

# Surgical Approach in Liver Hemangiomas with Special Emphasis on Lesion Diameter and Type of Surgery: A Retrospective Cohort of 69 Patients

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## ABSTRACT

**Purpose:** Liver hemangioma (LH) being the most common benign tumor of the liver is a rare indication for liver surgery. Indications include symptomatic disease, suspicion of malignancy, increase in lesion size, and Kasabach-Merritt syndrome. Surgical treatment mainly consists of enucleation or liver resection (LR). The study aimed to evaluate surgical outcomes in patients with LHs.

**Methods:** In this study, surgical treatment for liver hemangioma in a single center were retrospectively reviewed. Demographics, preoperative and postoperative laboratory values, imaging studies, and follow-up data of patients were collected.

**Results:** The mean age was 51.9±11.0 years and 69.6% were female. Abdominal pain was present preoperatively in 32 (46.4%) cases. Mean lesion diameter was 7.5 (1.2-20) cm. Giant hemangioma was reported in 54 (78.3%) patients. LR and enucleation were preferred for 37 (53.6%) and 32 (46.4%) patients, respectively. Intraoperative transfusion requirement was more common in enucleation than LR (78.1% vs. 48.6%, p=0.012). Intraoperative erythrocyte transfusion was more frequently in operations of giant hemangiomas (68.5% vs. 40.0%, p=0.044). Complications were observed more frequently in giant hemangioma group regardless of grades (40.7% vs. 13.3%, p=0.049). Preoperative thrombocytopenia was found more frequent in cases with serious complications (66.7% vs 22.2%, p=0.019).

**Conclusion:** Emerging percutaneous intervention and imaging modalities are expected to decrease number of surgeries for liver hemangiomas. Although enucleation, LR and even liver transplantation are still required for a set of patients. Enucleation and LR have similar outcomes, but transfusions are more common according to the present study. Size of LHs is related with complications and transfusion requirements.

**Keywords:** hemangioma, liver resection, enucleation

## Karaciğer Hemanjiyomlarında Lezyon Çapına Ve Cerrahi Tipine Göre Cerrahi Yaklaşım: 69 Hastadan Oluşan Retrospektif Bir Kohort

### ÖZET

**Amaç:** Karaciğerin en sık görülen benign tümörü olan karaciğer hemanjiyomlarının (KH) tedavisinde karaciğer cerrahi nadir bir endikasyondur. Endikasyonlar arasında semptomatik hastalık, malignite şüphesi, lezyon boyutunda artış ve Kasabach-Merritt sendromu sayılabilir. Cerrahi tedavi esas olarak enükleasyon veya karaciğer rezeksiyonundan (KR) oluşur. Bu çalışma, KH'li hastalarda cerrahi sonuçlarını değerlendirmeyi amaçladı.

**Yöntem:** Bu çalışmada karaciğer hemanjiyomunun cerrahi tedavisi tek merkezde retrospektif olarak gözden geçirildi. Hastaların demografik bilgileri, ameliyat öncesi ve sonrası laboratuvar değerleri, görüntüleme çalışmaları ve takip verileri toplandı.

**Bulgular:** Ortalama yaş 51,9 ± 11,0 iken; hastaların %69,6'sı kadındı. 32 (%46,4) olguda ameliyat öncesi karın ağrısı mevcuttu. Ortalama lezyon çapı 7,5 (1,2-20) cm idi. 54 (%78,3) hastada dev hemanjiom olduğu görüldü. Sırasıyla cerrahi tedavi olarak 37 (%53,6) ve 32 (%46,4) hastada KR ve enükleasyon tercih edildi. İntraoperatif transfüzyon gereksinimi enükleasyon yapılanlarda KR'lere göre daha fazlaydı (%78,1'e karşı %48,6; p=0,012). Dev hemanjiomların ameliyatlarında intraoperatif eritrosit transfüzyonu daha sıkı (%68,5'e karşı %40,0; p=0,044). Dev hemanjiom grubunda evreden bağımsız olarak komplikasyonlar daha sık gözlemlendi (%40,7'ye karşı %13,3; p=0,049). Ciddi komplikasyon gelişen olgularda preoperatif trombositopeni daha sık bulundu (%66,7'ye karşı %22,2; p=0,019).

**Sonuç:** Gelişen perkütan girişim ve görüntüleme yöntemlerinin karaciğer hemanjiyomlarına yönelik ameliyat sayısını azaltması beklenmektedir. Enükleasyon, KR ve hatta karaciğer transplantasyonu bir dizi hasta için hala gereklidir. Enükleasyon ve KR benzer sonuçlara sahip olsa da bu çalışmaya göre enükleasyon grubunda transfüzyon daha yaygındır. KH'lerin boyutu komplikasyonlar ve transfüzyon gereksinimleri ile ilişkilidir.

**Anahtar Kelimeler:** hemanjiyom, karaciğer rezeksiyonu, enükleasyon

Liver hemangiomas (LH) are vascular malformations being the most common benign tumors of the liver. Its incidence in autopsy series is ranging between 0.4% and 7.3%. It is more common in women with a female-to-male ratio of 4-6:1 (1). First diagnosis is made by ultrasonic examination in most cases and confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI). Spontaneous rupture of LH is rarely reported. Treatment is indicated only for patients with intractable symptoms of pain proven to be related directly to the LH, with uncertain diagnosis, with increased size of lesions under follow up or with lesions causing Kasabach-Meritt Syndrome (1,2). Although liver resection is an old and still used approach among surgical options, enucleation is also applied as a parenchyma-sparing surgical approach after the 80s (2). In this study, hemangioma surgeries performed in a single center were examined retrospectively in terms of surgical technique, lesion size, patient characteristics and the effect of these features on the outcomes.

## MATERIAL AND METHODS

Patients who underwent surgery with the diagnosis of LH between January 2007 and December 2018 at our institute were retrospectively extracted from the hospital database for this cohort study. The characteristics, preoperative and postoperative laboratory values, imaging studies, and follow-up of patients and hemangiomas were obtained from the hospital database, patient files and partially prospectively maintained hepatobiliary database. Diagnosis of cases were confirmed histologically as LH. Operations in which the hemangioma is selectively removed from the liver parenchyma border are named enucleation, and the operations in which the hemangioma is removed anatomically or non-anatomically with some liver parenchyma surrounding it are named liver resection. Four centimeters was considered as the lower limit for the definition of giant hemangioma (2). The surgical approach was chosen by the related surgeon. Complications were classified according to Clavien-Dindo classification, and accordingly, those with grade 3a and above, that is, those requiring intervention, progressing to organ failure or resulting in death, were defined as serious complications (3). Thrombocytopenia was defined as blood platelet count below  $150 \times 10^3/\text{mL}$ . The patients were informed about the surgeries in advance and their informed consents about surgeries and data collection for scientific purposes were obtained. Datafile is anonymized before analysis and original file was destroyed. The study has been reported in line with the STROCCS criteria (4). This study was approved

by the Ethics Committee of Ankara University School of Medicine (İ07-457-22) and was registered at Clinicaltrials.gov (NCT04669314).

In the comparisons, categorical variables were shown as percentages and compared with the Chi square test, while continuous variables were shown with the mean and compared with Student's t-test. In cases where the number of cases of the compared groups was less than 30 and variances were not equal, the Mann-Whitney U Test was preferred for continuous variables and variables were shown with the median and minimum-maximum values. The data were analyzed with SPSS 20.0 and the 2-sided significance level was chosen as 0.05.

## RESULTS

Forty-eight (69.6%) of 69 patients were female and mean patient age was  $51.9 \pm 11.0$  (33-79). Reported indications of surgery were abdominal pain, enlarging or giant tumors, unidentified liver masses or thrombocytopenia, Abdominal pain was present in 32 (46.4%) patients. Moreover, hemangiomas were incidentally found in 32 (46.4%) among the patients. Mean lesion diameter was 7.5 cm (1.2-20) while 54 (78.3%) patients had lesions with diameters >4 cm so those are identified as giant hemangioma in most of the current literature. 27 (39.1%) of patients had multiple hemangiomas. Liver resection and enucleation were preferred for 37 (53.6%) and 32 (46.4%) patients respectively. Laparoscopic operation was performed for 8 (11.6%) patients. 43 (62.3%) patients required intraoperative erythrocyte transfusion. However, two patients (2.9%) experienced biliary leakage. Clavien-Dindo Grade 1 to 4b complication occurred in 24 (34.8%) cases. Grade 3a and more serious complication were reported in 6 (8.7%) cases. Median postoperative hospital stay was 9.6 days (2-137). No mortality occurred.

Intraoperative transfusion requirement was more common in enucleation than resections (78.1% vs. 48.6%,  $p=0.012$ ). Two groups were found to be similar in terms of patient characteristics, disease presentation, complications and postoperative laboratory values (Table 1). Lesion diameters were also reviewed, and study cohort was splitted into two groups one with lesions with diameter of more than 4 cm (giant hemangioma) and one with lesions with diameter of 4 cm or less. Giant hemangiomas were found to be more common in females than males (85.4% vs. 61.9%  $p=0.029$ ). Intraoperative erythrocyte transfusion requirement was more frequently reported in operations of giant hemangiomas (68.5% vs. 40.0%,

$p=0.044$ ). Complications were observed more frequently in giant hemangioma group regardless of grades (40.7% vs. 13.3%,  $p=0.049$ ) (Table 2).

	Mean ( $\pm$ SD) or n (%)
Female gender	48 (69.6%)
Age (years)	51.9 $\pm$ 11.0
Incidental	32 (46.4%)
Pain	32 (46.4%)
Platelet count ( $10^3/mm^3$ )	193.1 $\pm$ 64.3
Giant hemangioma	54 (78.3%)
Lesion diameter (cm)	7.5 $\pm$ 4.2
Number of lesions	1.6 $\pm$ 1.4
Enucleation	32 (46.4%)
Liver resection	37 (53.6%)
Laparoscopy	8 (11.6%)
Hospital stays (days)	9 (5-28)
Erythrocyte transfusion	43 (62.3%)
Postoperative peak ALT (U/L)	201.3 $\pm$ 307.8
Postoperative peak bilirubin (mg/dL)	1.1 $\pm$ 0.6
Postoperative biliary leak	2 (2.9%)
Complication	24 (34.8%)
$\geq$ Grade 3a complication	6 (8.7%)

	Small (n = 15)	Giant (n = 54)	P
Female gender	7 (46.7%)	41 (75.9%)	<b>0.029</b>
Age (years)	55.7 $\pm$ 10.5	50.8 $\pm$ 11.0	0.124
Incidental	7 (46.7%)	25 (47.2%)	0.973
Pain	4 (26.7%)	28 (51.9%)	0.084
Platelet count ( $10^3/mm^3$ )	175.3 $\pm$ 54.2	197.7 $\pm$ 66.3	0.248
Thrombocytopenia	5 (35.7%)	13 (24.1%)	0.379
Enucleation	6 (40.0%)	26 (48.1%)	0.576
Liver resection	9 (60.0%)	28 (51.9%)	0.576
Number of lesions	1.1 $\pm$ 0.4	1.8 $\pm$ 1.5	<b>0.001</b>
Margin positivity	3 (20.0%)	10 (18.5%)	0.897
Laparoscopy	3 (20.0%)	5 (9.3%)	0.250
Hospital stays (days)	6 (5-9)	7 (5-28)	0.593
Erythrocyte transfusion	6 (40.0%)	37 (68.5%)	<b>0.044</b>
Peak ALT (U/L)	143.1 $\pm$ 154.5	216.7 $\pm$ 336.3	0.430
Peak bilirubin (mg/dL)	1.3 $\pm$ 0.7	1.0 $\pm$ 0.5	0.168
Biliary complication	1 (6.7%)	1 (1.85%)	0.276
Any complication	2 (13.3%)	22 (40.7%)	<b>0.049</b>
$\geq$ Grade 3a complication	2 (13.3%)	4 (7.4%)	0.471

Characteristics of incidentally discovered lesions were found to be statistically similar with symptomatic cases. Hospital stay, complications and serious complications also found to be similar between these groups. Pain is more frequently reported as a symptom in females than males. (54.2% vs 28.6%,  $p=0.044$ ). Laparoscopic operations were performed for only female patients (16.8% vs 0%,  $p=0.047$ ). There was no significant difference between male and female gender in terms of complications and other preoperative characteristics.

Hence no mortality occurred after surgeries in the study, complications after surgery compared as endpoint of the study. Patients evaluated as two groups: complicated, 24 (34.8%) patients, experiencing any grade of complications and non-complicated, 45 (65.2%) patients without any complications. Giant hemangiomas are more likely to experience any complication ( $p=0.049$ ). Mean lesion diameter of complicated cases were also significantly greater (10.5  $\pm$  4.8 vs. 5.9  $\pm$  2.7,  $p=0.001$ ) than mean lesion diameter of non-complicated cases. Median duration of hospital stay of complicated cases was found to be significantly longer than non-complicated cases (16 days vs. 6 days,  $p=0.001$ ). Transfusion requirement was more frequent in complicated cases than non-complicated cases (79.2% vs. 53.3%,  $p=0.035$ ). Mean postoperative peak total bilirubin level was found significantly higher than mean postoperative peak total bilirubin level of non-complicated cases (1.3  $\pm$  0.7 vs. 0.9  $\pm$  0.5 mg/dL,  $p=0.042$ ) (Table 3).

	Complicated (n = 24)	Not complicated (n = 45)	p
Female	16 (66.7%)	32 (71.1%)	0.702
Age (years)	49.9 $\pm$ 10.7	52.9 $\pm$ 11.1	0.289
Incidental	12 (50.0%)	20 (45.5%)	0.720
Pain	11 (45.8%)	21 (46.7%)	0.947
Platelet count ( $10^3/mm^3$ )	186.8 $\pm$ 72.0	196.5 $\pm$ 60.3	0.559
Thrombocytopenia	8 (33.3%)	10 (22.2%)	0.343
Enucleation	14 (58.3%)	18 (40.0%)	0.146
Liver resection	10 (41.7%)	27 (60.0%)	0.146
Giant hemangioma	22 (91.7%)	32 (71.1%)	<b>0.049</b>
Lesion diameter	10.5 $\pm$ 4.8	5.9 $\pm$ 2.7	<b>0.000</b>
Number of lesions	1.5 $\pm$ 0.7	1.7 $\pm$ 1.6	0.677
Laparoscopy	1 (4.2%)	7 (15.6%)	0.159
Hospital stays (days)	16 (7-28)	6 (5-14)	<b>0.001</b>
Erythrocyte transfusion	19 (79.2%)	24 (53.3%)	<b>0.035</b>
Peak bilirubin (mg/dL)	1.3 $\pm$ 0.7	0.9 $\pm$ 0.5	<b>0.042</b>
Peak ALT (U/L)	310.4 $\pm$ 480.9	140.4 $\pm$ 107.7	0.100

Cases were evaluated according to grade 3a or higher (serious) complications. Preoperative thrombocytopenia was found more frequent in cases with serious complications (66.7% vs 22.2%,  $p=0.019$ ). Mean preoperative platelet count of cases with serious complication was found lower than cases with low grades of complications or without complication ( $124.5 \pm 58.9 \text{ } 10^3/\text{mL}$  vs  $199.7 \pm 61.2 \text{ } 10^3/\text{mL}$ ,  $p=0.005$ ). As can be expected median postoperative hospital stay was found longer in cases with serious complications (15.5 days vs. 7 days,  $p=0.004$ ). Mean postoperative peak total bilirubin level was found higher in cases with serious complications ( $1.8 \pm 0.8 \text{ mg/dL}$  vs.  $1.0 \pm 0.5$ ,  $p=0.001$ ).

## DISCUSSION

First endpoint of the study, comparison of enucleation and resection, resulted with no significant difference in terms of complications and hospital stay. Groups characteristics were similar by chance making the comparison more valuable. Although transfusion requirement is more common in enucleation group conflicting with most of the literature. Probably high number of non-anatomic and anatomic resections as well as living donor liver surgeries made the surgeons of the unit more familiar to resections than enucleations that are performed limited numbers of cases less than ten annually. Enucleation of LH was first reported by Alper et al. (5) in 1988 ninety years after first resection for LH was performed by Hermann Pfannenstiel in 1898 (6). Resections if performed in a standardized manner using meticulous technique under low central venous pressure cause minimum blood loss, especially anatomical resections following intersegmental planes that are including only tiny pedicles under Pringle maneuver. In the literature search, authors met two recent meta-analyses comparing the type of surgery of LH and including mostly same studies. In the first one including 9 studies blood loss, surgical time and hospital stay were found significantly lower in enucleation which is why it should be preferred operation for suitable lesions according to the conclusion of this analysis (7). Meta-analysis of Cheng et al. included 7 studies involving 913 patients. Authors reported less blood loss, shorter operation time and lower rate of postoperative complication according to pooled analysis of studies while the analysis revealed similar transfusion rates and inflow occlusion times (8). Our results are more in line with the retrospective study of Giuliani et al. including 40 surgeries for LH and resulting with no significant difference between enucleation and resection in terms of transfusion, duration of postoperative hospital stay, duration of surgery and morbidity (9). In

another study including 86 patients with giant LHs larger than 10 cm Zhang et al. (10) reported no significant difference between enucleation group and resection group in terms of amount of blood loss, transfusion requirement, surgical time and postoperative hospital stay.

Although there are authors who suggest a higher diameter limit for the definition of giant hemangioma, here we assumed 4 cm as a limit for definition of giant LH. Higher transfusion rates in giant LH operations may be due to the larger surface of the plane between the LH and the liver parenchyma. Zhang et al. (10) reported significantly more intraoperative blood loss and higher complication rates and longer operation times among patients with lesions  $\geq 15$  cm than patients with lesions  $< 15$  cm. Longer operation times and might be because of the time spent for ligation of vessels on the larger surface. Giuliani et al. (9) concluded risk of bleeding and blood transfusion was related more with the large size of the tumor than the type of surgical technique in his series. In the era of modern surgical practice size of LH is not considered to be a sole indication for surgery. But patients undergoing surgery for larger lesions should be informed about increased risk of adverse events and probable necessity of transfusion. Complication rates were found to be higher in our series as well.

In comparisons pain symptom is more frequent in female gender probably due to the larger mean size of LHs in females. Interestingly eight laparoscopic operation were performed in female patients. Probably cosmetic concerns took place in decision for the type of operation. Operative trends for benign disease demonstrate that the proportion of cases performed laparoscopically is increasing. Laparoscopic liver resection for benign lesions has lower intraoperative blood loss, frequency of complications, postoperative analgesic requirements, time to oral intake, and a shorter hospital stay (11). However potential risk of uncontrollable bleeding and gas embolism are major concerns of many surgeons.

We experienced no mortality as it is rarely seen in hemangioma surgery, but adverse events occurred. Patients which experienced serious complications had significantly lower platelet counts while lesion diameters were similar. Probably it was because of high blood flow inside the lesion theoretically have potential to result with loss of thrombocytes (12). When we are evaluating any grade of complication occurred lesion size seems to be a risk factor as mean lesion diameter is greater in complicated cases.



This factor should be taken into account before surgery and while informing patients before consent. Proportion of transfusion requirement was found to be greater in complicated cases as well indicating cause of significant proportion of complications were results of bleeding.

Rate of hemangioma surgeries are decreasing in recent year. Non operative treatments and observation deserve attention in evaluating patients with LH. In a meta-analysis including 1485 patients 402 of whom underwent surgery authors concluded that surgery might take more risks than benefits for non-emergency LH patients (13). In another retrospective study from US 289 patients with giant hemangioma responded the survey. Life threatening events occurred 2% in non-operated group and 7% in surgery group without statistical significance in a mean follow up of 11 years and observation is preferred in most patients. Authors concluded that surgical treatment should be reserved for patients with severe symptoms or disease-associated complications. Persistence of symptoms were reported in only 11% of non-operated patients (14).

Non-surgical interventions including microwave or radiofrequency ablation and angioembolization in the treatment of LHs have been increasingly accepted worldwide. Transarterial angioembolization have promising results to replace surgery in most cases in the future. Furumaya et al. (15) found decrease in lesion size in 89.9% of patients and relief of preoperative symptoms in 98.5% of patients in a review of 18 cohort studies including 1284 cases of transarterial embolization or lipiodolization. In the same article only 2.7% of cases underwent surgery after transarterial intervention. This option also takes role in control of bleeding of ruptured hemangioma and decreasing risk of intraoperative bleeding by preoperative embolization of feeder arteries (16). Response rate of 98% without fatal complications was reported in a meta-analyze of 21 publications including 1450 patients (17). Radiofrequency ablation which can be applied percutaneously, laparoscopically or as an open procedure is considered as a safe, feasible, and effective procedure for LHs, even huge LHs in a consensus report from a Chinese panel of experts. Minimal invasiveness, definite efficacy, high safety, fast recovery, relatively simple operation, and wide applicability were listed as advantages of the procedure (18). There are also several reports regarding to successful utilization of microwave for hemangioma ablation (19–21). Radiotherapy albeit effective is rarely applied to hemangiomas because of adverse effects such as radiation hepatitis, veno-occlusive disease, and hepatoma (22,23). Sixteen patients were reported to be underwent liver transplantation for

LH until 2019. Main indications were respiratory distress, massive hemorrhage and Kasabach-Merritt syndrome. No mortality reported after transplantation (24).

Although study cohort is one of the largest series in the literature limitations of this study include the retrospective design and the absence of long term follow up for late complications.

## CONCLUSION

LH has been a very rare indication for surgery due to emerging interventional treatments and imaging modalities. Although there is still a set of patients requiring surgery even liver transplantation. Enucleation and liver resection are two main surgical approaches with similar outcomes while enucleation is associated with higher transfusion rates according to our study. Morbidity after surgery for hemangioma is more related with the size of the lesion and preoperative thrombocytopenia.

## DECLARATIONS

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### Conflict of Interest

The authors declare that they have no conflict of interest.

### Ethical Approval

This study was approved by the Ethics Committee of Ankara University School of Medicine (İ07-457-22) and was registered at Clinicaltrials.gov (NCT04669314). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

### Availability of Data and Material

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' Contributions

Elvan Onur KIRIMKER: Conceptualization, data curation, project administration, formal analysis, writing – original draft, writing – review and editing. Süleyman Utku ÇELİK: Data curation, formal analysis, writing – original draft, writing – review and editing. Deniz KÜTÜK: Data curation, writing – original draft, writing – review and editing.

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