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

Marko Stojanović[1,2], Vesna Brzački[1,2], Katarina Terzić[2,3], Ilija Golubović[2,3], Aleksandar Stanojević[2,3], Jelena Živadinović[2,4], Aleksandar Nikolić[2,4], Aleksandar Tasić[2,5], Nataša Miladinović-Tasić[2,6], Miroslav Stojanović[2,3]

Serbia is a well-known endemic region for hydatid liver (LH) disease. Although surgery remains the primary treatment modality, significant changes have occurred in the diagnosis and treatment of this disease in recent years. The aim of this study was to retrospectively analyze the demographic and clinical characteristics of patients who had undergone surgical treatment for LH at a tertiary referral center 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). A higher incidence in females (1:2.2), cyst localization, and rate of complications have remained consistent over time. The latest standard diagnostic procedures include Ultrasonography (US), Computed tomography (CT), Enzyme-linked immunosorbent assay (ELISA) and Indirect hemagglutination assay (IHA) test. While the management of LH shifts towards less invasive procedures, open surgery remains the gold standard. The tissue-sparing operations were performed in most cases (61.91%). However, there has been a slight increase in 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)—may be the preferred method as it balances the need for radical treatment with tissue preservation in LH surgery. Minimally invasive techniques such as punation aspiration irrigation and respiration (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).

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Key words: *echinococcosis, hydatid disease, liver, diagnosis, therapy*

[1]University Clinical Center Niš, Gastroenterology and Hepatology Clinic, Niš, Serbia
[2]University of Niš, Faculty of Medicine, doctoral studies, Niš, Serbia
[3]University Clinical Center Niš, Digestive Surgery Clinic, Niš, Serbia
[4]University Clinical Center Niš, Anesthesiology and Intensive Therapy Clinic, Niš, Serbia
[5]University Clinical Center Niš, Radiology Clinic, Niš, Serbia
[6]Public Health Institute Niš, Niš, Serbia

Contact: Marko Stojanović
48 Dr. Zorana Djindjića Blvd., 18000 Niš, Serbia
E-mail: marcss994@gmail.com

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 are 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).

Aim

This study aimed to retrospectively analyze the main demographic and clinical characteristics of the patients surgically treated for liver

hydatidosis (LH) in a tertiary referral institution (University Clinical Center Niš) in the period of 60 years between 1960 and 2020. The authors used comparative analysis for the three 20–year periods (I period from 1960 to 1980, II period from 1980 to 2000, and III period from 2000 to 2020).

Materials and Methods

Over the past 60 years, 323 adult patients have been surgically treated for liver hydatidosis. One hundred and three patients underwent surgery in the first 20 years (1960–1980); 146 within the second period (1980–2000); and 74 patients were invasively treated in the third period (2000–2020)

Results

The number of patients who underwent surgery for LH at the University Clinical Center in Niš dramatically decreased in relation to the total operations performed, from 5.15‰ to 4.86‰ and 1.23‰ in observed periods, respectively. The male-to-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, hylar, 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 preoperatively discovered cysto-biliary fistulas in the last period (10.8% versus 6.4% in the former periods) (Table 1).

Table 1. Demographic and clinical characteristics of patients treated for LH

	I period 1960–1980	II period 1980–2000	III period 2000–2020	Total
Number	103	146	74	323
% of total N^{o} of OP performed in 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%)
Abscesses	6 (2.4%)		2 (2.5%)	8/323 (2.5%)
Perforation	20 (8%)		4 (5.4%)	24/323 (7.4%)

Table 2. Therapeutic approach in LH

	I period	II period	III period	TOTAL
	1960–1980	1980–2000	2000–2020	
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	II period	III period	TOTAL
	1960–1980	1980–2000	2000–2020	
TISSUE-SPARING				
Papadimitriou (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%)
Capitonnage	8 (7.76%)	-	-	8 (2.47)
Marsupialization	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				
Nonanatomical LR (total pericystectomy)	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 main diagnostic procedures in the first 20-year period were clinical data, plain radiography, scintigraphy, and basic laboratory (eosinophillia and Casoni–Botteri 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 1980s of the 20th 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 antihelmintic regimen was done with one or more cycles of Albendazole (10 mg/kg BM for 4 weeks), after its discovery in 1975, and Mebendazole during the first observed period. All patients underwent some form of invasive procedure. In the first and second observed periods, open surgery was the only way to operate on liver hydatidosis. Percutaneous and laparoscopic approaches were gradually introduced in the last two 20-year periods, in a small number of strongly selected cases, with increasing rate from 2% to 10.8% and 3.4% to 8.1%, respectively (Table 2). 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 Papadimitriou (partial cystopericystectomy plus omentoplasty—PCPCO) were most frequent (133 cases or 41.17% in total). Capitonnage 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).

The rate of true relapses is very rare, and in our material it amounted to below 5%. The cumulative complication rate at the University Clinical Center in Niš was 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 average length of hospitalization was the shortest in the third period (4.6 days) compared to the first (20 days) and second (12.4 days) periods. The mortality rate in the first and second periods was 3.21% (equivalent to eight patients) (Table 4).

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%)
Abscesses	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%)
Hospitalization (days)	20	12.4	4.6	
Mortality	8 (3.21%)		-	8/323 (2.47%)
Recurrence	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 World Health Organization (WHO), the incidence of hydatid disease has an almost unbelievable range from 1 to 200 cases per 100,000 population (2). *E. granulosus* is an endemic disease in great 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 sheep. 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. In 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 (Figure 1). According to the statistical data of the Institute of Public Health in Niš, the average level of cumulative incidence of echinococcosis in the Southern and Eastern Serbia for the period 1988–2001 was 5.83, and 4.028 for the period 2002–2006 (8).

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 pandemic (1) (Figure 2).

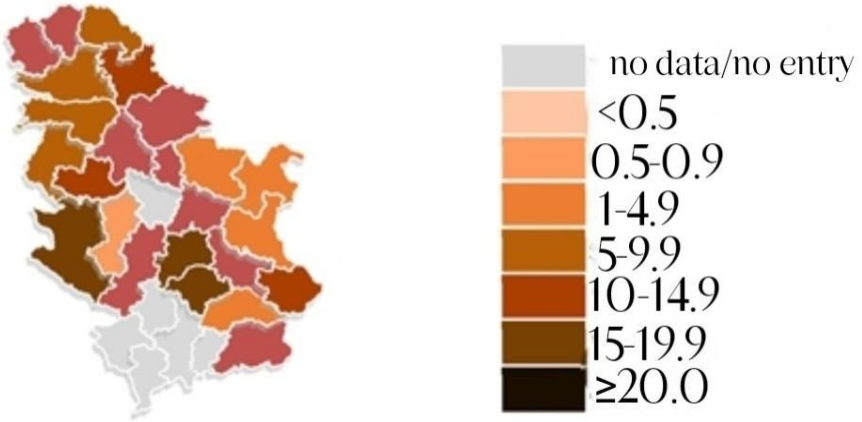

Figure 1. Cumulative incidence of echinococcosis/100,000 inhabitants in Serbia in 2014–2023 period

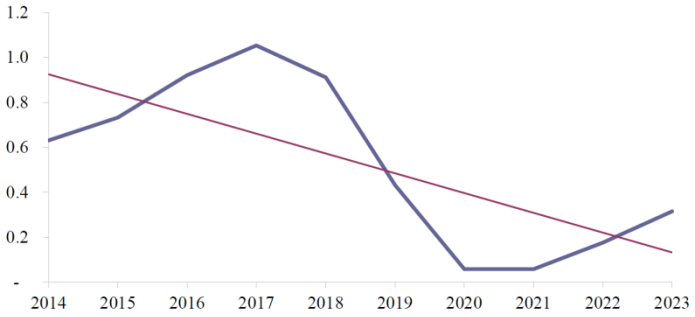

Figure 2. Incidence trend of echinococcosis/100,000 inhabitants in Serbia in 2014–2023 period

University clinical Center in Niš 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-to-female ratio was 1:2.2, with the patient's age 44.2 years, similar in all observed periods. Over 75% of hydatid diseases are situated in the liver—liver hydatidosis. The most common localisation in the liver is the right lobe, probably due to its larger size and portal flow (2). Our results are similar, with exactly 2/3 of cysts located in the right lobe. Other common localisation are the lungs with about 20%. Hematogenous dissemination after passing through the hepatic and pulmonary filters is very rare, with a relatively small number of cases reported in the brain, heart, bones, joints, pericardium, and pelvis (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 associated with 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, Casoni–Botteri test, etc.). Ultrasound and computerized tomography were introduced in clinical practice at our institution during the early 1980s of the 20th century, and were used in the diagnosis of LH in almost the patients. CT examination with high sensitivity rate of 95%, represents the method of choice used in preoperative planning. It enables a precise anatomical picture of the liver, position of the cyst(s), and relation to the great vessels and bile ducts (2, 11) (Figure 3). Magnetic resonance and magnetic resonance cholangio-pancreatography 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, 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 (2, 3). 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 antihelmintic 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. The most used drug is Albendazole (10 mg/kg daily for 4 weeks) 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.

Despite advancements in effective medications for treating parasites, surgery remains the preferred method for addressing liver hydatid disease. The main goal of surgical intervention is to remove the cyst and its contents while preventing contamination of the peritoneal cavity (2, 5). Although the concept of management of liver hydatidosis is changing and going to less invasive procedures, open surgery is still the 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 4).

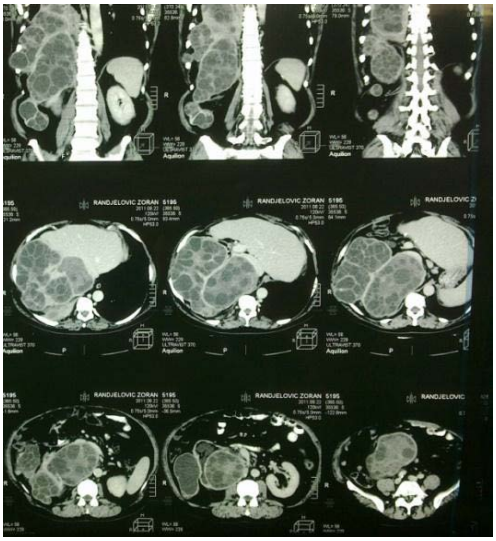

Figure 3. MSCT of giant LH.

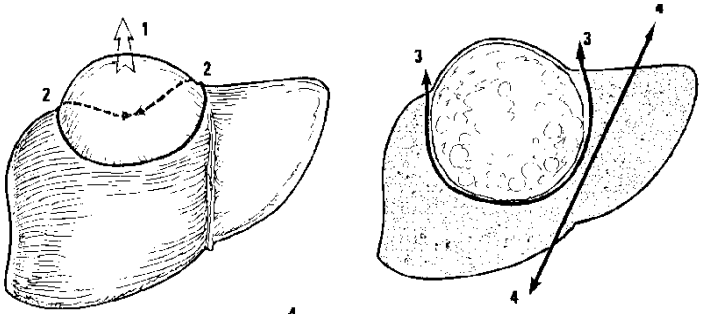

Figure 4. Different types of surgical interventions:
1. Drainage, 2. Partial pericystectomy, 3. Total pericystectomy, 4. Liver resection

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 the number of radical surgeries (from 25.4% in the first to 43.15% in the second and 46% in the third period). Capitonnage and marsupialization were abandoned in the last period. 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 in 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 (10). 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 was 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 concepts in liver surgery and minimally invasive methods has reduced the average length of hospitalization (11). It was the 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% (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 Papadimitriou (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, lower cost, and shorter hospital stay (20). However, laparoscopy for liver hydatidosis could be a very complex and challenging procedure in the cases of centrally located disease and suspected biliary complications (20–22). Laparoscopic surgery of the LH was performed in the last two periods in 11 cases of peripherally located and solitary, non-complex cysts (3.4%). There were no conversions to open surgery nor any complications. Nonoperative, percutaneous treatment of liver hydatidosis consists of punction, aspiration, irrigation and reaspiration (PAIR) (Figure 5). The most commonly used scolicidal reagents are hypertonic (20–30%) NaCl solution, povidone-iodine and 95% ethanol. It was introduced in the mid-1980s. In this treatment modality, the aim is to destroy the germinal layer using scolicidal agents or to evacuate the entire endocyst.

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 localised cysts, and cysts that communicate with the biliary tree are also contraindicated for PAIR. Percutaneous cyst drainage is an effective and safe procedure, with a low complication rate (13, 23, 24). At the University Clinical Center in Niš, 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). There was only 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 ranges from 4.6% to 22.0% (25, 26). In present 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.

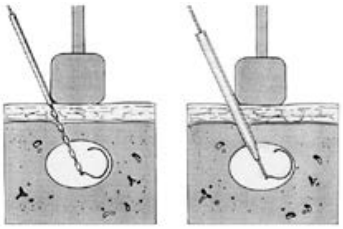

Figure 5. PAIR procedure

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 unechoic 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 a solid matrix	Transitional	Contraindicated
CE4	Type IV	Cyst with heterogenous contents No daughter cysts	Inactive	Contraindicated
CE5	Type V	Solid cyst with calcified wall	Inactive	Contraindicated

Conclusion

Based on the present research, it can be concluded that the incidence of liver echinococcosis is decreasing in the area covered by the University Clinical Center in Niš. In the third period, the ratio of surgeries performed for 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 the rate of complications have been consistent over time. Standard diagnostic procedures employed during the last two periods include US, CT, ELISA, and 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, could be the preferred method as it balances both radicality and tissue preservation in LH surgery.

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PROMENA STAVOVA U DIJAGNOSTICI I LEČENJU EHINOKOKUSA JETRE U ŠEZDESETOGODIŠNJEM PERIODU: ISKUSTVO TERCIJARNE INSTITUCIJE U ENDEMSKOM PODRUČJU U EVROPI

Marko Stojanović[1,2], Vesna Brzački[1,2], Katarina Terzić[2,3], Ilija Golubović[2,3], Aleksandar Stanojević[2,3], Jelena Živadinović[2,4], Aleksandar Nikolić[2,4], Aleksandar Tasić[2,5], Nataša Miladinović Tasić[2,6], Miroslav Stojanović[2,3]

[1]Univerzitetski klinički centar Niš, Klinika za gastroenterologiju i hepatologiju, Niš, Srbija
[2]Univerzitet u Nišu, Medicinski fakultet, student doktorskih studija, Niš, Srbija
[3]Univerzitetski klinički centar Niš, Klinika za digestivnu hirurgiju, Niš, Srbija
[4]Univerzitetski klinički centar Niš, Klinika za anesteziju, реаниматологију i intenzivnu terapiju, Niš, Srbija
[5]Univerzitetski klinički centar Niš, Klinika za radiologiju, Niš, Srbija
[6]Zavod za javno zdravlje Niš, Niš, Srbija

Kontakt: Marko Stojanović
Bulevar dr Zorana Đinđića 48, 18000 Niš, Srbija
E-mail: marcss994@gmail.com

Srbija je dobro poznat endemski region kada je reč o hidatidnoj bolesti jetre. Premda hirurgija ostaje primarni modalitet lečenja, došlo je do značajnih promena u dijagnostici i lečenju ove bolesti u poslednje vreme. Cilj ovog istraživanja bio 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 Nišu) u poslednjih šezdeset godina (1960–2020). Izvršena je komparativna analiza triju perioda od dvadeset godina: perioda I (1960–1980), perioda II (1980–2000) i perioda III (2000–2020). U poređenju s ukupnim brojem operacija, procenat operacija urađenih zbog hidatidne bolesti jetre bio je značajno manji u poslednjem periodu (1,23‰) nego u prvom i drugom periodu (5,15‰, odnosno 4,86‰). Pokazalo se i da je incidencija veća kod žena (1 : 2,2). Lokalizacija cisti i procenat uočenih komplikacija nisu se menjali s vremenom. Standardne dijagnostičke procedure u novije vreme obuhvataju ultrazvuk (engl. *ultrasound* – US), kompjuterizovanu tomografiju (engl. *computed tomography* – CT), enzimski imunosorbentni test (engl. *enzyme-linked immunorbent assay* – ELISA) i imunohemaglutinaciju (engl. *indirect hemagglutination* – 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. Ispostavilo se da su u celokupnom posmatranom periodu u najvećem broju slučajeva (61,91%) rađene poštedne 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. Prema mišljenju autora, metodu izbora predstavlja operacija po Papadimitriouu – parcijalna pericistektomija sa omentoplastikom – budući da se njome postiže balans između potrebe za radikalnošću i principa poštednosti tkiva jetre. Minimalno invazivne procedure poput perkutanih drenaža i laparoskopije postepeno su se uvodile u pažljivo odabranim slučajevima u poslednjim dvama analiziranim periodima; primećeno je da se njihov broj povećao sa 3,4% na 8,1%.

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