Surgical Management of Giant Hepatic Hemangiomas: Complications and Review of the Literature

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Background: Hepatic hemangiomas are the most common benign hepatic tumors, and they are usually asymptomatic with normal liver function. When hepatic hemangiomas reach 4 cm, we define them as giant hemangiomas. Treatment options for giant hemangiomas are observation, surgical resection, and transcatheter arterial embolization. The aim of this study was to identify the risk factors for surgical complications.

Methods: In this study, the records of 61 patients with giant hepatic hemangiomas treated with surgical resection at Chang Gung Memorial Hospital, Linkou were retrospectively reviewed. Data on clinical variables including symptoms, the size, number, and location of the tumors, preoperative liver function tests, operative method, operation time, and operative blood loss were collected and analyzed.

Results: There were 8 patients (13.1%, 95% confidence interval 5.8% to 24.2%) with complications after resection or enucleation. Postoperative complications were associated with large tumor size (p = 0.021) and tumors that were symptomatic (p = 0.017). In addition, complications were associated with greater use of intraoperative inflow control (p = 0.053), longer operative time (p = 0.001), and greater intraoperative blood loss (p = 0.022). Most complications could be treated conservatively, but invasive interventions such as endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangial drainage were required for management of grade III complications.

Conclusions: Most giant hepatic hemangiomas can be treated with enucleation or resection. Important factors associated with complications were large tumor size, the presence of symptoms, surgical bleeding, and prolonged surgery. Most complications were grade I and could be treated conservatively. Both resection and enucleation were relatively safe with an acceptable complication rate (13.1%) and no mortality in our study.

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Key words: liver, hemangioma, hepatectomy, complication

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Hemangiomas are the most common benign hepatic tumor, and the prevalence ranged from 3-20% in autopsy series.[1-4] The wide use of abdominal ultrasonography and computed tomography (CT) for various indications has increased the diagnostic rate of hepatic hemangiomas. The etiology of hepatic hemangiomas is not completely understood. They usually originate from the proliferation of vascular endothelial cells, and enlarge by ectasia rather than hyperplasia. They are well-circumscribed tumors with a clear fibrous sheath that separates them from the hepatic parenchyma,[5] and their blood supply originates from the hepatic artery. No malignant changes have been reported in hepatic hemangiomas in long-term follow-up.[6]

Several diagnostic modalities are used for hepatic hemanangiomas. Sonography is usually used to screen liver nodules and a hepatic hemangioma presents as a well-defined, lobulated, homogenous hyperechoic mass. Sometimes there is a hypoechoic portion because of hemorrhage, fibrosis, or calcification. For treatment, multiphasic CT has been used to show peripheral nodular or globular enhancement and typical centripetally progressive enhancement. Magnetic resonance imaging is used to define the anatomical relationship of liver Glissonian pedicles and hemangiomas.

The incidence of hemangiomas is highest in the 3rd to 5th decades of life, and they are more common in women.[7-10] The growth of hemangiomas may be related to hormone levels, and exposure to high levels of estrogen and progesterone, such as occurs with multiparity, pregnancy, and oral contraceptive use, may be the reason the condition is more common in women. However, the pathogenesis of hepatic hemangiomas is still controversial.

Hepatic hemangiomas are usually asymptomatic, patients have normal liver function, and the course is typically long and uneventful.[10] Because of the absence of symptoms, the size of hepatic hemangiomas can vary greatly when discovered. Giant hemangiomas are defined as tumors with a diameter > 4 cm, and symptoms rarely appear unless the tumor size exceeds 4 cm.[11-13] The symptoms of giant hemangiomas vary from a mild abdominal compressive sensation to hemoperitoneum due to tumor rupture.[12] Many treatment options are available for hepatic hemangiomas. Close observation should be reserved for asymptomatic tumors, and surgical resection is offered for symptom relief of complicated hemangiomas or lesions in which the diagnosis is uncertain.[7,13,14] When surgical intervention is required, enucleation is the preferred option for giant hepatic hemangiomas because it provides better preservation of the normal liver parenchyma compared with a lobectomy.[13-15]

Since hepatic surgery is a significantly invasive procedure for a benign lesion, the surgical benefits and complications must be carefully weighed. Therefore, the purpose of this study was to identify associated risk factors for postoperative complications, classify the severity of the complications and review the approaches to their management.

METHODS

Between January 2000 and July 2010, 61 patients who underwent hepatic resection for giant hemangiomas (> 4 cm) were reviewed at Chang Gung Memorial Hospital, Linkou. Indications for hepatic resection included abdominal pain (n = 26), compression symptoms (n = 13), enlarging tumor size (n = 11), incidental findings during laparotomy (n = 1), tumor bleeding (n = 2) and uncertain diagnosis (n = 8). Data on clinical variables including sex, age, symptoms, the size, number, and location of the tumors, preoperative liver function tests, operative method, operative time, blood loss, length of hospital stay, and complications were collected for analysis. Tumors with medial or right anterior segment involvement or hilum attachment were classified as centrally located, whereas others were classified as peripherally located. The tumor was measured during pathological examination of the surgical specimen, and the largest diameter was recorded if there were multiple tumors.

The operative methods for the management of hepatic hemangiomas included enucleation and lobectomy (or resection). Enucleation was performed by dissecting the tumor from the surrounding hepatic parenchyma along the plane of the tumor capsule. Hepatic lobectomy was carried out by removing the hepatic parenchyma containing the hemangioma, and blood vessels and bile ducts were ligated and divided as necessary. Pringle's maneuver was used to reduce operative bleeding in select cases by alternating 15 minutes of ischemia with 5 minutes of reperfusion. A Jackson-Pratt drainage tube was placed to detect

postoperative bile leakage or bleeding. Postoperative complications were evaluated according to the Clavien- Dindo classification of surgical complications.[16]

The 95% confidence interval of the complication rate was calculated by the binominal test and the t-test was used for comparison of continuous variables. Data were expressed as mean ± standard deviation (SD). A value of $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using SPSS version 13.0 software (SPSS Inc., Chicago, IL, U.S.A.) or STATA 9.2 (College Station, Tx, U.S.A.).

RESULTS

Patient data are presented in Table 1. Forty-five (73.8%) of the 61 patients, were women. The tumors

Table 1. Baseline and Clinicopathological Characteristics of Patients with and without Complications

	All patients (n = 61)	Complications (n = 8)	No complications (n = 53)	*p* value
Age (years)	47.3 ± 11.1	48.4 ± 6.5	47.2 ± 11.6	0.777
Sex			1.0	
M	16	2 (12.5)	14 (87.5)	
F	45	6 (13.3)	39 (86.7)	
Symptoms				0.017
Yes	36	8 (22.2)	28 (77.8)	
No	25	0 (0)	25 (100)	
Tumor location				
Right	24	5 (20.8)	19 (79.2)	0.887
Left	26	2 (7.7)	24 (92.3)	
Bilateral	11	1 (9.1)	10 (90.9)	
Central	35	7 (20.0)	28 (80.0)	0.067
Peripheral	26	1 (3.8)	25 (96.2)	
Tumor number				0.423
Single	44	7 (15.9)	37 (84.1)	
Multiple	17	1 (5.9)	16 (94.1)	
Tumor size (cm)	10.0 ± 4.1	13.1 ± 4.4	9.5 ± 3.9	0.021
Aspartate aminotrans ferase	23.6 ± 17.8	16.50 ± 6.1	24.7 ± 18.7	0.227
Alanine aminotransferase	26.5 ± 31.8	15.3 ± 7.5	28.2 ± 33.7	0.287
Total bilirubin	1.0 ± 1.1	1.0 ± 0.5	0.940 ± 1.2	0.866
Alkaline phosphatase	72.4 ± 98.8	77.0 ± 29.2	71.7 ± 105.5	0.888
Hemoglobin	12.5 ± 1.8	12.2 ± 1.6	12.5 ± 1.8	0.583
Platelets	231.3 ± 61.7	196.1 ± 63.4	236.6 ± 60.3	0.084
International normalized ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.490
Surgical method				0.125
Lobectomy	36	7 (19.4)	29 (80.6)	
Enucleation	25	1 (4.0)	24 (96.0)	
Inflow control				0.053
Yes	31	7 (22.6)	24 (77.4)	
No	30 (49.2)	1 (3.3)	29 (96.7)	
Operative time	248.4 ± 91.9	349.1 ± 82.5	233.2 ± 83.9	0.001
Blood loss (ml)	609.8 ± 827.4	1718.8 ± 1232.9	442.5 ± 606.3	0.022
Hospital stay (days)	11.2 ± 3.9	15.3 ± 6.5	10.6 ± 2.9	0.084

Continuous variables are represented by mean ± SD, and categorical data are shown by number (percentage).
Fisher's exact test and the independent-*t* test were used for analysis.

were located in the left lobe in 26 patients (42.6%), right lobe in 24 patients (39.3%), and bilaterally in 11 patients (18.1%). Multiple tumors were found in 17 patients (27.9%) and the tumors were symptomatic in 36. The clinical analysis of these 61 patients showed there were no significant differences in tumor size (10 cm) and clinical symptoms (p = 0.201) between patients with and without complications. Nine out of 25 patients with tumors larger than 10 cm had symptoms (36%) whereas 16 out of 36 (44%) with smaller tumors (< 10 cm) had symptoms.

A total of 36 lobectomies and 25 enucleations were performed. Chi-square analysis showed no significant relationship between the type of surgery (enucleation or lobectomy) and the number or location of tumors. The data are shown in Table 2 and Table 3 (p = 0.624 and 0.593, respectively).

Pringle's inflow control was applied in 31 patients (50.8%). Eight patients had complications, including bile leakage (n = 2), ileus (n = 4), gastrointestinal bleeding (n = 1), and a wound infection (n = 1). The complication rate was 13.1% (95% CI 5.8% to 24.2%), and no mortalities occurred.

The clinical and pathological data of patients with and without surgical complications were compared (Table 1). The presence of surgical complications was not related to age, sex, tumor location or number. There was a trend that centrally located tumors had a higher incidence of complications, but it was not significantly different (p = 0.067). Preoperative liver function was also comparable in both groups. However, the 8 patients who experienced complications were all symptomatic, and had larger tumors than patients without complications (mean, 13.1 cm vs. 9.5 cm, respectively; p = 0.021). Patients with surgical complications also had a higher rate of lobectomies (n = 7; 87.5%), a longer operative time (349 min vs. 233 min, respectively; p = 0.001), and greater intraoperative blood loss (1718 ml vs. 442 ml, respectively; p = 0.022) than those without complications. More Pringle's inflow controls were used in the group with surgical complications. The hospital stay was also longer for patients with surgical complications (15 days vs. 10 days, respectively), but the difference was not statistically significant.

In this study, grade I complications including a wound infection and postoperative ileus were successfully managed with conservative treatment (Table 4). Postoperative ileus was the most common complication (n = 4), but no surgical intervention was required in our series. Grade II complications, including one gastrointestinal bleeding and two minor cases of bile leakage occurred in our series, and were all managed non-surgically. Neither endoscopic treatment nor transfusion was required for the patient with gastrointestinal bleeding. Medical treatment with an intravenous proton pump inhibitor and intravenous fluid supplements were adequate for this patient. Conservative treatment with percutaneous drainage was successful in both cases of bile leakage.

One case developed obstructive jaundice after hepatectomy because of angulation and stenosis of the right intrahepatic duct. Interventional treatment finally solved this problem. One case with a grade IIIa complication was treated with endoscopic retrograde cholangiopancreatography (ERCP). Internal biliary stenting was attempted initially, but failed because of sharp angulation of the right intrahepatic duct and common bile duct (Table 4).[16] Percutaneous transhepatic cholangiography and drainage (PTCD) was then performed. In addition to external drainage, the PTCD catheter was successfully advanced to the common bile duct, and bile could be drained into the duodenum without a stent 6 months later. Follow-up after 5 years revealed no biloma recurrence or biliary tree dilatation (Table 4).

Table 2. Association of Tumor Location and Operative Method

	Right lobe	Left lobe	Both lobes
Lobectomy	13 (36.1%)	15 (41.7%)	8 (22.2%)
Enucleation	11 (44.0%)	11 (44.0%)	3 (12.0%)

p-value = 0.624 by Fisher's exact test.

Table 3. Relationship between Number of Hepatic Hemangiomas and Operative Method

	One tumor	Two tumors	Multiple tumors
Lobectomy	24 (66.7%)	6 (16.7%)	6 (16.7%)
Enucleation	20 (80.0%)	3 (12.0%)	2 (8.0%)

p-value = 0.593 by Fisher's exact test.

Table 4. Characteristics of Patients with Complications

No.	Sex	Age (years)	Symptoms	Tumor size (cm)	Central or Peripheral	Operation method	Inflow control	Blood loss (ml)	Complication	Management	Grade of complication	Hospital stay (days)
61	F	45	Jaundice, bleeding	14.5	Central	Lobectomy	Yes	3800	Wound infection	Open dressing	I	10
3	F	42	Pain	11.5	Central	Lobectomy	Yes	1200	Ileus	Conservative	I	9
9	F	46	Mass	19	Central	Lobectomy	Yes	4400	Ileus	Conservative	I	11
10	M	42	Pain	9	Central	Lobectomy	Yes	850	Ileus	Conservative	I	7
47	F	51	Pain	9	Peripheral	Enucleation	No	600	Ileus	Conservative	I	7
12	M	54	Pain	20	Central	Lobectomy	Yes	2500	GI bleeding	Conservative	II	8
4	F	41	Mass	14.1	Central	Lobectomy	Yes	1500	Bile leak	Drainage	II	7
42	F	58	Pain	13	Central	Lobectomy	Yes	1000	Bile leak	PTCD and biliary stenting	III	27

Abbreviation: PTCD: percutaneous transhepatic cholangial drainage.

DISCUSSION

Giant hemangiomas are usually asymptomatic. Surgical treatment is considered when the lesion grow or symptoms occur. Operative management for hepatic hemangiomas must carefully consider the estimated risk of surgical complications.[7] In this study, we attempted to identify potential risk factors for complications, and reviewed the management of serious complications.

Rupture of a hemangioma is a rare complication that can result in death without treatment. Transcatheter arterial embolization (TAE) is one of the treatment options; however, there are only a few case reports of successful treatment of ruptured hemangiomas with TAE.[18] In our series, only two patients received angiographic embolization. The first patient had spontaneous hemoperitonium revealed by CT scan. An angiogram showed no active bleeding and the patient was stable hemodynamically. She received a hepatic resection and no postoperative complications occurred. The second patient had a 14.5 cm hemangioma at the hepatic hilum with intratumoral bleeding and presented with obstructive jaundice. Treatment with TAE failed to stabilize the patient hemodynamically, and an extended left lobectomy was performed. Her postoperative course was complicated by a wound infection that was managed with local wound care.

Management of complications is a concern because a hemangioma is a stable condition and patients have a good quality of life. In our series, grade I and grade II complications were managed conservatively.[16] Invasive procedures including ERCP and PTCD were applied for grade III complications.

A literature review of the surgical management of hepatic hemagiomas is presented in Table 5. Most studies report a difference in outcomes between enucleation and resection.[2,12-14,19-21] Our early study presented by Tsai et al showed effective indications for surgery for hemangioma.[20] Thirteen of 40 patients with residual tumor showed minimal progression. The tumors ranged from 2 to 10 cm.

In the present study we focused on large tumors because they carry high risks in operations and surgical management. The surgical methods have not differed in the past two decades, and this study showed there is no significant difference in complications. Managing complications in liver surgery is the key issue to a good clinical outcome because surgical intervention still carries some risks.

Table 5. Literature Review of Surgical Management and Complications of Hepatic Hemangiomas

Author	Number of patients	Number (%) of complications	Aim of study	Special remarks
Schwartz, et al.[2]	16	3 (18.8)	Review of the literature and single center experience	Mortality rate near 0% in all series Two subphrenic abscesses and one postoperative bleeding
Brouwers et al.[19]	24	5 (20.8)	Review the results of surgical treatment	Complications included bile leakage (2), pneumonia (1), wound dehiscence (1), upper gastrointestinal bleeding (1), and seroma (1) No progression of residual hemangioma during follow-up
Tsai et al.[20]	43	4 (9.3)	Symptomatic group vs. suspicious diagnosis	Resection for patients with symptoms and questionable diagnosis, including small and giant hemangioma One case of bile leakage required reoperation
Lerner et al.[14]	52	14 (26.9)	Enucleation vs. resection	Enucleation preferred technique Bile leakage (2), ileus (3), wound infection (1), angina (1), and fever (1)
Hamaloglu et al.[13]	22	3 (13.6)	Resection vs. enucleation	Enucleation was the choice of therapy Complications included pleural effusion (1), liver abscess (1), and wound infection (1)
Singh et al.[15]	21	5 (23.8)	Compare enucleation and liver resection	Enucleation was safer, quicker, and associated with less morbidity than liver resection
Fu et al.[21]	172	5 (2.97)	Central vs. peripheral	Complications were bile leakage (2) and pleural effusion (3) No difference in complications Technically more demanding for centrally located hemangiomas
Present study	61	8 (13.1)	Clinicopathological variables related to complications	Tumor size and symptoms were themost important factors associated with complications

In this study, the statistical power was limited because of the small sample size; therefore, a study with a larger sample size is needed to locate important factors associated with complications. Although enucleation and liver resection are both curative, enucleation offers greater preservation of normal hepatic parenchyma, less blood loss, less need for blood transfusions, fewer complications, and a shorter hospital stay. Thus enucleation is the preferred technique for suitable lesions.

In this study, the complication rates for enucleation and resection were 4.0% (1/25) and 19.4% (7/36), respectively, but the difference was not statistically significant ($p = 0.125$). Patients with large tumors or symptoms, indicating difficulty in surgery, should be carefully managed. Giant hemangiomas with a central location also carried higher risks of complications ($p = 0.067$). Delicate surgical management to prevent unnecessary bleeding and to shorten operative time is important for the surgical outcome.

Surgical intervention is indicated for giant hepatic hemangiomas with symptoms or hepatic lesions with an uncertain diagnosis. Resection and enucleation were both relatively safe with an acceptable complication rate (13.1%) in our series and there was no mortality.

Moreover, bile leakage and pleural effusion were the most common serious complications. The rate of bile leakage after hepatic resection has been reported to be 6-11%, and most patients recover with conservative treatment.[22,23] Endoscopic therapy such as ERCP, with or without sphincterotomy, or biliary stenting, offers another strategy for the management of surgical complications, and yields good results.[24] While testing for bile leakage during hepatic resection has been recommended, a randomized trial suggested this procedure offers no advantages.[25]

Conclusions

Surgical resection is the treatment option for symptom relief of complicated hemangiomas or lesions in which the diagnosis is uncertain. Both enucleation and liver resection offer curative treatment; enucleation is favored because of greater preservation of liver parenchyma and fewer complications. This study identified factors associated with surgical complications in the treatment of giant hepatic hemangiomas. Clinical features including large tumor size, symptomatic tumors, increased blood loss, and prolonged operative time, indicating higher risks, were associated with an increase in postoperative complications. When complications occurred, most could be treated conservatively. However, when grade III complications developed, remedial treatment with invasive interventions such as ERCP, spincterotomy, biliary stenting, and PTCD, were the choice of treatment. For giant hepatic hemangiomas with symptoms or hepatic lesions with an uncertain diagnosis, surgical intervention is indicated. Both resection and enucleation were relatively safe with an acceptable complication rate (13.1%) in our series there was no mortality.

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巨大肝血管瘤之外科治療：併發症及文獻回顧

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背 景： 肝血管瘤是肝臟最常見的良性腫瘤 (3~20%)，當腫瘤超過 4 公分時，我們就稱之爲巨大肝血管瘤。巨大肝血管瘤常見的治療爲觀察或手術切除。目前對於何種患者必須接受手術治療還未有定論，但對於無症狀的患者，持續的追蹤是合理的處理方式。而手術切除巨大肝血管瘤的常見適應症爲持續的症狀如腹痛或腹漲，無法確診腫瘤的性質爲良性或惡性，以及發生腫瘤的併發症如腫瘤破裂出血等等。手術的術式則視病人的臨床狀況及影像報告來決定，分爲腫瘤摘除 (enucleation) 以及部份肝切除 (hepatic resection or lobectomy)。許多文獻指出腫瘤摘除 (enucleation) 的併發症及流血等情況都比肝臟切除來的更少。

方 法： 此研究收集了林口長庚醫院自 2000 至 2010 年巨大肝血管瘤接受手術治療的患者共 61 位。分析臨床症狀，腫瘤位置及大小，開刀術式，手術時間及失血量，住院天數，以及是否有併發症等資料，並比較有併發症的患者與無併發症的患者的差異。

結 果： 這 61 位患者當中，共有 8 位在手術後產生併發症，比率爲 13.1% (95% confidence interval 5.8% to 24.2%)。手術前有症狀的病人術後有併發症的比率較高 ($p = 0.017$)，腫瘤較大的病人 ($p = 0.021$)，手術時間久 ($p = 0.001$)，以及失血量較多的病人 ($p = 0.022$) 也有較高的比例有手術併發症。最常見的併發症爲腸阻塞 (n = 4)，患者在保守治療後都可恢復。一位患者因手術傷口感染接受開放式傷口照護。一位患者在術後併發上腸胃道出血，保守治療成功，並未接受上消化道內視鏡或是輸血的治療。另外有兩位患者併發膽汁滲漏。其中一位出院後於門診移除手術中的引流管，另一位則接受經皮穿肝膽管引流。

結 論： 回顧其他文獻，我們的資料首次指出在術前有症狀及腫瘤較大的病人在手術的執行較困難而且較容易有術後併發症。而大部分的巨大肝血管瘤都可經由手術安全的切除，手術的併發症也以保守治療爲主。但由於樣本數少，統計學的效力也受到限制，因此未來包含更多患者的研究才能更進一步的釐清各個變數與併發症的關係。
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關鍵詞： 肝，肝海綿狀血管瘤，手術切除，併發症

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