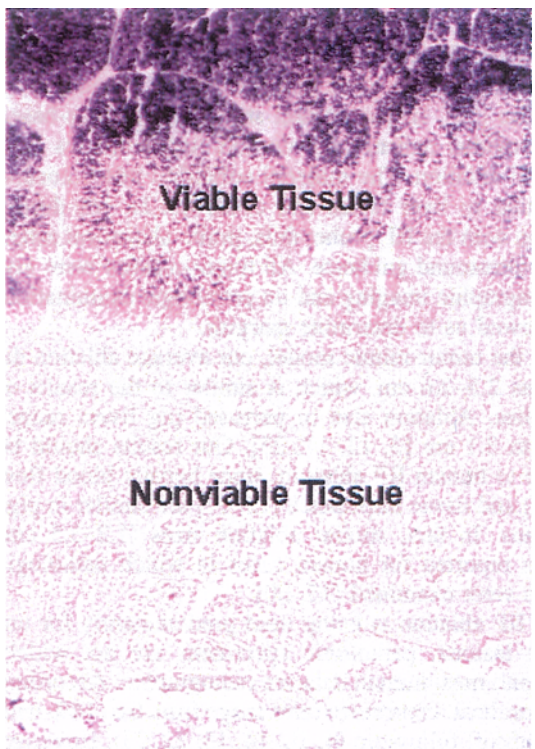

Fig. 4. Microscopic section (NADH stain) of ablated tissue at ×20 magnification. Viable tissue is blue; nonviable tissue is white.

Table 1. Laparoscopic vs open ablation characteristics

	Laparoscopic ($n = 15$)	Open ($n = 11$)	p value[a]
Warm-up[b] time (min)	20.2 ± 14.0	10.7 ± 7.5	0.049
Pre–warm-up			
Temperature (°C)	37.0 ± 1.3	35.7 ± 0.9	0.003
Impedance (Ω)	45.4 ± 4.6	50.3 ± 5.8	0.052
Power (W)	50.0 ± 0.0	50.0 ± 0.0	0.979
Post–warm-up			
Temperature (°C)	105.7 ± 3.7	107.0 ± 4.5	0.189
Impedance (Ω)	46.1 ± 5.7	51.5 ± 9.1	0.163
Power (W)	47.8 ± 5.0	44.3 ± 9.8	0.237
Postablation			
Temperature (°C)	105.4 ± 2.8	105.6 ± 2.8	0.870
Impedance (Ω)	51.3 ± 7.7	52.9 ± 6.7	0.239
Power (W)	33.1 ± 11.3	27.9 ± 6.8	0.584

Values given as mean ± SD
[a] Mann-Whitney U test, laparoscopic vs open approach
[b] "Warm-up" refers to the period in which energy is applied in order to heat the tissue to 100°C.

Table 2. Laparoscopic vs open probe placement accuracy

	Laparoscopic ($n = 15$)	Open ($n = 11$)	p value[a]
Off-center distance[b] (mm)	3.5 ± 1.6	4.2 ± 1.4	0.312

Values given as mean ± SD.
[a] Mann-Whitney U test, laparoscopic vs open approach
[b] Off-center distance = distance between tumor-mimic and pathologic ablation centers

Table 3. Laparoscopic vs open ablation effectiveness

	Laparoscopic ($n = 15$)	Open ($n = 11$)	p value
Ablation diameter (mm)	24.7 ± 3.1	25.6 ± 3.8	0.584[a]
Round/ovoid shape	3 (20%)	7 (64%)	0.043[b]
Symmetrical ablation	6 (40%)	8 (73%)	0.130[b]
Positive margin	5 (33%)	1 (9%)	0.197[b]
Margin distance (mm)	1.1 ± 1.2	2.2 ± 1.6	0.058[a]

Values given as mean ± SD.
[a] Mann-Whitney U test, laparoscopic vs open approach
[b] Fisher's exact test, laparoscopic vs open approach

Ablation characteristics are listed in Table 1. The open group had shorter warm-up times and cooler pre–warm-up temperatures than the laparoscopic group. Otherwise, ablation characteristics were not significantly different for the two groups.

There were no significant differences in off-center distance, ablation size, symmetry, and margins (Tables 2 and 3) between the laparoscopic and open groups. Significantly fewer laparoscopic ablations were round or ovoid than open ablations (Table 3).

Discussion

Inaccurate probe placement may result in incomplete tumor ablation [11, 20, 23]. Previous porcine [3] and human [22]

studies have documented the feasibility of laparoscopic RF ablation, but the accuracy of this technique has not been established. Our data indicate that probe placement using the laparoscopic approach was significantly more difficult than for the open approach. Despite the increased level of difficulty, laparoscopic probe placement was accurate. We consistently achieved placement to within 3–4 mm of the tumor-mimic center using either the laparoscopic or open approach. Even though the same ports were used for tumor-mimic creation and laparoscopic ablation, the abdominal wall locations were different for insertion of the needle for agarose injection and for the RF probe. Thus, using the same ports did not appreciably decrease the difficulty of laparoscopic ablations. Palpation could have affected open ablations. During open ablations, a vague fullness in the area of liver containing the tumor-mimic could be palpated, which may have aided in initial probe placement; however, accurate probe placement ultimately depended on ultrasound guidance.

Operative time was longer for the laparoscopic group than for the open group. The added difficulty level associated with laparoscopic probe placement may partially account for the difference, but warm-up time had a large impact on operative time. Warm-up time was almost twice as long for laparoscopic ablations as for the open group, even though the tissue was colder in the open group at the pre–warm-up interval. After the warm-up phase, no differences in temperature, impedance, or power (Table 1) were detected.

Although there was no difference in ablation size, we found a significant difference in shape between the open and laparoscopic ablation groups. Open ablations resulted in more spherical shapes. Similarly, open ablations tended to have greater symmetry and larger margins than laparoscopic ablations, although the differences were not statistically significant. Had more ablations been performed in each group, statistical significance may have been reached. Since this study was limited by its sample size, firm conclusions regarding the relative effectiveness of laparoscopic vs open ablation cannot be made. Several observations, however, are worth discussing.

The differences in both warm-up time and shape may have been related to blood flow. Blood vessels carry heat away from tissue during ablation and create heat sinks. A direct relationship has been established between blood flow and ablation size and shape [13, 17]. Increased hepatic blood flow during laparoscopy would account for the prolonged warm-up time and nonspherical shapes that we observed. Hepatic blood flow may be altered during laparoscopy by two mechanisms. CO_2 gas may be absorbed systemically and lead to changes related to hypercarbia. Hypercarbia has been shown to lower mesenteric vascular resistance and increase portal venous flow [18, 24]. On the other hand, increased intraabdominal pressure has been shown to decrease hepatic blood flow [5, 8, 9, 18, 21]. The effects of increased intraabdominal pressure are usually seen at pressures of $\geq$18 mmHg [8], but impaired hepatic blood flow may occur at pressures as low as 8 mmHg [21].

In our study, hepatic blood flow was not measured, and the net effect of the CO_2 pneumoperitoneum is unknown. The nonspherical shapes and prolonged warm-up time suggest that the hypercarbic effect may have prevailed and that perfusion was increased. However, end-tidal CO_2 readings were maintained within normal limits. Although systemic hypercarbia was not detected, the CO_2-rich environment within the peritoneal cavity may have affected hepatic perfusion. Our insufflation pressure was 10–12 mmHg, which may not have been high enough to impair hepatic blood flow. The physiologic consequences of RF ablation using a CO_2 pneumoperitoneum are not clear, and we are currently investigating this area. Studies using alternative gases may be helpful.

Preliminary work in our laboratory suggests that temperature may also affect hepatic blood flow. Pre–warm-up tissue temperature was significantly warmer for the laparoscopic group (37.0°C) than for the open group (35.7°C). Heat losses from the laparotomy incision may have caused visceral vasoconstriction and a state of hepatic hypoperfusion in the open group. Furthermore, temperature-related hypoperfusion may have accounted for some of the observed differences in warm-up time and shape.

Whether the laparoscopic or open approach was used, the effectiveness of the ablation was questionable. Based on pathologic examination, six of 26 ablations (23%) had positive margins. The average margin was 1–2 mm. Since the probe diameter was 3 cm when the electrodes were deployed, we expected to achieve a 3-cm ablation. With a 1-cm lesion and a 3-cm spherical ablation, a 1-cm margin, which is considered adequate for liver resections [1], should be achieved (Fig. 5A). Instead, our average ablation size was ~2.5 cm, which limited the maximum potential margin to 7.5 mm (Fig. 5B). When accuracy was factored in (4 mm off-center), the potential margin was limited to 3.5 mm (Fig. 5C). Small ablation size and irregular, nonspherical ablation geometry caused close and positive margins (Fig. 5D, E).

We previously validated the tumor-mimic model and showed that the model does not alter tissue impedance or ablation size [19]. In our current study, the agarose-based mixture provided realistic and durable tumor-mimics suitable for RF ablation. The material solidified into a consistency similar to liver tissue and could not be felt during penetration with the RF probe; thus, probe placement relied solely on ultrasound guidance. All tumor-mimics were visible on songraphic imaging and on pathologic examination, which allowed us to determine margins.

Using the tumor-mimic model, our average ablation diameter was 2.5–2.6 cm, which is similar to the results of other studies. Ablation size in perfused pig livers ranges from 1.2 to 3.1 cm [3, 13, 17, 23]. Our results should be applicable to human RF ablation, since hepatic blood flow [8, 12, 21] and tissue impedance [15, 17] are similar in pigs and humans. In fact, similar ablation sizes (1.2–3.5 cm) have been reported for human cases in which pathologic specimens were examined [15, 20].

Since RF ablation is being used predominantly for unresectable lesions, pathologic specimens are not widely available and most human data are radiographic. According to CT scans, local recurrence rates range from 0 to 14% with 3–15 months of follow-up [4, 10, 14, 15, 22, 23]. However, CT scans may have a false negative rate as high as 10–20% [15, 23] and may not detect residual tumor. In three studies [15, 16, 20], postablation tissue specimens were examined. These studies collectively included 19 patients who under-

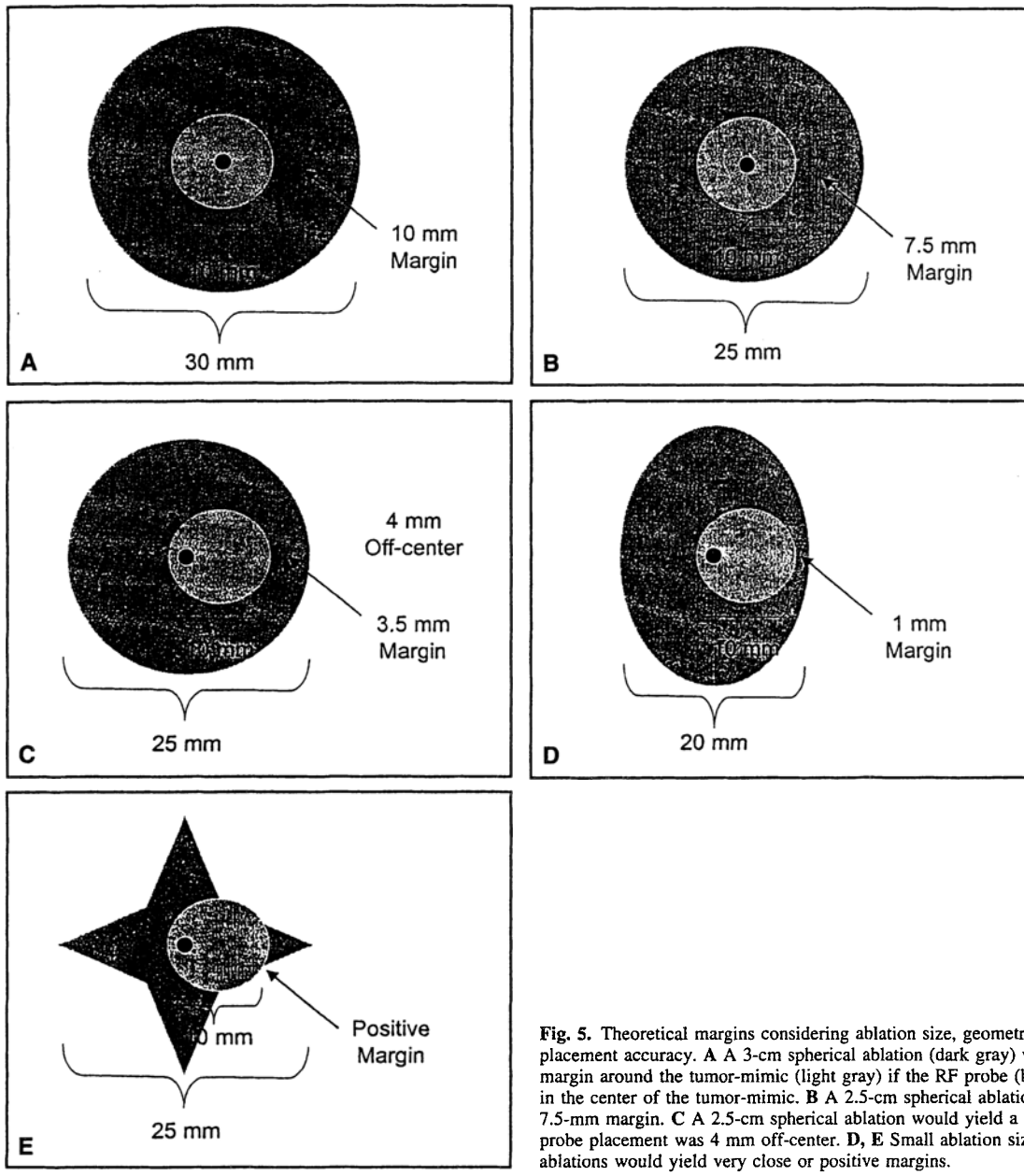

Fig. 5. Theoretical margins considering ablation size, geometry, and probe placement accuracy. **A** A 3-cm spherical ablation (dark gray) would yield a 1-cm margin around the tumor-mimic (light gray) if the RF probe (black) was placed in the center of the tumor-mimic. **B** A 2.5-cm spherical ablation would yield a 7.5-mm margin. **C** A 2.5-cm spherical ablation would yield a 3.5-mm margin if probe placement was 4 mm off-center. **D, E** Small ablation size and nonspherical ablations would yield very close or positive margins.

went both RF ablation and resection or examination at autopsy; residual tumor was found in four specimens.

Additional studies to improve the effectiveness of RF ablation are warranted. New equipment and methods are needed to achieve thermal lesions that are larger, more predictable in size, and more regular in shape. Manufacturers are beginning to introduce probes that encompass a larger volume of tissue (≤5 cm in diameter), probes with cluster designs (three parallel needle electrodes), cooled-tip electrodes (designed to decrease impedance), and more powerful generators (150–200 W). No information is yet available regarding the efficacy (in terms of pathologic tumor–free margins) of these new systems. The use of a Pringle maneuver (hepatic inflow occlusion) may also result in more effective ablations [4, 10, 11, 13, 17, 22]; however, protocols have not yet been standardized, and data concerning safety are lacking (especially for laparoscopic ablations performed with a Pringle maneuver).

If ablation effectiveness is improved, the laparoscopic approach may be optimal. Compared to the open approach, morbidity is less and recovery is quicker with the laparoscopic approach [22]. Compared to the percutaneous approach, laparoscopy allows direct visualization, which may be safer. Current limitations of the percutaneous approach are the potential for visceral injury during probe placement, collateral thermal damage to viscera during ablation, inability to reach lesions near the diaphragm [15], and pain associated with ablating subcapsular lesions [4, 10, 23]. Additionally, intraoperative ultrasound has greater sensitivity than transcutaneous ultrasound [2], and a Pringle maneuver,

which has been shown to improve size and shape during open ablations [4, 10, 13, 17, 22] may be performed during laparoscopy [7, 25].

In conclusion, this study demonstrated that comparable accurate probe placement can be achieved using either the laparoscopic or the open technique in the porcine tumor-mimic model. Physiologic effects related to the CO_2 pneumoperitoneum and hepatic blood flow may account for the differences in ablation shape and warm-up time that were observed in the two groups. Additional studies are needed to develop more effective ways of achieving complete tumor destruction with tumor-free margins. RF ablation is a promising new technology, and the laparoscopic approach may prove beneficial.

Acknowledgments. Funding was provided by the Southwestern Center for Minimally Invasive Surgery as supported in part by an educational grant from United States Surgical, a division of Tyco Healthcare Group. Equipment was provided by RITA Medical and B & K Medical Systems, Inc., 267 Boston Road, Bldg A, North Billerica, MA 08162, USA

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