

Original article

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Changing Trends in the Diagnosis and Treatment of Liver Hydatidosis Over a 60-Year Period: Experience of a Tertiary Referral Center in an European Endemic Region

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Serbia is a well-known endemic region for hydatid liver disease (LH). Although surgery remains the primary treatment modality, there have been significant changes in the diagnosis and treatment of this disease in recent years. The aim of this study is to retrospectively analyze the demographic and clinical characteristics of patients who underwent surgical treatment for LH at a tertiary referral institution over the past 60 years. The authors conducted a comparative analysis across three 20-year periods: Period I (1960-1980), Period II (1980-2000), and Period III (2000-2020). The ratio of surgeries performed due to LH in the last period (1.23‰) was significantly lower than in the first two periods (5.15‰ and 4.86 ‰ respectively). Higher incidence in females (1:2.2, cyst localisation and complications rate has been consistent over time. Ultrasound, computed tomography, ELISA and IHA test was during the last two periods. While the management of LH shifts towards less invasive procedures, open surgery remains the gold standard. The tissue-sparing operations was performed in most cases (61.91%). However, there has been a slight increase of the radical surgeries, rising from 25.4% in the first period to 43.15% in the second and 46% in the third period. The surgical approach by Papadimitriou, -partial cystopericystectomy plus omentoplasty (PCPCO), maybe the preferred method as it balances the need for radical treatment with tissue preservation in LH surgery. Minimally-invasive techniques such as PAIR and laparoscopy have gradually been introduced over the last two periods, in a small number of carefully selected cases (increasing from 3.4% to 8.1%, respectively).

Key words: echinococcosis, hydatide disease, liver, diagnosis, therapy

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Promena stavova u dijagnostici i lečenju ehinokousa jetre u 60 –godišnjem periodu: iskustvo tercijarne institucije u endemskom području Evrope

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Srbija je dobro poznati endemski region za hidatidnu bolest jetre. Iako hirurgija ostaje primarni modalitet lečenja, poslednjih godina došlo je do značajnih promena u dijagnostici i lečenju ove bolesti. Cilj ovog istraživanja je da retrospektivno analizira demografske i kliničke karakteristike pacijenata koji su podvrgnuti hirurškom lečenju hidatidne bolesti jetre, u tercijarnoj referentnoj ustanovi (Univerzitetskom kliničkom centru) u poslednjih 60 godina (1960-2020). Autori su izvršili komparativnu analizu tri 20-godišnja perioda: period I (1960-1980), period II (1980-2000) i period III (2000-2020). Procenat operacija urađenih zbog LH u odnosu na ukupan broj operacija, u poslednjem periodu (1,23%) bio je značajno manji nego u prva dva perioda (5,15% odnosno 4,86%). Odnos muškaraca i žena ukazuje na veću incidencu kod žena (1:2,2). Lokalizacija cisti i procenat uočenih komplikacija nisu se menjali tokom vremena. Standardne dijagnostičke procedure u novije vreme uključuju ultrazvuk (US), kompjuterizovanu tomografiju (CT), enzimski imunosorbentni test (ELISA) i imunoheماغلutinacija (IHA). Iako se u lečenju hidatidne bolesti jetre sve više primenjuju minimalno-invazivne procedure, otvorena operacija ostaje zlatni standard za postizanje potpunog izlečenja, posebno u komplikovanim slučajevima. U celokupnom vremenskom periodu, u najvećem broju slučajeva (61,91%) radjene su poštredne hirurške intervencije. Međutim, registrovano je blago povećanje broja radikalnih operacija, sa 25,4% u prvom periodu na 43,15% u drugom i 46% u trećem periodu. Operacija po Papadimitriou, - parcijalna cisto-pericistektomija sa omentoplastikom, je po mišljenu autora -metoda izbora, jer balansira potrebu za radikalnošću sa jedne strane i princip poštrednosti tkiva jetre, sa druge strane. Minimalno-invazivne procedure poput perkutanih drenaža i laparoskopije postepeno su uvedjene u pažljivo odabranim slučajevima, u poslednja dva analizirana perioda, uz porast sa 3,4% na 8,1%.

Ključne reči: ehinokokus, hidatidna bolest, jetra, dijagnoza, terapija

INTRODUCTION

Hydatid disease is a worldwide zoonosis produced by the larval stage of the Echinococcus tapeworm, with endemic prevalence in the great grazing regions. Serbia has been a very well-known endemic region for decades, with an average annual incidence of 0.32 / 100.000 inhabitants (1). Over 75% of hydatid diseases are situated in the liver and almost exclusively treated with surgery (2). Although there has been an increase in early disease detection due to new diagnostic methods, the incidence of liver hydatid disease has slightly decreased, reflecting changing trends both globally and in our region (1). Although surgery still remains the primary treatment modality, in recent times, there have been notable changes in the diagnosis and treatment of this disease (3-5).

THE AIM

The aim of this study is to retrospectively analyze the main demographic and clinical characteristics of the patients surgically treated for liver hydatidosis in a tertiary referral institution /University Clinical Center at Niš/ in the last 60 years (1960-2020). The authors used comparative analysis for three 20-year periods (I period from 1960- 1980, II period from 1980-2000, and III period from 2000-2020).

PATIENTS AND METHODS

Over the past 60 years, 323 adult patients were surgically treated for liver hydatidosis. During the first 20 years (1960-1980), 103 patients were operated on; during the second period (1980-2000), 146; and in the third period (2000-2020), 74 patients were invasively treated.

RESULTS

The number of patients who underwent surgery for LH in our institution dramatically decreased in relation to the total operations performed, from 5.15 ‰ to 4.86 ‰ and 1.23‰ in observed periods (respectively). The male/female ratio was 1/2.2, with the patient's age being 44.2 years, similar in all observed periods. Cysts were solitary in ¾ of cases and located mainly in the right lobe (66.6%). Bilobar localization was registered in 12.4%. So-called "complex" cysts /hyalar and caval /hepatic venous encasement or infiltration/ were registered in 20 patients (6.2%), but the incidence was significantly higher in the last observed period (9.5% versus 5.2%). The complication rate was almost similar in

both groups (17.4% in total), with a slight increase in preoperative discovered cysto-biliary fistulas in the last period /10.8% versus 6.4% in the former periods/ (table 1.).

Table 1. Demographic and clinic carateristics of patients treated of LH.

	I period /1960- 1980/	II period /1980- 2000/	III period /2000-2020/	Total
Number	103	146	74	323
% of total N° of OP performed /20 yrs	103/ 20.000 (5.15‰)	146/30.000 (4.86‰)	74/60.000 (1.23‰)	
Age	44.1		44.3	44.2
Male / female (1: x))	72 / 177 (1/2.45)		28/46 (1/1.65)	100/223 (1:2.23)
Number				
Solitary	190/249 (76.3%)		60/74 (81.1%)	250/323 (77.39%)
Multiple	59/249 (23.7%)		14/74 (18.9%)	73/323 (22.6%)
Localisation				
Right lobe	167/249 (67.1%)		48/74 (64.9%)	215/323 (66.6%)
Left lobe	52/249 (20.1%)		16/74 (21.6%)	68/323 (21%)
Bilobar	30/249 (12.8%)		10/74 (13.5%)	40/323 (12.4%)
Complex (problematic)	13/249 (5.2%)		7/74 (9.5%)	20/323 (6.2%)
Complicated	42 (16.9%)		14/74 (18.9%)	56/323 (17.4%)
Cysto-biliary communication (CBC)	16 (6.4%)		8 (10.8%)	24/323 (7.4%)
Abscessus	6 (2.4%)		2 (2.5%)	8/323 (2.5%)
Perforation	20 (8%)		4 (5.4%)	24/323 (7.4%)

The main diagnostic procedures in the first 20-year period were clinical data, plain radiography, scintigraphy, and basic laboratory (eosinophyllia and Cassoni-Boteri reaction). The most common clinical symptoms and signs of the disease were pain in the right hypochondrium and hepatomegaly. In the first period imaging method of choice was scintigraphy. However, it is replaced by more simple and precise methods like ultrasound (US), computerized tomography (CT) and magnetic resonance (MR) during the early 80's of the XXth century. MR and MRCP were selectively used in 18.57% (60 cases). The indirect hemagglutination test (IH) and the enzyme-linked immunosorbent assay (ELISA) were the

initial screening tests of choice. Standard preoperative antihelminthic regimen was done with one or more cycles of Albendazol (4 weeks -10 mg/ kg BM), after its discovery in the 1975 year, and Mebendzol during the first observed period. All patients underwent some form of the invasive procedure. In the first and second observed periods, open surgery was the only way to operate liver hydatidosis. Percutaneous and laparoscopic approach were gradually introduced in the last two 20-year periods, in small number of strongly selected cases, with increasing rate from 2% to 10.8% and 3.4% to 8.1% respectively (table2). Tissue-sparing or conservative surgical operations were performed in most cases (61.91%). However, we noticed a slight increase in radical surgery (from 25.4% in the first to 43.15% in the second and 46% in the third period). Operations according to Papadimitrou (partial cystopericystectomy plus omentoplasty –PCPCO), were most frequent (133 cases or 41.17% in total). Cappitonage and marsupialisation were abandoned in the last period of time. Increasing tendency of anatomical liver resection from 8.73% to 10.27% and 24.32% during the three observed time periods was registered (table 3).

Table 2. Therapeutic approach in LH

	I period /1960- 1980/	II period /1980- 2000/	III period /2000- 2020/	TOTAL
Percutaneous	0	3 (2%)	8 (10.8%)	11 (3.4%)
Laparoscopic	0	5 (3.4%)	6 (8.1%)	11 (3.4%)
Open	103	138 (94.5%)	60 (81%)	301 (93.2%)
TOTAL	103	146	74	323 (100%)

Table 3. Tissue sparing (conservative) and radical operations in LH.

	I period /1960-1980/	II period /1980- 2000/	III period /2000-2020/	TOTAL
TISSUE-SPARING				
Papadimitrou (PCPCO)	39 (37.86%)	68 (46.57%)	26 (35.13%)	133/323 (41.17%)
Drainage only	24 (23.3%)	10 (6.84%)	14 (18.91%)	48 (14.86%)
Cappitonaqe	8 (7.76%)	-	-	8 (2.47)
Marsupialisation	6 (5.82)	5 (3.42%)	-	11 (3.4%)
TOTAL	77 /103 (74.75%)	83/146 (56.84%)	40/74 (59.45%)	200/323 (61.91%)
RADICAL				
Non-anatomical LR(total peri-cystectomy)	17 (16.50%)	48 (32.87%)	16 (21.62%)	81 (25.07%)
Anatomical LR	9 (8.73%)	15 (10.27%)	18 (24.32%)	42 (13%)
TOTAL	26/103 (25.24%)	63/146 (43.15%)	34/74 (46%)	123/323 (38.08%)

The rate of true relapses is very rare and on our material it amounts to below 5%. The cumulative complication rate at our institution is 17.31%, showing a decreasing trend from 19.42% in the first period to 17.80% in the second, and finally to 13.51% in the third observed period. Average length of hospitalization was shortest in the third period (4.6 days) compared to the first (20 days) and second periods (12.4 days). The mortality rate in the first and second period was 3.21% (equivalent to eight patients) (table4).

Table 4. Results of surgical treatment of LH by the observed period.

	I period /1960-1980/	II period /1980-2000/	III period /2000-2020/	Total
Biliary fistula	8/103 (7.76%)	7/146 (4.79%)	3/74 (4.05%)	18/323 (5.57%)
Absscessus	7/103 (6.82%)	15/146 (10.27%)	3/74 (4.05%)	25/323 (7.73%)
Pulmonary	5/103 (4.85%)	4/146 (2.73%)	4/74 (5.4%)	13/323 (4.02%)
Total	20 (19.42%)	26 (17.80)	10 (13.51%)	56 (17.3%)
Hospitalisation (days)	20	12.4	4.6	
Mortality	8 (3.21%)		-	8/323 (2.47%)
Reccurence	4 (1.60%)		4 (5.40%)	8/323 (2.47%)

DISCUSSION

Hydatid disease is a worldwide zoonosis produced by the larval stage of the Echinococcus tapeworm. The two main types of hydatid disease are caused mostly by *E. granulosus* and less often by *E. multilocularis* (2). According to WHO, the incidence of hydatid disease has almost unbelievable ranges from 1 to 200 cases per 100.000 population (2). *E. granulosus* is an endemic disease in reat grazing regions like the Mediterranean region, Africa, South America, the Middle East, Australia, and New Zealand. Previously rare, today it is increasingly common in the countries of Western Europe and North America due to the large influx of emigrants, who bring the disease with them. Hydatid disease has been practically eradicated in some countries, thanks to programs to combat this disease, which include systematic anthelmintic vaccination of dogs, pigs and sheeps. Based on that program, new cases of hydatid disease have not been registered in Norway since 1982 (2), and incidence has also significantly dropped in some island countries (as epidemiologically closed systems) like Iceland, South Cyprus, part of Argentina and Chile, Tasmania and New Zealand (6). In Serbia, the most frequent intermediate hosts for *E. granulosus* are pigs, with a percentage of infected animals ranging between 4.6% and 57.6% (7). Exact information about the real incidence of human infection in Serbia is uncertain and underestimated due to incomplete and inadequate reporting by clinicians. During 2023, 21 new cases of echinococcosis were reported in the Republic of Serbia, with an annual incidence rate of 0.32 per 100,000 inhabitants. There is a large difference in reporting by gender and region. The highest cumulative incidence rates of

echinococcosis were registered in the territory of Zlatibor, Toplica, and Rasina districts. According to the statistical data of the Institute of Public Health in Nis, the average level of cumulative incidence of echinococcus in southeastern Serbia for the period 1988-2001. was 5.83., and 4,028 for the period 2002-2006 (8).

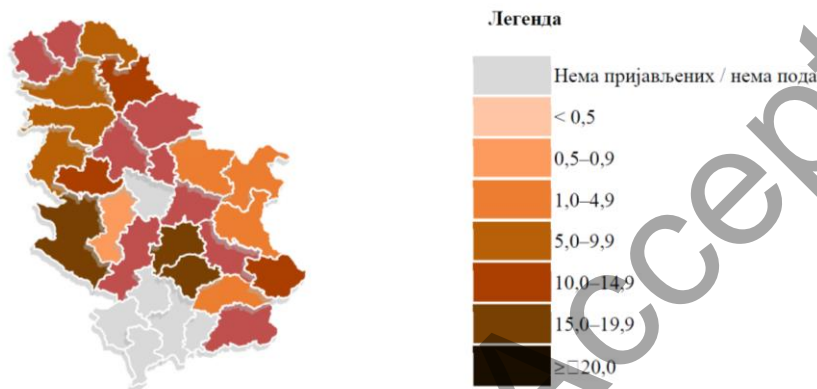


Figure 1. Cummulative incidence of Echinococcosis / 100.000 inhabitants in Serbia in period 2014-2023 years.

Over the last ten-year period, echinococcosis In Serbia has shown a downward trend in the number of cases, with the highest incidence rate registered in 2017, and the lowest rates recorded in 2020 and 2021, during the period of the Covid -19 pandemy (1).

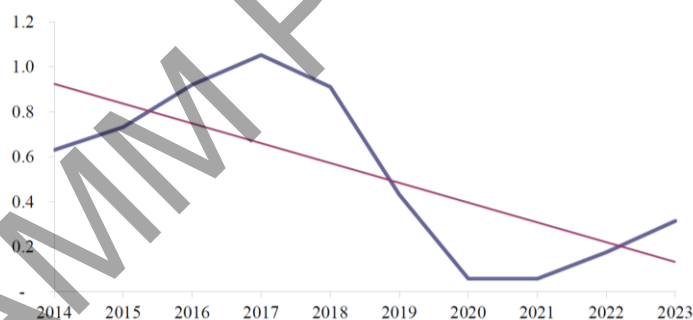


Figure 2. Incidence trend of Echinococcosis / 100.000 inhabitants in Serbia in period 2014-2023 years.

Our institution is a tertiary referral health institution covering an area of 2.5 million inhabitants in the middle of an endemic region. Although the total number of surgeries performed in the last period was significantly higher than in the first two periods, the ratio of surgeries performed due to LH

(1.23‰) was significantly lower than in the first two periods (5.15‰ and 4.86 ‰ respectively). The male/female ratio was 1/2.2, with the patient's age being 44.2 years, similar in all observed periods. Over 75% of hydatid diseases are situated in the liver –liver hydatidosis (LH). The most common localization in the liver is the right lobe, probably because of the bigger size and portal flow (2). Our results are similar with exactly $2/3$ cysts located in the right lobe. Other common localisation are lungs in about 20%. Hemathogenic dissemination after passing of the hepatic and pulmonary filters is very rare, with relatively small number of case reported the brain, heart, bones, joints, pericardium, pelvis localisation (9).

Hydatid cysts can often be asymptomatic for many years and are sometimes discovered incidentally during imaging studies (10,11). In most cases, symptoms are coming like the results of LH complications, which occurred in 17.4% in our study. The most frequently registered complication was inflammation in 7.4% and rupture into the bile ducts with cysto-biliary communication (CBC or fistula) formation 7.4%, abdominal or chest cavity (7.4%). Some complications can even lead to fatal outcomes, for example, anaphylaxis after a cyst's perforation, which we did not note. During the first twenty-year period (1960-1979), the diagnosis of LH was determined by numerous complicated procedures with low sensitivity and specificity (native radiography: angiography, splenoportography, intravenous cholangiography, scintigraphy, Cassoni-Botteri test,etc.). Ultrasound (US) and computerized tomography (CT) were introduced in clinical practice at our institution during the early 80's of the XXth century, and performed in the diagnosis of LH in almost all of the patients. CT examination with high sensitivity rate of 95%, represents the method of choice used in preoperative planning. It enables precise anatomical picture of the liver, position of the cyst(s), and relation to the great vessels and bile ducts. (2,11). Magnetic resonance (MR) and magnetic resonance cholangio-pancreatography (MRCP) at our institution were selectively used in suspected cystobiliary communication (18.57% of the patients) (11,12). Routine blood tests may show non-specific changes. Eosinophilia could be noted in only 25–40% of cases (2,11). Serological tests include enzyme-linked immunosorbent assay (ELISA), indirect hemagglutination assay (IHA) and Western blotting (WB). ELISA is the method of choice with a sensitivity of 93.5% and specificity of 89.7%. IHA testing has a sensitivity of 90%; however, if the result is positive, it may remain positive for several years after that.23. WB serology for liver CE has a high sensitivity of 80–100% and a specificity of 88–96% (13,14).

There are various treatment modalities for this disease. Medical therapy with antihelminthic agents by itself, is indicated in cases where surgical intervention is not possible for any reason, after multiple relapses and in the alveolar form of the disease. Most used drug is Albendazol (4 weeks -10 mg / kg daily) as a neoadjuvant or adjuvant therapy in combination with interventional and surgical procedures (2,12). However, long-term and non-critical use of Albendazole can lead to liver fibrosis and cirrhosis, as seen in our patients after two years of non-critical continuous use (see figure 3).

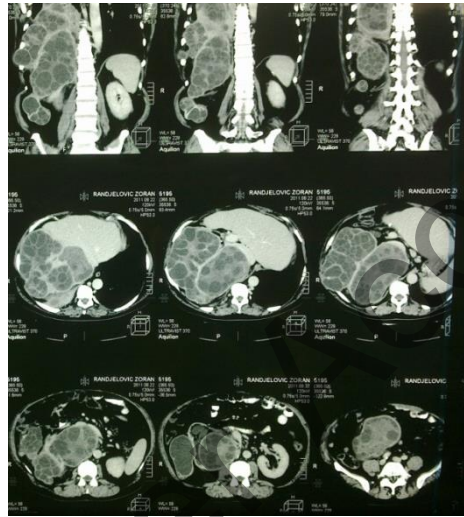


Figure 3. MSCT of giant LH.

Despite advancements in effective medications for treating parasites, surgery remains the preferred method for addressing liver hydatid disease (LH). The main goal of surgical intervention is to remove the cyst and its contents while preventing contamination of the peritoneal cavity (2,5). Although concept of management of liver hydatidosis is changing and going to less -invasive procedure, open surgery is still gold standard for complete cure in the complicated cases (15,16). Surgical techniques can vary, ranging from liver-sparing methods like endocystectomy to more aggressive approaches, including partial or total pericystectomy and various types of hepatectomy (17) (figure 3).

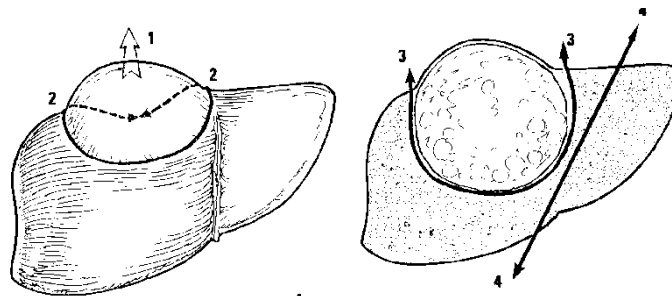


Figure 4. Different types of surgical interventions:
1-drainage; 2-partial pericystectomy; 3-total pericystectomy; 4-liver resection.

When deciding on the most appropriate surgical procedure, several factors must be considered: the location and size of the cyst, its proximity to vascular and biliary structures, and the characteristics of the pericyst (including thickness and infiltration) (2). Since liver echinococcosis is classified as a benign condition, it is vital to minimize the surgical risks to patients. Because of that primary idea, tissue-sparing or conservative surgical operations were suggested for decades (17). We performed these in most cases (61.91%). However, we noticed a slight increase in number radical surgeries (from 25.4% in the first to 43.15% in the second and 46% in the third period). Cappitonnage and marsupialisation were abandoned in the last period of time. The introduction of a new concept in liver surgery over the past 25 years has led to an increase in anatomical liver resections, rising from 8.73% to 10.27% and then to 24.32% across three observed time periods. Immediate and late results of open surgery are very good. Free of recurrence rate after 1, 5 and 10 years was 100 %, 90,9 % and 87,9 %, respectively (10,12,18). The rate of true relapses is very rare and on our material it amounts to below 5%. However, open surgery is associated with significant morbidity (15-25%) and mortality rate (up to 6,5%) and long hospital stay [Nagabeskov]. The relationship between surgical techniques and outcomes is notable: the more radical the surgery, the higher the operative risk, but the lower the risk of recurrence, and vice versa. Radical surgery is considered superior to conservative surgery due to lower morbidity (3%-24% compared to 11%-25%), lower mortality (1%-1.8% compared to 2%-5%), and lower recurrence rates (2%-6.4% compared to 10.4%-40%) as reported by specialized liver centers (19). The cumulative complication rate at our institution is 17.31%, showing a decreasing trend from 19.42% in the first period to 17.80% in the second, and finally to 13.51% in the third observed period. The introduction of new concept in liver surgery and minimally invasive methods has reduced the average length of hospitalization (11). It was shortest in the third period (4.6 days) compared to the first (20 days) and second periods (12.4 days). The mortality rate in the first and second period was 3.21% (equivalent to eight patients). The causes of death were as follows: uncontrolled abdominal sepsis in five patients, cardiopulmonary insufficiency in one patient, hepato-renal insufficiency in another patient. Additionally, one patient died on the operating table due to bleeding from a retrohepatic lesion of the inferior vena cava. No deaths were registered in the third observed period.

Every day, surgeries are performed by general surgeons in underdeveloped countries, where the philosophy is that "benign disease needs benign therapy" (17,19). Operation according to Papadimitrou (partial cystopericystectomy plus omentoplasty-PCPCO) could be the operation of choice that encompasses both concepts of radicality and sparing in LH surgery. It was the most frequent operation on our material as well (41.17%).

Newer minimally invasive methods of treatment such as laparoscopic and robotic surgery have the advantage of less morbidity, low cost, and shorter hospital stay (20). However, laparoscopy for liver hydatidosis could be very complex and challenging procedure in the cases of centrally located disease and suspected biliary complications (20-22). We started laparoscopic surgery of the LH in the last two periods in 11 cases of peripherally located and solitary, non-complex cysts (3.4%). There was no conversion to open surgery nor complication. Nonoperative, percutaneous treatment of liver hydatidosis consist of punction, aspiration, irrigation and reaspiration (PAIR). The most common used scolicial reagents are hypertonic (20-30%) NaCl solution, Povidone -jodid and 95% ethanol. It was introduced in the mid-1980^s [Kuro Mueler]. In this treatment modality, the aim is to destroy the germinal layer with scolicial agents or to evacuate the entire endocyst.

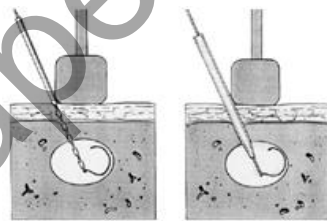


Figure 5. PAIR procedure

Table 5. Comparative description of the WHO-IWGE and Gharbi ultrasound classifications of echinococcal cysts.

WHO /IWGE	Gharbi	Description	Stage	PAIR

CE1	Type I	Unilocular anechoic cystic lesion with double line sign.	Active	Indicated
CE2	Type III	Multiseptated "rosette-like" "honeycomb" cyst.	Active	Contraindicated
CE3 A	Type II	Cyst with detached membranes [water-lily-sign].	Transitional	Indicated
CE3 B	Type III	Cyst with daughter cysts in solid matrix.	Transitional	Contraindicated
CE4	Type IV	Cyst with heterogeneous contents. No daughter cysts.	Inactive	Contraindicated
CE5	Type V	Solid cyst with calcified wall	Inactive	Contraindicated

According to the current guidelines, the best results with PAIR achieved in >5 cm CE1 (unilocular) and CE3a cysts (with detached membrane) (table 5). Early pregnancy, lung cysts, superficially localized cysts, cysts that communicate with the biliary tree are also contraindicated for PAIR. Percutaneous cyst drainage has been shown to be an effective and safe procedure, with a low complication rate.(23-25). At our institution, PAIR has been gradually introduced in the last two 20-year periods, in a small number of strongly selected cases (from 3.4% to 8.1% respectively). We noticed with just one severe complication - obstructive jaundice caused by necrotic debris one week after PAIR. It was successfully treated by open surgery.

Recurrence after invasive therapy for liver hydatid disease (LH) ranges from 4.6% to 22.0% (26, 27). In our study, the rate of true relapses is very rare, accounting for less than 5%, regardless of the type of intervention used. The main reasons for recurrence appear to be the microscopic spillage of live parasites, failure to remove all viable cysts from inaccessible or difficult locations, and leaving behind a residual cyst wall after the initial operation.

CONCLUSIONS

Based on our research, we conclude that the incidence of liver echinococcosis and is decreasing in the area covered by our institution. The ratio of surgeries performed due to LH (1.23‰) was significantly lower than in the first two periods (5.15‰ and 4.86 ‰ respectively). Higher incidence in females (1:2.2, predominant cyst localisation in the right lobe and complications rate has been consistent over time. Standard diagnostic procedures employed during the last two periods include ultrasound (US), computerized tomography (CT), ELISA, and indirect hemagglutination test (IH). Although the management of liver hydatidosis is shifting towards less invasive procedures, open surgery remains the gold standard for achieving a complete cure in complicated cases. Laparoscopic techniques

and PAIR treatment should be utilized more frequently for treating LH, but only in carefully selected cases. The surgical approach described by Papadimitriou, which involves partial cystopericystectomy plus omentoplasty (PCPCO), could be the preferred method as it balances both radicality and tissue preservation in LH surgery.

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