Hydatid disease of the liver: thirty years of surgical experience

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Riassunto

L'idatidosi epatica rappresenta una patologia ancora relativamente frequente in diversi Paesi. Mentre la storia naturale della malattia è quasi completamente nota, numerose complicanze possono verificarsi nei casi non responsivi a trattamento o recidivanti. Lo studio, riprendendo la nostra casistica degli ultimi 30 anni, si propone di evidenziare come la chirurgia radicale dell'idatidosi a localizzazione epatica rappresenti un trattamento efficace e sicuro. Vengono, inoltre, raffrontate le esperienze più significative di gruppi internazionali.

Sono stati valutati, con uno studio retrospettivo, i casi di echinococcosi a localizzazione epatica trattati chirurgicamente dal gennaio 1973 al dicembre 2003. Sono stati inclusi 216 pazienti, 98 maschi e 118 donne. Il confronto di sopravvivenza si è ottenuto con il metodo di Kaplan-Meier, usando il log-rank per la comparazione dei dati. Differenza della *p* minore di 0.05 è stato posto come limite di significatività.
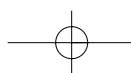
Complessivamente, sono state trattate 279 cisti da echinococco. Sono state effettuate 122 cistopericistectomie, 73 delle quali con tecnica chiusa. Sono state inoltre praticate 19 resezioni atipiche, 10 segmentectomie, 20 lobectomie e 2 trattamenti percutanei. In oltre il 90% dei casi il dato preoperatorio è stato completato e precisato dall'ultrasonografia intraoperatoria. La morbidità complessiva è risultata del 13%. Il tasso di ricorrenza è stato del 4.3% a 5 anni e del 7% a 10 anni: di questi, 6 casi sono stati osservati dopo chirurgia non radicale e 2 dopo cistopericistectomia o resezione epatica (*p* < 0.001).

L'avanzamento tecnico e la consolidata esperienza permettono un trattamento sicuro dell'echinococcosi epatica mediante un trattamento chirurgico radicale, con il minimo rischio di recidiva: tale approccio rappresenta perciò trattamento di scelta rispetto alle resezioni incomplete. I trattamenti percutanei, così come l'approccio laparoscopico, rimangono indicati solo per indicazioni selezionate.

Parole chiave: idatidosi epatica, pericistectomia, resezione epatica, tecnica PAIR

Introduction

Human echinococcosis is a zoonotic infection caused by larval forms (metacestodes) of the tapeworm of the *genus echinococcus* found in the small intestines of carnivores. Human infection is acquired from ingestion of the parasite eggs from infected animals. *Echinococcus granulosus* causes echinococcosis in humans, a condition that is found throughout the world and is endemic in large sheep-raising areas in Europe, Asia, the Mediterranean, South America and northern Kenya[1,2]. The most frequent site of hydatid cyst is the liver (accounting for 50 to 70 percent of cases), followed by the lungs (20 to 30 percent) and less frequently, the spleen, kidneys, heart, bones, central nervous system, and elsewhere. Cystic echinococcosis is usually asymp-

tomatic but a substantial number of infections cause morbidity, with occasional mortality[3].

Liver hydatid disease is a relatively frequent disease (endemic in many parts of the world) especially in sheep-rearing areas. It continues to be a serious public health problem, because it is endemic in some regions of Europe, the Mediterranean (Greece, Turkey, Tunisia, Israel and some regions of Italy), Australia and New Zealand, where although prophylactic measures had been taken, it still remains a significant disease in various endemic areas[4]. Whereas the natural history has been evidenced in all areas, several complications may occur, especially when the diagnosis is late. With immigration, the prevalence of the disease has increased in Europe and North America. Despite on going efforts around the world, with different preventive measures and vaccination programs, only a few countries have achieved a substantial reduction in Echinococcus infestation. The distribution of *Echinococcus granulosus* depends on agricultural, economic and educational factors. The prevalence rate is variable: it is higher in areas where treatment is late, and long-term symptomatic patients persist (7-45/100,000 inhabitants for year), but also in most developed areas, where Echinococcus is endemic, the prevalence is substantial (15/100,000 a year in Tunisia, for example)[5]. The annual incidence of hydatid disease ranges from less than 1 to 220 per 100,000 inhabitants in various endemic areas. There has been a recent increase, due probably also to diagnostic improvements, both in imaging and in immunological techniques[6,7]. Italian regions have various incidence rates, with endemic areas in southern Italy[8]. Medical therapy with antihelminthics is fairly ineffective, and is often used as an adjunct to surgical treatment. The surgical approach, however, is controversial and may be radical or conservative. The choice will depend on many factors, such as the number of cysts, their location, their development stage, the presence of complications (especially involving the biliary tract), the morbidity and mortality respectively associated with each approach, the relapse risk, and the general state of health of the patient.

Pathogenesis

Hydatidosis is a parasitic disease due to the larval stage of a small tapeworm *Echinococcus granulosus*, taeniid canid. The entire worm consists of a head (or scolex, from the Greek *skoleks*, meaning a worm) and a body (or strobila, from the Greek *strobilos*, meaning a spinning top) made up of three or four proglottids. The parasite is member of the *Cestodes genus* (from the Greek *kestos*, meaning a belt). Its habitual host (definitive host) is a carnivore (generally a dog or fox). Human infection results from eating raw vegetables infected by faeces of dogs or by direct contact with infected dogs, mostly through the intimate contact between children and their pets[5]. The eggs are caught up in the coats of infected dogs; they are conveyed to the children's fingers and are ingested. Humans are accidental hosts and play little part in the transmission of the disease. Direct transmission of echinococcosis from human to human is impossible. The eggs, intermingled with fae-

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Summary

Hydatid disease of the liver: thirty years of surgical experience. *C. de Werra, S. Condurro, S. Tramontano, M. Perone, I. Donzelli, S. Di Lauro, M. di Giuseppe, R. Di Micco, A. Pascariello, A. Pastore, G. Diamantis, G. Galloro*

Hydatid disease of the liver is a relatively frequent disease. Although the natural history is almost completely known, several complications may occur. The aim of this study was to show that radical surgical resection of the hepatic hydatid cyst is a safe and very effective technique, based on our results after 30-year experience. A review of most significant studies was carried out. We retrospectively evaluated our surgical cases. From January 1973 to December 2003 we treated 216 patients, 98 males and 118 females. Survival was compared with the Kaplan-Meier test, using log-rank analysis to compare data. Differences with a *p* value less than 0.05 were considered significant. A total of 279 cysts were excised. We performed pericystectomy in 122 cases, 73 of which closed. We also performed 19 atypical resections, 10 segmentectomies, 20 lobectomies and 2 percutaneous treatments. In more than 90% of cases, preoperative data collection was completed by preoperative ultrasound. The cumulative morbidity was 13%. The recurrence rate amounted to 4.3% at 5 years and 7% at 10 years: of these, 6 occurred after non-radical surgery and 2 after total pericystectomy or liver resection (*p* < 0.001). Technical advances and accumulated experience permit safe treatment of hepatic hydatid cysts by radical resection, with an almost zero recurrence rate, making it the treatment of choice over partial resection. The utility of percutaneous treatment remains confined to limited indications, such as laparoscopy.

Key words: liver hydatidosis, pericystectomy, hepatic resection, PAIR technique

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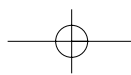
ces, are generally ingested by sheep or other herbivores (intermediate host). After hatching in the intestine, the oncosphere, they penetrate the intestinal wall. They reach the blood and the lymphatic system and disseminate possibly everywhere in human body, where they can form a hydatid cyst. In the affected organ, the cyst is made of an outer layer produced by the mechanical effect of gradual enlargement of the cyst on the surrounding tissue, called the pericyst. Inside, the endocyst consists of two more layers. The inner one is the active membrane (the proligera) which produces protoscolices and brood capsules. The outer layer has no active role, being acellular (sometimes called the ectocyst). The central cavity of the cyst is filled with clear fluid called rock water[6,9].

Diagnosis

Generally, the diagnosis is late, because the uncomplicated hydatid cyst is asymptomatic, owing to an insidious evolution. Rarely, hydatidosis is discovered after systematic laboratory investigation, or occasionally, or after complications.

1. Clinical findings

The liver is the most commonly affected organ (70% of cases) and usually does not cause symptoms. A cyst may grow and then persist without change for many years, while others may rupture spontaneously or collapse and some may completely disappear. Hepatic hydatid cyst can rupture into the peritoneum, leading to anaphylaxis or peritoneal dissemination or

both; into the biliary tract causing cholangitis or cholestasis or both; or into the pleura or lung, causing pleural hydatidosis or bronchial fistula. Cysts may become infected and form liver abscesses. Pressure or mass effects on the bile ducts, portal veins, and hepatic veins and inferior vena cava can cause cholestasis, portal hypertension, and Budd-Chiari syndrome, respectively[10].

If complications occur, it will be generally due to compression or dislocation of the biliary tree (the main bile ducts, especially). Symptoms can also be due to the cyst rupturing into it. Rupture can be classified in three ways: in 'contained rupturÈ, only the endocyst is torn. 'Communicating rupturÈ implicates damage that allows the cystic content to filter into the bile ducts or bronchioles incorporated in the pericyst. In cases of 'direct rupturÈ the parasite will directly contaminate the peritoneal or pleural cavity. The symptoms of rupture usually include upper abdominal pain, jaundice, fever and pruritus with or without urticaria. Physical examination may reveal hepatomegaly, an abdominal mass or tenderness. Rupture can be complicated by allergic reactions, obstructive syndrome, secondary infections and metastatic diffusion of the parasite[11].

2. Radiological reports

Hydatid cyst has a typical radiological and ultrasonographic pattern. On an axial X-radiogram (ARX) four aspects may be present[12], as indicated in Table I.

Ultrasound (US) is the most suitable method for the diagnosis of hydatid cyst. It is helpful for defining the internal structure, number, location of the cysts and presence of complications, with a specificity of 90% (Gharbi classification[13]). Types II and IV are characteristic, while I and V are suggestive of hydatid disease only in endemic areas (Table II, Fig. 1).

A recent revision of the US classification considered three major groups, corresponding to clinical aspects that are associated with the US pattern and with the activity grade of the disease. The first clinical group starts with type I and type II cysts and such cysts are active, usually fertile cysts containing viable protoscolices. Type III cysts are cysts entering a transitional stage where the integrity of the cyst has been compromised either by the host or by chemotherapy, and this transitional stage is assigned to the second clinical group. The third clinical group comprises types IV and V, which are inactive cysts that have normally lost

Table I. Radiological aspects.

	Description
Type I	Elevation of right hemidiaphragm, curvilinear or ring-like calcifications in daughter cysts
Types II and III	Pleural effusion or fistula due to cyst rupture through the diaphragm
Type IV	Gas or fluid level due to infection within the cyst

Table II. US pattern: Gharbi classification.

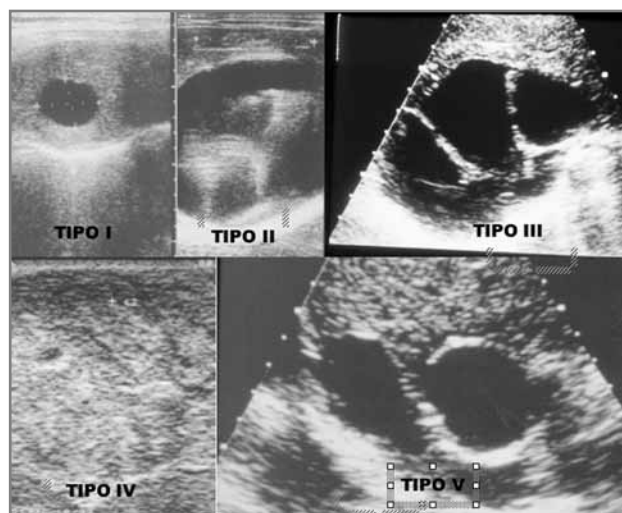|	Characteristics
Type I	Pure fluid collection (simplex cyst)
Type II	Fluid collection with a split wall (floating membrane)
Type III	Fluid collection with septa (honeycomb pattern)
Type IV	Various heterogenic echo patterns
Type V	Reflecting thick walls

Fig. 1. Gharbi's classification (see text).

their fertility and are degenerative. The use of the standardised US classification will facilitate the application of uniform standards and principles of treatment currently recommended for each type of cyst[14].

Computed tomography (CT) provides detailed information about the location, depth, volume, calcification and infection of the cyst: it indicates major complications, and any daughter cysts, explaining the vitality of the pathogen[15]. Similar data are furnished by magnetic resonance imaging (MRI).

A thorough imaging study of the cyst and biliary system should be performed to detect any rupture of a hydatid cyst. US, CT, MRI and MR-cholangiography have a complementary role[16]. Evacuation of the cystic contents without an endocyst tear is hard to diagnose, while its detachment and content voiding in the bile duct provide enough clues for detection. A dilated biliary radicle with a conical configuration of its end part in close proximity to the main cyst on appearance of hydatid material in the biliary system strongly suggests cyst rupture[17-19].

Another imaging method, endoscopic retrograde chlangiopancreatography (ERCP), seems to be useful for the diagnosis and treatment of complications related to involvement of the biliary tree; in the preoperative phase it indicates communication between the cyst and the bile ducts[20]. Its usefulness has been confirmed, especially with regard to biliary complications and resolution of cyst-related biliary obstructions[21,22]. In this context, ERCP has a high diagnostic sensitiviy[23] (Fig. 2). Table III presents a comparison between various diagnostic techniques used in hepatic echinococcosis.

3. Immunological tests

Non-specific immunological evaluation is essential, but will obviously not be specific in the diagnostic approach to hydatidosis: eosinophilia, usually normal, may be slightly increased at the beginning of infection or, in the case of cystic leakage, hepatic parameters may be altered, though only in cases of extensive hepatic diffusion (and destruction). High levels of total IgE (identified by means of a radioimmunological or immunoenzymatic test, are often seen during human parasitosis, without reference to cyst localisation and activity. Specific Ig isotypes can be measured by radioimmunology: elevated specific IgE levels are found in 75% of hepatic hydatidosis, such as in a cyst rupture or multiple localizations; specific IgMs are observed during acute disease or after cyst rupture, while specific IgAs are elevated in pulmonary localisations. IgG4 subclass antibody increases during the transition from asymptomatic to advanced symptomatic disease, indicating the need for pharmacological treatment[24,25].
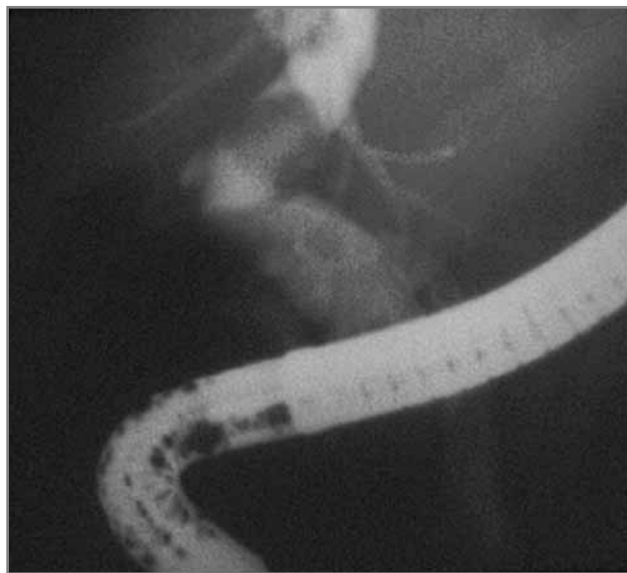
Fig. 2. Preoperative ERCP, showing many cysts inside the biliary tract.

Many immunological tests are helpful for diagnosing hydatid disease that relies mainly on epidemiological and clinical findings. The immunological evaluation includes cellular and humoral immunity studies: as regards the former, the intradermal Casoni test is well known, but the high risk of false-positive results limits its application; the human basophile degranulation test, performed with hydatid antigens, is more sensitive and specific, but there is a risk of persistence of a positive test after surgery (related to persistence of the antigen)[24]. Many serological techniques can be used to detect or quantify humoral immunity, using either whole parasites or soluble antigens (prepared from hydatid cyst fluid). In detail, the indirect immunofluorescence assay (IFA) is specific and sensitive, especially for hepatic localizations, but distinguishing between hydatidosis and alveolar echinococcosis is difficult[26]; indirect agglutination and indirect haemagglutination tests are easy to perform and complete results are available within two hours:

the cutoffs are 1:4 and 1:320, respectively, but they require another serological test for confirmation (screening test)[27]. The ELISA test (enzyme-linked immunosorbent assay), an enzymatic reaction used to quantify specific antibodies, has a sensitivity and specificity that depend on the antigen preparation, and is used mostly for IgG antibodies[28]; the ELIFA test (enzyme-linked immunoflow assay) allows isotypic analysis of the humoral response, with high sensitivity, but the test is too costly. Double diffusion in gel (DDG) and Western blotting (WB), analysing precipitation complexes, are less used, because of the lengthier study times involved (5-7 days) and the fact that the necessary instruments are to be found only in specialised laboratories[24]. If these tests are used in combination, their diagnostic accuracy is close to 80/95% in hepatic hydatidosis and 65% in pulmonary hydatid cases. Seronegativity cannot exclude hydatidosis. Serological tests are not substitute for clinical or imaging investigations[29]. They can, however, confirm the hydatid origin of the cyst. A serological investigation is necessary for the follow-up of operated or medically treated patients. Specific antibodies increase 4 to 6 weeks after surgery, after which they decrease slowly over the next 12 to 18 months[30]. The decrease in specific antibodies is too irregular to be a good indicator of recovery or relapse, but persistently high specific antibodies titers or a secondary increase in antibody titers 6 to 12 months after surgery indicate a relapse. False-positives can be due to cysticercosis or alveolar echinococcosis, because of the antigenic commonality among cestodes, so that concordance with clinical data is mandatory to make the correct di-

Table III. Diagnostic assessment.

Diagnostic study	Cost	Sensitivity	Specificity
US	+	99%	60-65%
CT	+	96-98%	86-98%
MRI	+	95%	98%
Scintigraphy	++	96%	15-20%
Angiography	++	96%	98%

+= low cost; ++= high cost.

agnosis[6,31]. A new step in the diagnostic work-up is the polymerase chain reaction and all molecular antigen analysis: this technique can differentiate between the granulosus and multilocularis types in clinical samples, on comparing restriction fragment length polymorphism (RFLP); however, this type of investigation remains an experimental evaluation due to the elevated costs and limited availability[32]. A comparison between the various tests is available in Table IV.

Materials and methods

From January 1973 to December 2003 in our department (General Surgery, University of Naples Federico II) we treated 216 patients, 98 males and 118 females, aged from 8 to 81 years. Preoperative study included careful clerking supplemented with radiological reports and immunological tests. Imaging studies of the cyst and biliary system were performed to detect any rupture of the hydatid cyst. US, CT, MRI and MR-cholangiography were all used.

Among our patients, 132 were affected by a single cyst, and 84 by multiple cysts. 104 cysts were located in the same hepatic lobe, while in 68 cases there was a bilateral localisation. In all, 279 cysts were excised. None of the patients complained of a specific symptom: right hypochondriac pain was the most frequent (24.6%); itching (15.7%), epigastric pain (13%), nausea (10.9%) and right shoulder pain (6.1%) were also described. Nearly half of the cases presented hepatomegaly, isolated or combined with systemic manifesta-tions. Only 12 patients had an abdominal mass, and 18 presented a skin rash. All the symptoms are listed in Table V.

Surgery is the WHO recommended treatment for liver hydatid cysts. We applied a surgical approach to all patients that were eligible, evaluating general condition, age, comorbidity, locations and number of lesions. When surgery was not possible, it was necessary to sterilise cyst bed, eliminating the parasite foci: this is also possible with a percutaneous technique, such as PAIR (based on puncture, aspiration of the cyst and reinjection of the parasitocidal agents), discussed above. Since 1987 we have been using albendanzole (10 mg per kg per day). We used only parasitocidal agents when: 1. an operation was excluded by our retrospective evaluation; they were not treated

Table IV. Immunological tests.

Diagnostic technique	Sensitivity	Specificity	Use in practice	Information about activity of disease	Cost
Intradermal Casoni test	+	++	++++	+	++++
Specific Ig	+	+++	++++	++	++++
Immunofluorescence assay (IFA)	+++	+++	++++	+++	++++
Agglutination and indirect haemagglutination tests	++	+++	+++	+++	++
ELISA	++	++	++	++	++
ELIFA	+++	+++	++	++	+
Double diffusion in gel (DDG)	+++	+++	+	+	+
Western blotting (WB)	+++	+++	+	+++	+
Polymerase chain reaction (PCR)	++++	++++	+	++++	+

+= *weak indication;* ++++= *strong indication.*

Table V. Symptoms at diagnosis.

Symptoms	Number (%)
Abdominal pain (diffuse or localised)	140 (64.8%)
Itching	45 (20.8%)
Hepatomegaly (isolated or combined)	98 (45.3)
Dyspepsia and epigastric pain	28 (12.9%)
Nausea and vomiting	25 (11.5%)
Fever	18 (8.3%)
Jaundice	13 (6.0%)
Anaphylactic reactions	10 (4.6%)
Asymptomatic	61 (28.2%)
Cutaneous manifestations	12 (5.5%)
Abdominal mass	18 (8.3%)

with percutaneous or surgical therapy (patients with high operative risk or refusing treatment), but received only pharmacological therapy. Patients were subjected to follow-up at 1, 6, 12 and 24 months: evaluation consisted in a clinic visit, laboratory test and ultrasonography (Fig. 3). As regards the laboratory tests, we preferred the indirect haemaglutination test as a screening test, with another specific test (such as RIA or the Casoni test) to confirm suspicious data.

Data were evaluated by univariate analysis. Survival was compared with the Kaplan-Meier test, using log-rank analysis to compare data. Differences with a p value less than 0.05 were considered significant.

Results

We performed pericystectomy in 122 cases (49 of which by opening and voiding the cysts). In 73 cases a closed pericystectomy was per-

formed. Closed pericystectomy is the ideal technique. It involves many risks and is technically demanding. We are keen to use this option in calcified, superficial and relatively small cysts (less then 10 cm). We also performed 36 partial pericystectomies, 19 atypical resections, 8 right lobectomies, 10 segmentectomies, 7 left lateral lobectomies and 5 left hepatectomies (Table VI). Intraoperative ultrasound is an useful procedure to evaluate the localisation of cysts and their relationships with the biliary and vascular structures (Fig. 4). It can also be used to detect exogenous vesicles by performing it from inside the opened, sterilised cyst. We applied this technique to all patients to reduce the risks of incomplete resection. In more than 90% of cases, preoperative data were corrected and defined by this examination. We also studied the cysts by opening them (after aspiration) to detect other daughter cysts and suspected areas of endogenous vesiculation (Fig. 5).

We performed two percutaneous treatments for inoperable cases (advanced age and numerous comorbidities). These patients were both hospitalised for 4 days after the procedure, without complications; none of them had recurrences during follow-up. The average hospital stay was 19.6 days, with a progressive decrease over the last 10 years, regardless of surgical technique.

Patients who died during the period of full hospitalisation or in the first 3 months after surgery amounted to 5 (2.3%), all occurring in the first 10 years of this analysis; deaths were often related to poor general status, without any significant correlation with type of surgery.

Fig. 3. Postoperative ultrasound, showing the residual cavity with dreinage inside.

Table VI. Type of surgery.

Radical operations	N.	Conservative operations	N.
Left hepatectomy	5	Partial pericystectomy	36
Right lobectomy	8	Cystic dome resection	0
Left lobectomy	7	Endoscopic drainage	2
Segmentectomy	10		
Wedge resection	7		
Atypical resection	19		
Open pericystectomy	49		
Closed pericystectomy	73		

The cumulative morbidity was 13% (28 patients). Biliary fistula was observed in 19 patients (8.8 %); there were indications for treatment with endoscopic therapy in 3 cases, while 4 cases underwent surgery and remnants were treated with medical therapy. At the moment we tend to utilize ERCP sphincterotomy and positioning of nasogastric suction tubes, reducing biliary pressure and monitoring clinical condition. Minor complications are indicated in Table VII. For biliary fistulae, there was a significant correlation with conservative surgery ($p < 0.001$; data non shown); total pericystectomy and liver resection were performed only in 4 cases. Several concomitant pathologies (also in Table VII) were discovered during surgery (25 patients). In 35 cases other resections were performed, generally for related pathologies or spread of echinococcosis (Table VIII).

At follow-up at 5 years, available for 195 patients, the recurrence rate was assessed as 4.3% (8 cases): of these, 6 occurred after non-radical surgery and 2 after total pericystectomy or liver resection ($p < 0.001$). At 10 years, the recurrence rate observed amounted to 7% (7 cases out of a total of 90 cases available); in this group, there was also a significant tendency to perform radical operations. The relationship between type of surgery and recurrence rate is shown in Table IX.

Discussion

Medical therapy of hydatid disease is based on benzoimidazole chemotherapy, which can induce reduction of the size of the cyst and density increment. The success of chemotherapy is limited as a single measure: after 1-2 years of therapy, the success rate amounts to 30-40%, whereas another 30% obtain significant disappearance or size reduction. Because of the high relapse rate (50% in older studies), chemotherapy is indicated for inoperable patients, with multiorgan spread of cysts and mostly before and during surgery or the PAIR technique (puncture, aspiration, injection, re-aspiration). In these latter cases the risk of relapses is reduced by obtaining systemic sterilisation, unless the cysts are rupture-prone (for this type chemotherapy is contraindicated)[33].

There is no doubt that surgery guarantees the best chance of resolution, but it is not clear what the most indicated surgical operation is. In surgical decision-making many factors have to be carefully integrated. A very important factor will be the economic development of the country. An improvement for detecting data on cysts
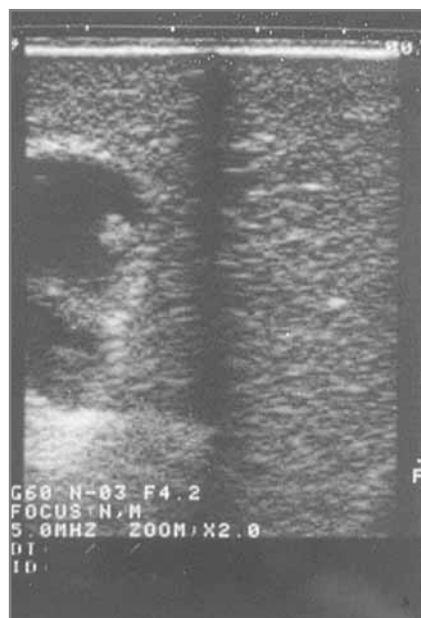

Fig. 4. Peroperative ultrasound showing the wall of the cyst and its relationship with liver parenchima and vessels.
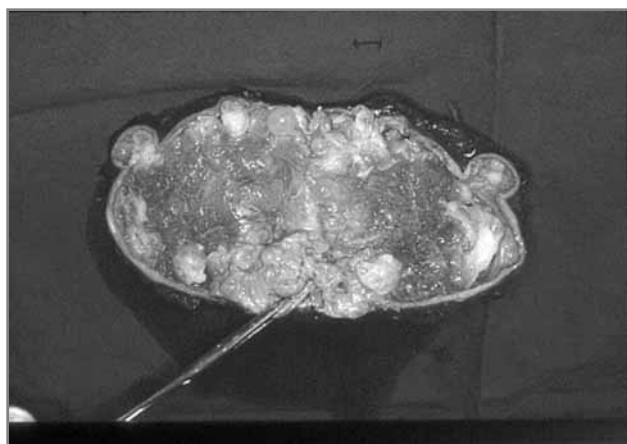
Fig. 5. Operative specimen showing the opened cyst with exogen vesciculation.

and daughter cysts seems to be preoperative ultrasonography, introduced almost three decades ago. In many centres specialised in hepatobiliary surgery, intraoperative ultrasonography (IOUS) has become a mandatory intraoperative diagnostic tool for intraoperative decision-making, providing additional information[34, 35]. This technique has yielded high intraoperative sensitivity (about 20%) in many studies[36,37]. Intraoperative ultrasonography has been thought to be beneficial for finding centrally localised cysts which may be inconspicuous, especially in cases of multiple cysts[33,37,38].

Surgical therapy includes radical and conservative approaches. Partial pericystectomy and cystic dome resection (conservative approaches) allow removal of the cystic contents, endocyst inner active layer (proligera membrane) and outer layer, leaving the pericyst. Marsupialisation or open conservative surgery, such as partial pericystectomy and pericystorraphy with capitonnage (closed conservative surgery), are rapid, more feasible and easy to repeat without hepatic mutilation. For this reason, if the risk of reduced regeneration of parenchyma persists, this surgery remains the first choice. It is necessary to treat residual areas (risk of daughter cysts, exogenous vesicles, cholangitis, haemorrhage). Though not being very technically demanding, at the same time they provide no guarantee regarding relapse (outer vesiculation) and are generally responsible for greater morbidity[38], because of difficult closure of the hard pericystic wall. Because part or all of the pericyst remains in the hepatic bed, the rate of recurrence remains higher. Right from the start of our experience, these factors forced us to limit conservative surgery, choosing it only for cases of extreme necessity, such as in patients presenting with severe local or general inflammation and especially those ones with cysts involving the hilum and central liver sites, or patients at very high operative risk, because in cases of post-surgery biliocystic fistula the mortality rate is too high. Many authors have discovered significant

Tab. VII. Post-surgical complications and other pathologies related to hydatidosis.

	Number (%)	Treatment
Biliary fistula	19 (8.8%)	Endoscopic (3) Surgical (4) Medical (12)
Infection of residual cavity (abscess)	2 (0.9%)	Medical (US-guided drain + drugs)
Residual jaundice	1 (0.5%)	Medical
Other extrahepatic complications	3 (1.3%)	Medical
Cholestasis (biliary rupture)	2 (0.9%)	Surgical
Biliary lithiasis	15 (0.69%)	Surgical (15)
Cholestasis (compression)	8 (0.3%)	Endoscopic + surgical (6) Endoscopic (2)
Metastatic carcinoma	2 (0.9%)	Medical (palliative)

Table VIII. Other resections associated with cystic resection (35 cases).

Type of surgery	N.
Cholecystectomy	18
Choledochoduodenostomy	2
Papillostomy	3
Splenectomy	6
Gastric resection	3
Transverse colectomy	1
Left nefrectomy	2

differences in recurrence rates between complete and incomplete surgery[39-41]. Even when these differences are not significant, there is a strong tendency towards total pericystectomy[38].

In detail, the conservative technique has not been confirmed by international surgeons because of the higher rate of complications. In the last few years many authors (especially radiologists) have published studies on the PAIR technique, with good results in terms of mortality and morbidity[42]. These data probably reflect good patient selection: accordingly, cysts have to be uncomplicated, mostly single, and relatively small with no major complications[43]. If cysts are larger than 5 cm, catheterisation is also required. Recent guidelines now indicate only the following for PAIR: anechoic lesions larger than 5 cm in diameter; type I and type II cysts according to the Gharbi classification; multiple cysts larger than 5 cm in different liver segments; cysts with a regular double-laminated layer[42]. Contraindications are honeycomb-pattern cysts, inaccessible or superficial cysts, cysts with echogenic lesions, inactive or calcific cysts, and when direct communications with the biliary ducts is strongly suspected, because there is a substantial risk of cholangitis related to scolicide substances[44]. A historic randomised trial by Khuroo confirmed the efficacy of PAIR for uncomplicated cysts, with a shorter period of hospitalisation and fewer complications (mostly fever) than surgery[45]. Recently, these indications have been re-assessed, due to the evolution of surgical techniques and the reporting of cases of systemic reactions after percutaneous treatment[46-48]. The risk of dissemination with anaphylactic shock is not really known; spillage of protoscolex-rich fluid amounts to 5-10%[49], and this rarely leads to anaphylaxis. In a study by Yaghan, this risk seems to be underestimated[50], because cases of anaphylaxis during percutaneous treatment were not reported[51,52]. Currently,

Table IX. Follow-up at 5 and 10 years.

5 years					
Type of surgery	N.	Hospital stay (range)	Morbidity	Mortality (during hospitalisation)	Recurrence
Conservative surgery	38	16.4 days (10-31)	6 (15.7%)	1	6 (15.7%)
Radical surgery	178	12.2 (6-18)	19 (10.6%)	1	2 (1.1%)
Statistical analysis		p: ns	p: ns	p: ns	$p < 0.001$
10 years					
Type of surgery	N.	Hospital stay (range)	Morbidity	Mortality (during hospitalisation)	Recurrence
Conservative surgery	70	12.4 days (10-26)	6 (8.5%)	0	1 (1.1%)
Radical surgery	20	10.8 (7-19)	2 (10.0%)	0	2 (10.0%)
Statistical analysis		p: ns	p: ns	/	$p < 0.001$

the indications for PAIR seem to be limited to patients of advanced age with a high surgical risk, and to central cysts located in the proximity of key vascular elements. Earlier WHO recommendations indicated percutaneous techniques only for inoperable patients or for those who refused surgery[42]. Radical operations (total or subtotal pericystectomy, hepatic resection and wedge resection) allow complete ablation of the lesion; knowledge of the pathophysiology of liver hydatidosis, in fact, attributed importance not only to parasitic foci, but also to the surrounding parenchymal zones altered by the cyst (the entire pericyst). At the same time, liver closure will be easier (healthy tissue) and morbidity lower[41,53]. A recent systematic review concluded that omentoplasty combined with radical or conservative treatment is efficient in preventing deep abscesses (level II evidence, grade A recommendation)[41]. Pericystectomy is sometimes very technically demanding but results in complete parasite eradication. When the cyst in located near major bilio-vascular structures, we tend to void the cyst. In the most difficult cases, part of the pericyst can be left in situ because the risk of exogenous vesicles is very low. Total pericystectomy is the only technique potentially capable of achieving non-recurrence: this resection, in fact, detects daughter vesicles, which are often unnoticed when approaching the cyst from the inside (conservative technique). These daughter cysts amount to about 20%, according to data by Magistrelli[54] and Assadourian[55]. Simple cystectomy with capitonnage has been correlated with a higher rate of recurrence in studies by Safioleas

(4.5% of cases) and Vagianos (6% of cases), indicating the risk of both residual cavity and abdominal dissection[56,57].
Hepatectomy or segmental liver resection have been seen as excessively aggressive operations for a benign disease, but this opinion is no longer tenable, especially if we consider that, in some developed nations, technical progress reduces hepatic resection-related mortality and morbidity almost to zero[53].
A good follow-up is of primary importance to improve the diagnosis of recurrence, defined as the appearance of new active cysts after therapy. After PAIR, indications for follow-up checks have been established: every week for the first month, then every other month for the first year, and then every year for 10 years; the minimum requirement is every 6 months for the first year, and then every year for 10 years[53].
Monitoring with imaging techniques and immunological tests, with a follow-up at least of 3 years, is essential for documenting the efficacy of therapy. Relapse is often asymptomatic[58], whereas blood titres decrease slowly, even years after diagnosis[59]. We monitored patients after surgical treatment with diagnostic tests for at least 10 years, first of all, with immunological test: the indirect haemagglutination test is the most sensitive in follow-up, and we chose this test as a screening test in asymptomatic patients. In diagnostic imaging, we used predominantly US and CT (98% of cases), both of these being techniques with reasonable specificity and sensitivity also for recurrence[60]. Recurrences occurred at the site of surgical cyst evacuation in 63% of cases, with typical signs of growth of the

cyst. The treatment options are similar to those for primary cysts: accordingly, more radical treatment may be proposed, such as hepatectomy. Some authors have indicated albendazole alone for the treatment of recurrence, especially if scolicidal agents have not been used for the primary disease[61]; it is more indicated in multidisciplinary treatment, reducing viable scolices in treated cysts and increasing the rate of dead daughter cysts[45].
More than 90% of hydatid cysts present communication with biliary tracts[53], generally asymptomatic, but only a small proportion of them presents passage of cystic contents into the biliary tree. Cystic rupture can occur in three ways: contained rupture (the cystic contents are confined within the pericyst), communicating rupture and direct rupture (tearing of both the endocyst and pericyst, with cystic contents released into the peritoneal or pleural spaces)[62]. In these cases, the bile ducts must be examined and washed, and many authors leave a T tube in place, or, if there is a papillary stenosis or the cyst is not correctly treatable, they undertake a sphincteroplasty or choledochoduodenostomy[63]. The preoperative use of ERCP seems to be demanded, because of the low percentage of frank biliary rupture[64]: recently, improvements in imaging techniques have enabled a sensitivity of 90% to be achieved in the diagnosis of biliary communication with US, and about 100% with CT[63, 65]. In our study, we used ERCP in 4 cases, treated in the first years of our experience: one for suspected passage of cysts in the choledochus, and three in the postoperative phase, for persistent jaundice related to residual material in

the bile ducts, all detected during the operation, or to biliary fistulae. Many diagnostic findings are provided by ERCP in preoperative patients: cystobiliary fistula, biliary dilatation or compression, daughter vesicles and hydatid material in the bile ducts; the papilla may be bulging, oedematous and hyperaemic[62]. The false-negative rate amounts to about 20%[66]; the success rate, with sphincterotomy, balloon and basket extraction and stent insertion[67,68], remains very high (85-100% in a recent review[69]). Rodriguez mentioned the role of preoperative sphincterotomy to avoid postoperative external fistulae[70]; these features, added to the therapeutic role of ERCP in completing the cure (observed in 25% by many Authors[71,72]), require a randomised, controlled trial, comparing ERCP with surgery. The postoperative role is diagnostic, clarifying the causes of recurrent symptoms, and therapeutic, resolving obstructions and cholangitis, and in the management of biliary fistulae, when performing sphincterotomy, nasobiliary drainage, or stent insertion, alone or in combination[69,73-75].

Laparoscopic treatment of liver hydatid disease has already been performed. We do not have any direct experience of this. International studies have reported low mortality rates[76-79]. The only confirmed role seems to be diagnostic, confirming suspected cysts and orientating surgery, as reported by Giuliante[80]. The risks of laparoscopic cystostomy and pericystectomy are rupture of the cyst and recurrence: in the former case, anaphylactic reactions have been reported, with a rate higher than that of open surgery[77]; in the latter case, recurrence is related to the non-occurrence of daughter cysts[81]. With proper patient selection, laparoscopic management of hydatid cysts of the liver is a feasible option with low rates of conversion. Cystotomy, partial cystectomy and omentoplasty have been widely performed laparoscopically[82,83]. The current indications for the laparoscopic approach seem to be limited to small, calcific cysts, and to superficial localisations[33,82].

Conclusions

Hydatid cysts must be treated surgically, given that parasitocidal effects are not effective in all cases and do not guarantee complete resolution. Greater experience and knowledge of the history of infection now permits total pericystectomy to be undertaken with low risk and minimum risk of relapse. Conservative surgery remains helpful for patients at high risk of radical operations, for critical localisations, although they are associated with a higher percentage of recurrence. Experience with PAIR by multiple groups in different countries has led to greater confidence in the efficacy and safety of the procedure, while it has also provided more insights into the precautions necessary to ensure the highest level of efficacy and safety. It should be performed only by teams experienced in liver punctures under ultrasound guidance, after specific training in this field. Laparoscopy needs to be confirmed by larger experiences.

In conclusion, we believe that the approach to this disease has to be drastic and perfect because, even though it is benign, it may tend to resemble a malignant disease (relapse, metastases etc.).

Abbreviations

ARX = axial X radiogram; US = ultrasound; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; IFA = immunofluorescence assay; ELISA = enzyme-linked immunosorbent assay); ELIFA = immunoflow assay; DDG = double diffusion in gel; WB = Western blotting; RFLP = restriction fragment length polymorphism; PAIR = puncture, aspiration, injection, reaspiration; IOUS = intraoperative ultrasonography.

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  OK così o in italiano?
- Nel paragrafo Materials and methods controllare frase "when: 1. an operation was excluded by our retrospective evaluation; they were not treated with percutaneous or surgical therapy (patients with high operative risk or refusing treatment), but received only pharmacological therapy.": manca un 2?