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Short- and Long-term Histological Changes in Liver Parenchyma After Different Resection Methods and Their Potential Role in Treatment of Colorectal Liver Metastasis

ANDRÁS PALKOVICS[1], ANDRÁS VERECZKEI[1], ANDRÁS FINCSUR[2], ISTVÁN KISS[3], BALÁZS NÉMETH[3], ILDIKÓ TAKÁCS[4] and ANDRÁS PAPP[1]

[1]*Department of Surgery, Medical School, University of Pécs, Pécs, Hungary;*
[2]*Department of Pathology, Medical School, University of Pécs, Pécs, Hungary;*
[3]*Department of Public Health Medicine, Medical School, University of Pécs, Pécs, Hungary;*
[4]*Department of Surgical Research and Techniques, Medical School, University of Pécs, Pécs, Hungary*

Abstract. *Background/Aim: Optimal surgical margins, parenchymal-sparing technique and the effect of the surgical devices on the liver resection surface are currently hot topics. The aim of this study was to set up a surviving animal model to detect histological changes on the resection surface induced by the resection method and the thermal effect of monopolar electrocautery in 'spray mode'. Materials and Methods: Eighteen male Wistar rats were used; all rats were subjected to standardized liver resection and resection surface coagulation. Resection surface samples were collected immediately after the operation from the first group, and at 1 week and 3 weeks after the operation from the second and third groups, respectively. The samples were histologically investigated. Results: Spray diathermy was shown to cause parenchymal destruction of varying depth on the resection surface due to immediate coagulation and consequent necrosis. Conclusion: Spray diathermy on the resection surface can also destroy the area that contains possible tumor cells after R1 resection and increases the tumor clearance without worse survival outcomes.*

Colorectal cancer (CRC) is the third most common malignancy according to the Global Burden of Cancer Study (GLOBOCAN), and the fourth most common cause of cancer-related deaths in the world (1). In the locoregional stage, the 5-year survival rate is around 71%, but in stage IV, when distant metastases are present, the survival rate is only 13% (2, 3). The most common first site of distant spread of colorectal cancer (CRC) is the liver. Half of all patients develop liver metastases during their illness. Approximately 25% of patients have synchronous liver metastases at the time of CRC diagnosis. Almost 40-50% of patients who undergo CRC resection develop metachronous liver metastases (4-6). Finally, 50-75% of patients develop new or recurrent metastasis after curative liver resection, but only one-fifth are suitable for repeated surgical resection (7-9).

The life expectancy of patients with CRC liver metastasis (CRLM) without any treatment is less than 8 months. Nowadays, the commonly used therapies are multi-modal chemotherapy, multiple ablative modalities and surgical hepatic resection, which is the most effective therapy (10-14).

Investigating the changes of the liver surface after CRLM resection is a popular research topic. According to previous publications, patients with a macroscopically positive (R2) resection margin have significantly worse survival chances. Some authors suggest that a microscopically negative (R0) surgical margin is significantly better than a microscopically positive one (R1). However, in the past few years, new evidence has made these findings ambiguous. According to the consensus in the 1980s, the best survival rate can be achieved by a surgical margin which is more than 1 cm (15-18). In contrast, in the past two decades, several publications revealed that a subcentimeter free resection margin has no significant effect on survival (19-23). In 2008, Haas *et al.* pointed out that in the era of modern customized multimodal therapy and modern surgical devices, R1 resection has no negative effect on the survival of patients with CRLM (24-26).

Whether parenchymal-sparing surgery (which is often achievable by vascular R1 resection) is oncologically acceptable or not is another controversial topic related to CRLM resection (27). The remnant liver volume and liver function can be frequent modifiers of resection radicality.

Correspondence to: András Palkovics, Department of Surgery, University of Pécs Medical School, Ifjúság Street 13, H-7624, Pécs, Hungary. Tel: +36 72536000, e-mail: palkovics.andras@pte.hu

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These ideas form the basis for the reduction of the surgical margin and parenchymal-sparing non-anatomical resection. According to a systematic review investigating 2,500 patients with CRLM, the safety and efficacy profile of parenchymal-sparing surgery are comparable to those of anatomical resection with an acceptable oncological outcome (28-30).

The resection margin status is defined by the resected specimen, but R1 does not necessarily mean that the surface of the remnant organ itself is microscopically positive because there is a distance between the surface of the resected specimen and the resection surface of the remnant organ. This distance is determined by the surgical technique used. The Kelly-clamp crashing technique is a gold-standard liver transection technique to expose and isolate small vessels and the biliary duct, which can be ligated or cut with bipolar electrocautery or modern vessel-sealing devices. During the Kelly-clamp crashing technique, the parenchyma is transected with a mosquito clamp. Nowadays, this technique can also be executed with sealing devices [*e.g.* Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA) or The Ligasure Vessel Sealing System (Covidien, Mansfield, MA, USA)] (31, 32). After using one of these tools, 2-4 mm of the parenchyma is destroyed on the resection line (33, 34).

Finally, the resected surface can be coagulated with a monopolar electrocautery device in 'spray mode' to prevent bleeding. This procedure can increase the distance between the two surfaces on the resection line, providing a higher tumor clearance. According to an *ex vivo* animal investigation performed on a sheep liver, spray diathermia causes 3-4 mm deep tissue destruction (35).

The aim of our study was to set up a surviving animal model to demonstrate and investigate the effect of monopolar electrocautery in spray mode.

Materials and Methods

Animals, housing and diet. Eighteen male Wistar rats (Charles River Breeding Laboratories, Isaszeg, Hungary) weighing between 510 and 690 g were used in our study. The animals were housed in a light-controlled and air-filtered room in individual cages. They were kept at room temperature and with free access to food and water. The food was withdrawn 12 hours before the experiment. The present study conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health and was approved by the local Institutional Committee on Animal Research of the University of Pécs (BA02/2000-29/2001) (36).

Liver resection model. The animals were anesthetized by an intraperitoneal injection of ketamine hydrochloride and diazepam on a heated pad. The ratio was 1:1. The skin was disinfected and a middle laparotomy through the *linea alba* was performed; 2 ml warm saline was injected into the abdominal cavity to maintain fluid balance.

The intermittent Pringle maneuver was performed with a soft rubber loop after fine preparation of the hepatic artery and the portal vein.

During the next step, we isolated the right and left medial lobes of the liver. The left medial lobes of all the rats were resected and coagulated without Pringle maneuver and the right medial lobes were resected and coagulated during Pringle maneuver. The resection was a standardized one, which meant that a 1-centimeter wide cut was made on the top of the lobes in all cases. After the resection, the resection surface was coagulated with monopolar electrocautery in spray mode with 120 W energy settings. Finally, the abdominal cavity was rinsed with warm saline and the abdominal wall was closed in two layers with absorbable suture.

Experimental groups. The rats were divided into three groups with six rats in each group. All rats were subjected to standardized liver resection and resection surface coagulation. In the first group, liver resection surface samples were collected immediately after the operation, in the second group they were collected 1 week after the operation, and in the third group, samples were collected 3 weeks after the operation; afterwards the animals were sacrificed by overdosing with ketamine hydrochloride and diazepam. All harvested liver tissue samples were between 1 and 2 cm, and these blocks were stored in 10% formaldehyde until histological examination.

Histological examination. The aim of the histological examination was to detect histological changes induced by the thermal effect and to compare these changes between the groups. The histological samples were made using the following method. The fresh tissue was fixed in 10% neutral buffered formalin for 24 h after the harvesting. After the fixation, the samples were dehydrated in a series of ethanolic solutions of increasing concentration. Ethanol was then displaced with xylene before the samples were infiltrated with histological wax (blocking). Sectioning was performed with a sledge microtome from the wax-embedded blocks, and after dewaxing with xylene and rehydrating with a series of ethanolic solutions of decreasing concentration, staining with hematoxylin and eosin was carried out with a carousel-type slide stainer at the Department of Pathology, Medical School, University of Pécs, Pécs, Hungary. Ten slices were created from every model. To evaluate the histological slices, Pannoramic Viewer software was used and a magnification of 200× was applied to identify and measure layers histologically. Twenty measurements were performed per slide. We measured the thickness of the coagulation, the necrotic and the different fibrotic zones. To rule out interobserver error, measurements were performed by the same investigator.

Statistical analysis. Statistical analysis was performed by IBM SPSS Statistics for Windows Version 22 (IBM, Armonk, NY, USA). All values are presented as means±SEM. Differences during the follow-up were investigated by paired-sample *t*-test. Independent sample *t*-test was used to compare parameters between groups. All differences with *p*-values lower than 0.05 were considered statistically significant.

Results

Group 1 – day zero. As a direct thermal effect, a coagulation zone appeared on the liver resection surface (Figure 1A). In the coagulation zone, the whole liver tissue had been destroyed. Between this completely destroyed zone and the residual structured liver tissue, towards the deeper tissue, spotty coagulation damage was found among living liver

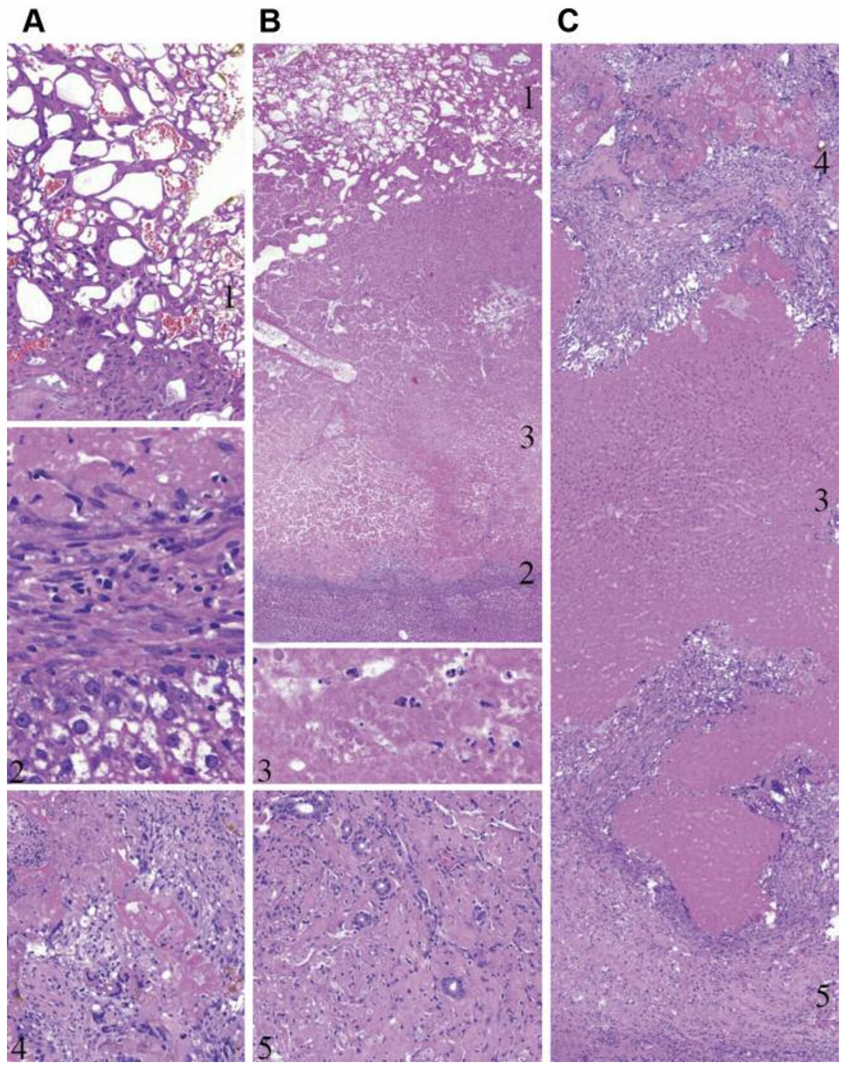

Figure 1. *Histological examination with hematoxylin and eosin immediately after (A), and 1 week (B) and 3 weeks (C) after resection. 1: Necrotic zone; 2: reparative hypercellular fibrotic zone with newly developed tissue elements and granulation tissue (200×). 3: Incomplete and complete coagulatory necrosis, with reduced nuclear staining and with disintegrated parenchymal structure in the deeper parts of the zone (200×). 4: Hypercellular low collagen content young fibrotic zone with polypoid newly formed tissue (150×). 5: Old fibrotic zone, a hypercellular, high collagen content zone with newly formed bile ducts, vessels, and mild chronic inflammatory infiltration (150×).*

cells. The mean depth of these zones was significantly ($p<0.001$) higher in the Pringle right lobe compared to that of the non-Pringle left lobe (Table I).

Group 2 – 1 week after resection. In group two, 1 week after the operation, three different zones were found in both non-Pringle and Pringle cases (Figure 1B). The coagulation zone in which the whole liver tissue was destroyed was the first zone. This zone was significantly ($p<0.001$) wider in Pringle cases than in non-Pringle cases. Moreover, the coagulation zone was significantly ($p<0.001$) wider 1 week after the operation compared to measurements performed immediately after the operation for both forms of resection.

The second zone was a necrotic zone. In this zone, uncompleted coagulatory necrosis was found. The physiological microscopic structure was recognizable, but the contours gradually became blurred. Overall, the staining of the effected hepatic cells was less than that of living tissue. A decrease in nuclear staining was conspicuous and loss of staining is a sign of completed necrosis. There were also completely necrotic areas, with the parenchymal structure having disintegrated in the deeper parts of the zone.

Table I. *Mean and median depth of thermal injury at 0 day, and 2 and 3 weeks after resection in non-Pringle and Pringle groups. Values are presented with the 95% confidence interval.*

	Non-Pringle			
Time after resection	Zone 1	Zone 2	Zone 3	∑ Zone
0 Day				
Mean (µm)	558 (548.63-568.41)			558 (548.63-568.41)
Median (µm)	553.65 (543.63-565.61)			553.65 (543.63-565.61)
1 Week				
Mean (µm)	893.76 (826.62-967.62)	3238.45 (3047-3408.04)	96.22 (89.62-102.25)	4228.43 (4001.27-4444.29)
Median (µm)	844.88 (781.35-938.58)	3250.50 (3072.39-3558.98)	93.03 (88.77-103.90)	4306.18 (4039.23-4463.20)
3 Weeks				
Mean (µm)	954.18 (848.23-1063.33)	1462.53 (1364.40-1572.80)	765.55 (671.85-860.90)	3182.27 (2996.06-3378.93)
Median (µm)	857.84 (755.02-933.23)	1306.05 (1238.05-1460.23)	638.24 (552.25-731.97)	2965.74 (2733.84-3254.10)
	Pringle			
Time after resection	Zone 1	Zone 2	Zone 3	∑ Zone
0 Day				
Mean (µm)	680.04 (643.70-716.30)			680.04 (643.70-716.30)
Median (µm)	664.94 (613.05-717.19)			664.94 (613.05-717.19)
1 Week				
Mean (µm)	1303.08 (1204.56-394.94)	3531.42 (3412.98-652.51)	111.96 (104.15-119.99)	4946.45 (4771.63-5108.35)
Median (µm)	664.94 (613.05-717.19)	3459.36 (3308.13-3745.94)	108.39 (96.222-119.49)	4880.34 (4670.97-5283.83)
3 Weeks				
Mean (µm)	1272.06 (1154.13-384.92)	1841.39 (1729.18-1954.99)	570.62 (543.26-596.37)	3684.07 (3553.21-3820.47)
Median (µm)	1213.08 (1066.54-345.06)	1940.04 (1805.81-2029.54)	588.49 (552.84-625.23)	3699.61 (3596.11-3824.88)

This zone was significantly (p=0.034) wider in Pringle cases than in non-Pringle cases.

The third zone identified was a reparative zone or fibrotic zone. In this zone, there were newly developed tissue elements, hypercellular connective tissue, and granulation tissue. Infiltration of inflammatory cells and bile duct reaction also appeared, and fibrocytes had grown into the necrotic tissue, suggesting regeneration of the liver tissue. This fibrotic zone was also significantly (p=0.003) wider in Pringle cases than in non-Pringle cases.

Finally, considering the three zones, in the case of the Pringle maneuver, the total damage induced by the thermal effect was significantly (p<0.001) thicker compared to that in the non-Pringle cases.

Under these three zones, normal structured, living liver tissue was identified (Table I).

Group 3 – 3 weeks after resection. Three weeks after the operation, three different zones were identified (Figure 1C). However, these zones were different from the zones described in the previous two groups. The first zone was a young fibrotic zone. From the plane of the liver capsule, polypoid newly formed tissue appeared, which surrounded the former necrosis and divided it into an insular form. This was a hypercellular zone with low collagen content. This zone was significantly (p<0.001) wider in Pringle cases than in non-Pringle cases. The second zone was a necrotic zone which was thickly encircled by the young granulation tissue. Deep in this zone, necrotic areas with disintegrated liver structures were seen. This zone was significantly (p<0.001) wider in Pringle cases than in non-Pringle cases. However, these zones were significantly (p<0.001) narrower after 3 weeks than after 1 week. The third zone was an old fibrotic zone, a hypercellular zone with high collagen content with newly formed bile ducts, vessels, and mild chronic inflammatory infiltration. This was significantly (p=0.034) wider in non-Pringle cases than in Pringle cases. After 3 weeks, these zones were significantly (p<0.001) wider than those at 1 week in both non-Pringle and Pringle cases (Table I).

Discussion

CRC is the most common cause of liver metastasis (4-6). Liver resection is the gold standard treatment of CRLM (10-14). Over the past decades, the surgical margin during CRLM resection has been a widely examined topic. In the light of recent evidence, the general consensus made in 1986 by Ekberg *et al.*, namely that the optimal surgical margin for better survival should be more than 1 cm, is changing (16). Some Authors suggest that even 2-5 mm and 1-4 mm is a sufficient surgical margin (14-18). Moreover, there is growing evidence that there are no disease-free survival differences between patients who underwent R1 and R0 CRLM resection (24-26). Finally, in 2014 Truant *et al*. suggested that in the era of modern chemotherapy, tumor biology is a more important factor in survival than surgical margin (24).

During liver resection, the technique for parenchymal transection is one of the most important and investigated factors (34).

In 2017, El Shobary *et al*. showed that spray diathermy with the Kelly-clamp crushing technique during liver parenchymaI transection is rapid, safe, and inexpensive. Furthermore, it results in less blood loss and less cost than modern parenchymal dissectors, with no increased morbidity (37).

It is well known that if this technique is used, 2-4 mm of the parenchyma can be destroyed at the resection surface as a result of the clamp transection of the liver parenchyma (33, 34).

Modern parenchyma dissectors (such as ultrasonic dissectors, harmonic scalpels or cavitron ultrasonic surgical aspirator) can destroy 2-4 mm parenchyma on the resection line. Moreover, cavitron ultrasonic surgical aspirator destroys liver cells and cancer cells on the resection surface, which are aspirated during the transection (31, 34).

These techniques and consequential parenchymal destruction on the resection line can explain how the surface of the remaining liver tissue can be tumor-free, even in the case of R1 resection and result in no survival differences being found between those who undergo R1 and R0 CRLM resection.

Finally, the most important factor, which is the foundation of our investigation, is that the routinely used resection surface coagulation is also capable of preventing bleeding.

After a comprehensive search, we were able to find only one article which investigated the effect of spray diathermy on the liver resection surface. In 2005, Gananadha *et al*. found spray diathermy caused 3- to 4-mm-deep liver tissue destruction in an *ex vivo* model (35). The main result of our study is that we also found spray diathermy can cause 3- to 4-mm-deep liver tissue destruction in an in vivo model and this destruction was significantly deeper in the case of resection under Pringle maneuver. As an immediate effect, one coagulation zone appeared on the liver resection surface due to the thermal effect. In the chronic model, after a few days, a wide necrotic zone developed below the coagulation zone, which was significantly deeper when the Pringle maneuver was performed.

As a result of the Pringle maneuver, the intermittent and reversible blockage of the portal vein and hepatic artery reduces bleeding during parenchymal transection (38). The Pringle maneuver has another positive effect, as it reduces the so called ‘heat-sink’ effect. The pathophysiological background of this cooling is perfusion-mediated cooling provided by local blood vessels. This is the same effect as that which reduces the effectivity of thermal ablation of liver tumors (39, 40). If the heat-sink effect is blocked, spray diathermy can increase tumor clearance during parenchymal-sparing liver resection.

On the other hand, it must be noted that approximately 50-75% of patients with CRLM develop new or recurrent metastases after curative liver resection but only one-fifth of these metastases are suitable for further resection, often because there would not be enough liver parenchyma left after the resection (7-9).

Although liver tissue can regenerate, functional regeneration is not as extensive as volume regeneration. Factors that can attenuate the regeneration are surgical time, intraoperative blood loss, blood flow blocking time, the patient’s own pathological status, and finally, one of the most important factors is chemotherapy. Chemotherapy can cause serious liver parenchymaI injury (41-43).

The expected survival of patients with CRLM is increasing, so too is the chance of having a second surgery. Consequently, parenchymal-sparing techniques are becoming more and more important. Many publications concluded that parenchymal-sparing liver resection is not an oncological compromise, and while there may be no difference in 5-year overall survival, it may give the opportunity for repeated resection (44, 45).

Based on the previous findings and our investigation, using spray diathermy for resection surface coagulation can increase the oncologically acceptable tumor clearance during parenchymal-sparing liver resection.

Conclusion

In the era of multimodal chemotherapy and advanced surgical techniques, parenchymal-sparing non-anatomic liver resection seems to be without any oncological disadvantages. During liver resection, coagulation of the resection surface prevents bleeding and enhances tumor clearance, resulting in higher oncological acceptable. Of course, the goal is to achieve a microscopically negative surgical margin, but if this is questionable, we suggest that the resection surface should be coagulated.

Conflicts of Interest

The Authors declare that there are no conflicts of interests regarding the publication of this article.

Authors’ Contributions

Conceptualization: AP, AP. Statistical analysis: AP. Methodology and histological investigation: IT, AF. Operation of animals: IT, AP, AP. Resources: IK, AV. Software: AF. Supervision: AV. Visualization: BN, PA. Writing - original draft: AP, AP. Writing, review and editing: NB.

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