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Examination of Factors Affecting the Development of Recurrence in Operated Cases with Liver Hydatid Cysts

Karaciğer Hidatik Kisti Nedeniyle Cerrahi Uygulanan Olgularda Rekürrens Gelişimini Etkileyen Faktörlerin Değerlendirilmesi

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Introduction: Hydatid disease is a serious parasitic infection caused by *Echinococcus granulosus*. The most effective treatment method is surgery. The recurrence of disease is an important long-term postoperative complication. The present study investigates the factors affecting recurrence in operated cases of liver hydatid cysts.

Material and Methods: The study examines the data who underwent surgical therapy for hydatid cysts with liver localization between 2008-2014. Age, gender, serological test results, radiological examination results, ASA score, operational technique, postoperative complications were reviewed retrospectively, making use of the hospital information system and the patient records.

Results: Total 166 patients with liver hydatid cysts were analyzed. Of the study group, recurrence developed in 26 (15.6%) patients and 15 (9%) patients were female. The indirect hemagglutination test (IHAT) was positive in 96 (65.8%) patients. Recurrence developed in 15.6% of the IHAT (+), 20.0% (n=8) of patients with a cystic lesion of >10cm. There was further no statistically significant difference between the diameter of cystic lesion, serological test results (IHAT), gender, age, Gharbi classification and recurrence development regardless of the type of surgical intervention (p>0.05). Multiple cystic lesions were identified in 44 (26.5%) patients and recurrence rate was 29.5% (n=13). The rate of recurrence in this group is significantly higher than patients with a single cystic lesion (p<0.05). Recurrence was observed to develop at a lower rate among patients undergoing radical surgery groups than conservative ones (5.9% v.s 22.2%, p<0.05).

Discussion and Conclusion: Recurrence is a very important issue in hydatid cyst surgery. Patients with multiple cysts having a significantly higher rate of recurrence. Likewise, radical surgical procedures reduce the development of recurrence rather than conservative ones, significantly. That said, radical surgical interventions are performed less frequently, as more experience is required, and this may be associated with the high recurrence rates.

Keywords: Hydatid cyst, surgery, recurrence, cyst characteristics.

Giriş: Hidatik hastalık, *Echinococcus granulosus* tarafından oluşturulan ciddi bir paraziter enfeksiyondur. En etkili tedavi yöntemi cerrahidir. Hastalığın nüksü, uzun dönem postoperatif dönemde önemli bir komplikasyondur. Bu çalışmada, karaciğer hidatik kisti nedeniyle ameliyat edilen olgularda nüks gelişimini etkileyen faktörlerin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmada, 2008-2014 yılları arasında karaciğer yerleşimli hidatik kist nedeniyle cerrahi tedavi uygulanan hastaların verileri incelenmiştir. Hastaların yaş, cinsiyet, serolojik test sonuçları, radyolojik inceleme bulguları, ASA skoru, uygulanan cerrahi teknik ve postoperatif komplikasyonları; hastane bilgi sistemi ve hasta dosyaları kullanılarak retrospektif olarak değerlendirilmiştir.

Bulgular: Toplam 166 karaciğer hidatik kisti hastası analiz edilmiştir. Çalışma grubunda 26 (%15,6) hastada nüks gelişmiş olup, bu hastaların 15'i (%9) kadındır. İndirekt hemagglütinasyon testi (IHAT) 96 (%65,8) hastada pozitif bulunmuştur. IHAT (+) hastaların %15,6'sında, çapı 10 cm'den büyük olan kistik lezyonu bulunan hastaların ise %20,0'sinde (n=8) nüks gelişmiştir. Kistik lezyon çapı, serolojik test sonuçları (IHAT), cinsiyet, yaş, Gharbi sınıflaması ve uygulanan cerrahi tekniğe bakılmaksızın nüks gelişimi arasında istatistiksel olarak anlamlı fark saptanmamıştır (p>0,05).

Kırk dört (%26,5) hastada multipl kistik lezyon saptanmış olup, bu grupta nüks oranı %29,5 (n=13) olarak bulunmuştur. Bu oran, tek kistik lezyonu olan hastalara göre anlamlı derecede daha yüksektir (p<0,05). Radikal cerrahi uygulanan hastalarda nüks oranı, konservatif cerrahi uygulanan hastalara kıyasla anlamlı derecede daha düşük bulunmuştur (%5,9'a karşı %22,2; p<0,05).

Tartışma ve Sonuç: Hidatik kist cerrahisinde nüks, oldukça önemli bir sorundur. Multipl kisti bulunan hastalarda nüks oranı anlamlı derecede daha yüksektir. Benzer şekilde, radikal cerrahi girişimler konservatif yaklaşımlara kıyasla nüks gelişimini anlamlı şekilde azaltmaktadır. Bununla birlikte, radikal cerrahi girişimler daha fazla deneyim gerektirdiğinden daha seyrek uygulanmakta olup, bu durum yüksek nüks oranları ile ilişkili olabilir.

Anahtar Kelimeler: Hidatik kist, cerrahi, nüks, kist özellikleri.

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INTRODUCTION

Cystic echinococcosis (CE) or hydatid disease is a serious zoonotic infectious disease caused by *Echinococcus granulosus*, which are seen mostly in Western China, Central Asia, Russia, South America, the Mediterranean countries, including Turkey and East Africa. Although CE mostly occurs in the liver (70%), the lungs (10%) and others (kidneys, spleen, pancreas, heart, brain and bones) (20%) can also be affected (Wen et al., 2019; Dietrich et al., 2020; Bhutani and Kajal, 2019).

Diagnosis is based on imaging methods and serological methods (IHAT, ELISA, latex agglutination, indirect agglutination, indirect fluorescent antibody test and Western blot). The occurrence of symptoms is not associated with the size or number of cysts, as it may also be related to the localization of the cyst in the organ and the pressure applied on the surrounding structures (Nunnari et al., 2012).

The treatment of liver CE involves antiparasitic therapy (mebendazole, albendazole), surgical methods (open and laparoscopic approach) and percutaneous interventions. Surgical therapy is the most effective approach to the treatment of liver CE. The goal of surgery is to fully excise the germinative membrane and to completely eradicate the parasites before they spread to other organs, and to ensure the sterilization of the cyst content. Radical surgery is associated with a lower risk of recurrence, but a higher operation risk. In contrast, conservative surgery is easier to perform, but comes with a higher likelihood of recurrence (Nunnari et al., 2012). It is seen in the literature that recurrence rates vary between 2-25% (Brunetti et al., 2010; McNanus et al., 2012).

The present study investigates the factors affecting the development of recurrence through a retrospective examination of characteristics and localization of the cyst, serological test results, radiological findings, administered treatments, surgical method, complications and recurrence development.

MATERIALS AND METHODS

Study Design and Population

The data of 166 patients who underwent surgical therapy for hydatid cyst with liver localization in İzmir Tepecik Training and Research Hospital between 2008 and 2014 was analyzed, garnered from the hospital information system, patient files and the medical records of the clinic. The patients' age, gender, serological test results (IHAT), biochemical values, radiological examination results (diameter, number and localization of cysts, Gharbi classification score), ASA score, operational technique, length of hospital stay, postoperative early and late complications, development of recurrence and associated were reviewed retrospectively. Patients younger than 18 years old, whose data cannot be reached and who are out of control were excluded from the study (n=16). All patients were administered albendazole and mebendazole as anti-parasitic medications before surgery for one month and after surgery for 6 months. For cases treated with the conservative surgical method, a 20% sodium chloride (NaCl) solution and povidone iodine were used as a scolicidal agent.

Statistical analysis

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistics (mean, standard deviation, median, frequency, percentage, minimum and maximum) were used for the evaluation of the study data. The normality of the distribution of the numerical values was tested with a Shapiro-Wilk test and graphic evaluations. The student's t test and Mann-Whitney U test were used for the comparison of quantitative variables, respectively with and without normal distribution, between the two groups; and a Pearson's Chi-square test, Fisher-Freeman-Halton test and Fisher's Exact test were used for the comparison of qualitative variables. The level of statistical significance was accepted as $p < 0.05$.

FINDINGS

Among the 166 patients operated on for liver hydatid cyst 105 (63.3%) were female. The mean age was 44 ± 1.7 (range: 16-84). The length of hospital stay did not differ between the conservative surgical intervention patients and radical ones ($p > 0.05$) (Table-4). Radical surgical approaches were used for 40.3 % ($n=67$) of the patients while complications and recurrences developed in 22 (32.8%) and four (5.9%) of these patients, respectively. The mean duration of recurrence development was 14.6 months among the patients who underwent radical surgery (Table 1). Conservative approaches were performed on a total of 99 (59.6%) patients, and complications and recurrences developed in 26 (26.2%) and 22 (22.2%) of these patients, respectively. The mean duration of recurrence development was 15.2 months among the patients receiving conservative surgery. A postoperative biliary fistula occurred in 9.1% ($n=9$ of the patients (Table 2). Complication of biliary fistula developed in one patient (1.0%) while other

than biliary fistula developed in 17.1% ($n=17$) of the patients including; surgical site infection, hepatic abscess, cyst perforation, diaphragmatic injury, gastric injury, bladder injury, respiratory failure, colon perforation, evisceration, obstructive icterus and anaphylaxis (Table 1). Omentopexy was the most commonly preferred method for the obliteration of the cyst location after the cystotomy, which was followed by capitonnage, introflexion and falciformepexy, respectively. Among the patients undergoing bile duct association of cysts that were primary repaired ($n=42$), of these biliary fistulas developed in 19% ($n=8$) (Table 1).

The most common complication among patients who underwent surgical therapy due to hydatid cyst revealed to be biliary fistula (9.0%) (Table-3). Among these complicated patients, the fistula closed spontaneously following symptomatic monitoring in eight (53.3%), while six (40.0%) were treated with an endoscopic retrograde cholangiopancreatography-endoscopic sphincterotomy (ERCP-ES).

Table 1. Surgical methods used for hydatid cyst surgery, and the associated complication and recurrence rates

	Number n (%)	Postoperative biliary fistula n (%)	Other Complications n (%)	Recurrence n(%)
<u>Conservative surgical methods</u>			**	
Cystotomy+Omentopexy	25 (25.3)	1 (1.0)	2 (2.0)	4 (4.0)
Cystotomy+Capitonnage	5 (5.1)	-	1 (1.0)	-
Cystotomy+Introflexion	4 (4.0)	-	1 (1.0)	-
Cystotomy+Falciformepexy	3 (3.0)	-	1 (1.0)	1 (1.0)
Cystotomy+drainage	16 (16.2)	-	4 (4.0)	5 (5.1)
Cystotomy	3 (3.0)	-	1 (1.0)	1 (1.0)
Cystotomy+Repair of Bile Ducts	42 (42.4)	8 (8.1)	7 (7.1)	11 (11.1)
Explorative Laparotomy	1 (1.0)	-	-	-
Total	99 (100)	9 (9.1)	17 (17.1)	22 (22.2)
<u>Radical surgical methods</u>			*	
Hepatic Resection	10 (14.9)	2(2.9)	5 (7.5)	-
Cystectomy	10 (14.9)	2(2.9)	1 (1.5)	2 (2.9)
Laparoscopic cystectomy	13 (19.4)	1(1.5)	4 (5.9)	1 (1.5)
Partial cystectomy	34 (50.8)	1(1.5)	6 (8.9)	1 (1.5)
Total	67 (100)	6(8.9)	16 (23.9)	4 (5.9)

****Other complications:** Surgical site infection, gastric injury, diaphragmatic injury, evisceration, hematoma.

***Other complications:** surgical site infection, gastric injury, diaphragmatic injury, hepatic abscess, cyst perforation, evisceration, bladder injury and biliary fistula, respiratory failure, hematoma, colon perforation, obstructive icterus, anaphylaxis.

Table 2. Postoperative complications, biliary fistula and recurrence development in hydatid cyst surgery

	All surgical procedures (%)	Radical procedures (%)	Conservative procedures (%)	p value
Complications	33 (19.8)	16 (23.9)	17 (17.1)	>0.05
Biliary fistula	15 (9.0)	6 (8.9)	9 (9.1)	>0.05
Recurrence	26 (15.6)	4 (5.9)	22 (22.2)	<0.05
Total	166 (100)	67 (100)	99 (100)	-

Table 3. The relationship between the Gharbi staging of the patients, and the cyst diameter, the surgical intervention performed and recurrence

		Gharbi Staging					Total (n:166)
		Type 1 (n:4)	Type 2 (n:44)	Type 3 (n:84)	Type 4 (n:34)	Type 5 (n:0)	
Cyst diameter	<10 cm	4 (2.4)	35 (21.1)	61 (36.7)	26 (15.7)	-	126 (75.9)
	>10 cm	-	9 (5.4)	23 (13.9)	8 (4.8)	-	40 (24.1)
Number of cysts	Single	3 (1.8)	28 (16.8)	66 (39.7)	25 (15.1)	-	122 (73.4)
	Multiple	1 (0.6)	16 (9.6)	18 (10.8)	9 (5.4)	-	44 (26.5)
Surgical method	Radical	2 (1.2)	21 (12.6)	27 (16.3)	17 (10.2)	-	67 (40.4)
	Conservative	2 (1.2)	23 (13.9)	57 (34.3)	17 (10.2)	-	99 (59.6)
Recurrence		-	9 (5.4)	10 (6.0)	7 (4.2)	-	26 (15.6)

Table 4. Analysis of the factors affecting the development of recurrence in hydatid cyst surgery

	Number (%)	Recurrence (%)	p value
Serology			
IHAT (+)	96	15 (15.6)	X ² =0.132
IHAT (-)	50	7 (14.0)	p>0.05
Age			
>65 years	18	4 (22.2)	X ² =1.73
<65 years	148	22 (14.9)	p>0.05
Gender			
Female	105 (63.3)	15 (14.3)	X ² =0.20
Male	61 (36.7)	11 (18.0)	p>0.05
Number of Cysts			
Single	122	13 (10.6)	X ² =4.86
Multiple	44	13 (29.5)	p<0.05***
Cyst Diameter			
>10 cm	40	8 (20.0)	X ² =0.561
<10 cm	126	18 (14.3)	p>0.05
Length of Hospital Stay (days)			
Conservative	7±0.7 (59.6)		t=-2.66
Radical	6±0.3 (40.4)		p>0.05
Gharbi classification			
1	4 (2.4)	-	X ² =2.51 p>0.05
2	44 (26.5)	9 (20.5)	
3	84 (50.6)	10 (11.9)	
4	34 (20.5)	7 (20.6)	
5	-	-	
Surgical methods			
Radical	67	4 (5.9)	X ² =4.122
Conservative	99	22 (22.2)	p<0.05***

IHAT: Indirect hemagglutination test

One (6.7%) patient was subjected to T-tube drainage due to an obstructive icterus along with a postoperative biliary fistula. In terms of the development of biliary fistula and other complications, there was no statistically significant difference between the radical and conservative surgery groups ($p>0.05$). That said, recurrence, which is a late complication, occurred at lower rates among those treated with radical surgical methods (5.9%) when compared to the conservative method group (22.2%), and the difference was statistically significant ($p<0.05$) (Table-2).

The follow-up period was 6–72 months, and the range of recurrence detection was postoperative months 10–24. The mean duration of recurrence detection was 15.1 months. i(range: 26-80) years. Among the patients suffering a recurrence, 11 were male and 15 were female. Recurrence was detected in four (22.2%) of the 18 patients above 65 years of age, while 22 (14.9%) of the 148 patients under the age of 54 had recurrence. There was no statistically significant association between age and recurrence ($p>0.05$) (Table-4). When the cysts were classified according to the Gharbi criteria, the most common cyst was found to be type-3 (50.6%). Recurrence was found to be most common among those with type 3 cysts (38.5%, $n=10$), followed by type-2 (34.6%, $n=9$) and type-4 (26.9%, $n=7$), respectively. There was no type-5 cyst in the present study, and no recurrence was observed in type 1 cysts (Table 3). When examined in terms of cyst type and recurrence development, however, no significant association was found between cyst types and recurrence rates ($p=0.473$).

There were multiple cystic lesions in 26.5% ($n=44$) of all the patients and recurrence was identified in 29.5% and 10.5% of the patients with multiple and a single cystic lesion, respectively. No radical surgery was performed on seven of the 13 patients with recurrence and multiple cystic lesions, four patients received radical surgical interventions, and two patients underwent radical and conservative surgery for multiple lesions. The rate of recurrence was found to be statistically significantly higher among those with multiple cystic lesions when compared to those with single cystic lesions ($p<0.05$) (Table-4). A serological examination

was made for 146 patients, and the indirect hemagglutination test (IHAT) was positive in 65.8% ($n=96$). Recurrence developed in 15.6% of the IHAT(+) and 14.0% of the IHAT(-) patients. There was no statistically significant difference in recurrence development between the IHAT(+) and IHAT(-) patients ($p>0.05$) (Table-4).

When the association between the diameter of the cystic lesion and recurrence was examined, recurrence developed in eight (20.0%, $n=40$) patients with a cystic lesion of >10 cm, and in 18 (14.2%, $n=126$) with a cystic lesion of <10 cm. There was no statistically significant relationship between cystic lesion diameter and recurrence development ($p>0.05$) (Table-4). According to the Gharbi classification, no statistically significant association between cyst type and recurrence, regardless of the type of surgical intervention ($p>0.05$) (Table 3). A comparison of recurrence development in the radical and conservative surgery groups of patients revealed that recurrence developed in four (5.9%) and in 22 (22.2%) patients, respectively. Recurrence was observed to develop at a lower rate among the patients undergoing radical surgery than those undergoing conservative surgery and the difference was found to be statistically significant ($p<0.05$) (Table-4).

RESULTS AND CONCLUSION

The annual incidence of CE in endemic regions varies from 1 to 200 per 100,000. Turkey is among the high endemic regions (1). Considering the studies conducted in our country to date, as in our work, patients are middle-aged and the male/female ratio varies from 1:2 to 3:7 (Kaya et al., 2019; Islami Parkoohi et al., 2018; Mor et al., 2018).

No statistically significant association was found between recurrence development and age, which was consistent with literature (Kaya et al., 2019; Islami Parkoohi et al., 2018) (Table 4).

In the present study, IHAT was positive in 96 (65.7%) of 146 patients. Müftüoğlu et al. (2005)

examined 235 patients with hydatid cysts, and reported IHAT positivity in 186 (90.2%) of 206 patients. The sensitivity of IHAT has been reported in the 80–94% range, and was found to be 65.7% in the present study (Gönlüğü et al., 2004). The IHAT results of the 20 patients included in the present study could not be accessed. Such low rates may be associated with missing patient data. Literature lacks sufficient data on the seropositivity and recurrence relationship, although the present study could establish no significant relationship between seropositivity and recurrence (Table 4).

The Gharbi classification, which uses the morphological characteristics of liver hydatid cysts, is infrequently used today for the classification of cysts based only on their radiological characteristics. It is suggested that percutaneous aspiration, injection and reaspiration (PAIR) therapy to patients with type I and type II cysts, while type III and type IV cysts were subjected to surgical therapy. In the present study, the most common type is type III, followed by type II and biliary fistula – a postoperative early complication – to be more common with type III and IV cysts who underwent surgery, in consistency with literature (Yagci et al., 2005; Ezer et al., 2019). No statistically significant association was identified between cyst type and recurrence development ($p > 0.05$), although the recurrence rate was significantly higher in those with multiple cysts than in those with single cysts ($p < 0.05$) (Table 4).

Surgical interventions for hydatid disease usually take two forms, being radical or conservative. The problems associated with hydatid cyst surgery include recurrence and complications. Biliary fistula is the most common complication and requires additional interventional procedures, and may also cause biloma and biliary peritonitis. The rate of biliary fistula is reported to vary in the range of 3.2–18.0% (Göksoy and Düren, 2019; Aydın et al., 2008; Botezatu et al., 2018; Albayrak et al., 2008). It is controversial whether the rates of biliary fistula development vary between the radical and conservative surgical interventions or not. In our study it was not statistically significant ($p > 0.05$) (Table 4). When it comes

to recurrence, which is a late complication in hydatid cyst surgery, is a considerable problem for both the patient and surgeon. Recurrence develops due to the incomplete resection of cysts in hard-to-reach locations, leaving residual cyst wall and cyst reformation by live parasites through microscopic spillage. The surgical method performed is reported to have an effect on recurrence. It has been reported that recurrence rates increase up to 24% with conservative surgical interventions, while the reported rates vary in the range of 1.2–4.0% with radical surgical interventions (Nunnari et al., 2012; Ammann and Eckert, 1996; Prousalidis and Cosmidis, 2012; Sielaff et al., 2001; Velasco-Tirado et al., 2017).

Aydın et al. (2008) performed either radical or conservative surgical procedures on 221 patients, and found that the single factor affecting recurrence was the type of surgical procedure, and that radical surgical procedures significantly reduced recurrence. The authors concluded that similar results had been reported by Tagliacozzo et al. (2011) in their comparison of radical and conservative surgery groups, and that radical surgical procedures are a determining factor in the prevention of recurrence. In Botuguno et al.'s (2010) study including 38 cases with complex cysts (>10 cm, multiple and recurrent), all underwent radical surgical procedures, and recurrence occurred in only one patient. The authors highlighted the preferability of radical surgical interventions for this type of complex cyst. In the present study, recurrence development was lower in patients undergoing radical procedures than conservative ones (5.9% v.s 22.2%) and the difference was found to be statistically significant ($p < 0.05$). Among the cysts localized in the liver, 44 (26.5%) were multiple and in accordance with literature, the recurrence rate among those with multiple cysts was statistically significantly higher ($p < 0.05$). Age, gender, serological test result, larger than 10 cm cyst and Gharbi grade had no effect on recurrence ($p > 0.05$), and no statistically significant difference was noted in the length of hospital stay after radical and conservative procedures ($p > 0.05$) (Table 4).

Several case series have stated that radiological follow-up is important for the identification and

reveal timely treatment of recurrence, and that a minimum three-year follow-up is required (Botrugno et al., 2010 ; Bayrak and Altıntaş, 2019; Prousalidis and Cosmidis, 2012; Yetim and Erzurumlu, 2013).

The follow-up period in the present study was in the range of 6–72 months. The identification range was 10–24 months for the patients with recurrence, which was considered consistent with literature, although the follow-up of some patients is continuing.

Patient mortality can occur due to several reasons in a benign condition like hydatid disease. Reasons such as centrally localized cysts, major vessel involvement, central nervous system (CNS) localization and anaphylactic shock increase the risk of mortality. In the present study, only one patient died, attributable to anaphylactic shock caused by a ruptured cyst as a result of trauma. Previous studies have reported mortality rates of 1.8% with conservative procedures and 2.3–4.0% with radical surgical procedures (Müftüoğlu et al., 2005; Aydın et al., 2008; Prousalidis and Cosmidis, 2012; Bedioui et al., 2012).

Aydın et al. (2008) reported a mortality rate of 1.8% in a series of 221 cases, while the review study by Müftüoğlu et al. (2005) established a mortality rate of 0.5–4% in cases undergoing surgical therapy. Another study involving 391 cases reported a mortality rate of 0.07% (Bedioui et al., 2012)

It can be ascertained from previous studies of hydatid disease that the prevalence of this parasitic disease is high in our country, and that the most effective treatment approach is surgical therapy. The goal of surgical therapy is to completely eliminate the parasite and to prevent recurrence. Recurrence is rarer among patients undergoing radical surgical methods (hepatectomy, segmentectomy, cystectomy and pericystectomy). In recent years, radical methods have been preferred more often, especially in selected patient groups. It is recommended, however, that such methods should be performed by experienced centers

with experience in hepatobiliary surgery (Branci et al., 2010; Gupta et al., 2011).

The findings of the present study demonstrate that radical methods reduce recurrence development.

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The study was conducted in line with the principles of the "Helsinki Declaration."

Availability of Data and Materials: The datasets from the current study can be obtained on request from the corresponding author.

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