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Management of cystic echinococcosis in the last two decades: what have we learned?

--Manuscript Draft--

Article Type:	Full Length Article
Full Title:	Management of cystic echinococcosis in the last two decades: what have we learned?
Abstract:	Background: Management options for Cystic Echinococcosis (CE) remain a great problem. The first aim of this study was to examine the selection and complications of treatment applied in patients with CE. The second aim was to evaluate the mortality rate and causative factors. Methods: We conducted a retrospective descriptive study of patients diagnosed with CE between 1998 and 2015 according to ICD-9 (code 122·0 to 122·9) criteria in the Complejo Asistencial Universitario of Salamanca, Spain. Results: Of the 491 patients diagnosed with CE disease, 342 received surgery: 166 (33.8%) patients received only surgery and 176 (35.8%) received a combination of surgery and drugs. A total of 193 (39.4%) patients were medically treated:123 (63,7%) patients used albendazole alone, and 70 (36,3%) patients used a combination of albendazole & praziquantel. 65 patients (19.0%) had complications after surgery and 7 of them (2%) died. Only 15 (7.8%) cases had side effects of anthelmintics. The strategy of Watch & Wait was conducted in 131 (26.7%) patients. Throughout the study period, 80 (16.3%) patients died, 14 (2.9%) of them due to CE disease. Conclusions: Complications of CE are one of the most common causes of mortality in CE patients, with size, location, and number of cyst and the "Watch & Wait" treatment strategy being the main factors associated with mortality.
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Management of cystic echinococcosis in the last two decades: what have we learned?

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Abstract

Background: Management options for Cystic Echinococcosis (CE) include surgery, percutaneous management, drug therapy, and the *Watch & Wait* option. Therefore, the lack of advances in the management of CE remains one of the major problems. The first aim of this study was to examine the treatment applied in a cohort of patients with CE, the factors involved in the treatment selection and the treatment complications. The second aim was to evaluate the mortality rate and causative factors. **Methods:** We conducted a retrospective descriptive study of patients diagnosed with CE between 1998 and 2015 according to ICD-9 (code 122·0 to 122·9) criteria in the Complejo Asistencial Universitario of Salamanca, Spain. **Results:** Of the 491 patients diagnosed with CE disease, 342 received surgery: 166 (33.8%) patients received only surgery and 176 (35.8%) received a combination of surgery and drugs. A total of 193 (39.4%) patients were medically treated:123 (63,7%) patients used albendazole alone, and 70 (36,3%) patients used a combination of albendazole & praziquantel. 65 patients (19.0%) had complications after surgery and 7 of them (2%) died. Only 15 (7.8%) cases had side effects of anthelmintics. The strategy of *Watch & Wait* was conducted in 131 (26.7%) patients. Throughout the study period, 80 (16.3%) patients died, 14 (2.9%) of them due to CE disease. **Conclusions:** Complications of CE are one of the most common causes of mortality in CE patients, with size, location, and number of cyst and the "Watch & Wait" treatment strategy being the main factors associated with mortality.

Key words

Cystic echinococcosis; *Echinococcus granulosus*; Hydatidosis; Albendazole; Praziquantel; Treatment; Chronic diseases; Survival

Introduction

Cystic echinococcosis (CE) is a chronic, complex and neglected zoonotic disease caused by the larval stage (metacestode) of *Echinococcus granulosus*. CE occurs worldwide but it is endemic in central Asia, northern and eastern Africa, Australia, South America and the Mediterranean Basin.[1-3] In humans it may result in a wide spectrum of clinical manifestations, ranging from asymptomatic infection to fatal disease.[4] The clinical management of CE is complex and fundamentally based on three pillars: surgical, pharmacological and percutaneous treatment, which are sometimes administered as complementary treatments.[5,6] Surgical treatment is currently the technique of choice; however, there are several alternative techniques available. For example, PAIR (*puncture-aspiration-injection-reaspiration*) is one such technique that has recently been introduced and that may possibly replace surgery in specific cases[7-9] Other techniques such as modified catheterization technique (MoCaT), modified percutaneous evacuation (PEVAC), immunological or chemo-radioisotope therapies and radiofrequency thermal ablation (RFA) will merit more attention in the future[8]. Anthelmintics, mainly benzimidazoles alone or in combination with other drugs such as praziquantel, have so far been reserved for non-operated patients and have had a secondary role[10,11], in reducing the risk of anaphylaxis, dissemination and/or postoperative recurrence[12] .However, in select patients, the option of "*Watch & Wait*" is being validated[13].

Therefore, despite advances in surgical techniques, the use of chemotherapy and others treatments, and attempts made by WHO, the management of CE disease remains a major problem[14]. Today, there is still no consensus on the management of CE[15], and consequently, the ''best'' treatment is still a subject of debate[13,16]. As such, it is essential to develop clinical studies comparing treatments in homogeneous groups of patients. However, there are a lot of important difficulties in developing prospective clinical assays for CE, such as the long-term

evolution of this infection, the heterogenicity of patients and cysts, and the absence of clinical tools for detecting infection or relapse in early stages of infection. Thus, based on retrospective work, we must to examine the evolution of CE patients with different types of treatment. The first aim of this study was to examine the treatment applied in a cohort of patients with CE, the factors involved in the treatment selection and the treatment complications. The second aim was to evaluate the mortality rate and the causative factors.

Material and Methods

The design of this study was a descriptive longitudinal-retrospective study that was performed in two phases. First, we describe, in our cohort, the treatment applied and the factors involved in the treatment selection and the treatment complications. We reviewed all patients diagnosed with CE according to the ICD-9 (code 122·0 to 122·9) criteria who were admitted to CAUSA between January 1998 and December 2015. CAUSA is a tertiary care hospital that covers an area of 12 350 km^2, and it accommodated 342.459 inhabitants in 2014 (National Institute of Statistics (INE); http://www.ine.es/)[17] and is located in western Spain. Clinical and epidemiological data were collected after review of medical records. Diagnosis and classification of CE were assessed according to the criteria proposed by the World Health Organization Informal Working Group on Echinococcosis for CE[15]. Surgical complications were defined as any deviation from the normal postoperative course[18]. Hypertransaminasemia was defined as having serum transaminase levels at a value greater than 5 times the upper limit of normal (UI/L). Second, we evaluated the mortality rate in patients who attended follow-up at our hospital and the causative factors. Follow-ups were defined with two or more clinical controls. Patients with duplicate records, without follow-up or with missing data were excluded from the study.

Statistical analysis

The results were expressed as percentages for categorical variables and as the mean and standard deviation (SD) for continuous variables. To perform bivariate analysis, a chi-square test was used to compare the association between categorical variables, such as clinical and demographics variables, and the measured outcome was expressed as the odds ratio (OR) together with the 95% CI for OR. Continuous variables were compared with Student's t-test, analysis of variance (ANOVA) or Mann-Whitney test for two groups, depending on their normal or non-normal distribution, and *Least Significant Difference (LSD)* post hoc test. Additionally, we applied the logistic regression model to perform multivariate analysis of variables that influenced mortality of the cohort, estimating the parameter B, standard error (E.T.), and statistical significance with the Wald test and the estimation of the OR (Exp (B)) with 95% CI. Multi-correspondence analysis was performed to help interpret the relationships between the categories of the variables. Survival rates were analyzed by a Kaplan-Meier method. We considered a p-value <0.05 as a statistically significant difference. All data were analyzed with *SPSS Statistics 23 (Statistical Package for the Social Sciences)*.

Ethics statement

The study was approved by the Ethics Committee of CAUSA. Because this was an epidemiological study, written consent was not obtained and was specifically waived by the approving institutional review board. All data were analyzed anonymously.

Results

A total of 571 patients with new CE-related diagnosis codes 122.0 to 122.9 were registered in CAUSA between January 1998 and December 2015. Of these patients, 80 patients with missing data were excluded from the study. Thus, 491 patients with new CE diagnosis were

included in the study, and the patient data are shown in **Table 1**. A total of 288 patients were male (58.7%), the mean age (±SD) was 59.5±20.4 years, 360 (73.3%) patients received medical and/or surgical treatment and 131 (26.7%) patients decided on the *"Watch & Wait"* option. The temporal evolution of the different strategies implemented in the cohort during the study period is presented in **Figure 1. T**here are significant differences in the percentage distribution over the study period between different treatment groups, and thus, while surgery alone or anthelmintics only were the more common treatment strategies at the start of the cohort study, the combination of both therapies was the most frequent treatment strategy at the end of the cohort study ($p<0.001$).

The mortality rate was analyzed in 247 (50.3%) patients who attended follow-up our hospital.

Surgery treatment

Of all the patients, 342 (69.6%) were treated by any surgical method, and of these, 166 (48.5%) received surgery as the only treatment, and 176 (51.5%) received surgery in combination with anthelmintics.

Variables associated with an indication of surgical intervention of CE were location of CE, which was more frequent in thoracic cyst than hepatic locations (62/69 (89.9%) *vs* 274/410 (66.8%)), (OR=4.46, 95% CI, 1.99-9.99; $p<0.001$). The main surgical techniques are shown in **Table 2**.

After surgery, 65/342 (19.0%) patients had complications, with the most frequent being postoperative fistula (17); these complications are shown in **Figure 2.** Between the variables associated with surgical complications, the location of the cyst was the most prominent. We found less postoperative complications in lung cysts (7/62 (11.3%)) than in the remaining locations (65/321 (20.2%)), which include the liver (56/274 (20.4%)), disseminated or other locations (9/47 (19.1%)); however, these results were not statistically significant (OR=2.05,

95% CI, 0.88-4.74, p=0.087). Between the patients with hepatic CE, there was an increased risk of complications when surgery involved liver segments IV (OR=2.20; 95% CI, 1.12-4.31; p=0.019) and VIII (OR=1.96; 95% CI, 1.05-3.64; p=0.030). In contrast, segments III (OR=0.34; 95% CI, 0.11-0.98; p=0.042) and V (OR=0.31; 95% CI, 0.10-0.91; p=0.026) had three times fewer complications than other segments. Also, there were increases in the risk of complications (OR=1.83, 95%CI 1.05-3.22, p=0.032) when the cyst size was greater than 7 centimeters (23.3% *vs* 14.2%). Patients who underwent interventions for CE complications (superinfections, fistula, etc.) had similar postoperative complications as CE patients with elective surgery (p=0.220). We also did not find differences between the different techniques applied (p=0.404).

Postoperative complications were not associated with age, sex, comorbidity, or any immunodeficiency. Among the surgically treated patients, 7 (2%) patients died from postoperative complications: 6 patients from sepsis and 1 patient from massive hemoptysis. We detected a higher mortality rate depending on the age (7/7 deaths involved patients older than 60 years, OR=2.31; 95% CI, 2.04-2.61; p=0.003) and comorbidity (6/7, OR=10.61; 95% CI, 1.26-89.18; p=0.007).

Medical treatment

A total of 193 (39.3%) patients received medical treatment: 176 (91.2%) combined with surgery, and only 17 (8.8%) patients received anthelmintics treatment only. Regarding the use of anthelmintics, 123 (63.7%) patients received treatment with albendazole alone, and 70 (36.3%) received a combination of albendazole & praziquantel. There were differences in the treatment used; while albendazole was the most common strategy followed at the beginning of the study, the combination of albendazole & praziquantel was the most common treatment strategy at the end of the cohort (p=0.001). With respect to the modes of management, 88

(50.0%) patients received preoperative treatment (mean (±SD): 13.5±20.3 weeks) and 138 (78.4%) patients received postoperative treatment (mean (±SD): 30.9±31.8 weeks). Only 56 (31.8%) patients received both pre- and postoperative medical treatment.

Only 15 (7.8%) patients presented complications secondary to drug treatment (**Figure 2**), which occurred more frequently in patients with albendazole & praziquantel than in patients with albendazole alone (9/70 (12.9%) *vs* 6/123 (4.9%)) [OR=2.87, 95%CI 1.01-8.45, p=0.047]. The most frequently detected complications were digestive intolerance (8) and hypertransaminasemia (6) (**Figure 2**). All cases were resolved after drug discontinuation. These complications were not related to age, sex or comorbidity (p>0.05).

Watch & Wait strategy

A *Watch & Wait* strategy was conducted in 131 (26.7%) patients in the cohort. The main factors associated with *Watch & Wait* included age over 60 years old [117 (89.3%) vs 14 (10.7%); OR 9.76; 95% CI, 5.40-17.65; p<0.001)], any condition causing comorbidity [92 (70.2%) vs 39 (29.8%) (OR=3.75; 95% CI, 2.43-5.76; p<0.001)] and stage 5 of WHO [68 (54.8%) *vs* 56 (45.2%) in other stages; (p<0.001)]. Ninety-nine (75.6%) patients were asymptomatic. Patients who underwent the *Watch & Wait* strategy presented several complications: 19 (14.5%) infections, 10 (7.6%) mechanical, 3 (2.3%) both.

Overall survival & mortality

Of the total cohort, only 247 (50.3%) patients attended follow-up our hospital with two or more revisions, with a mean (±SD) duration of 3.36±3.50 years. The Kaplan-Meier curve of the study period is shown in **Figure 3**, which was associated with age, immunosuppression and comorbidity (p<0.001) and was not associated with gender, clinical diagnosis, complications or recurrences (p>0.05).

Eighty (16.3%) patients died along the study, 14 of them (2.9%) were directly caused by CE disease or other complications (**Table 1**). Other causes of mortality not related to echinococcosis were as follows: cancer (26, 32%), cardiovascular (17, 21%), other non-related infectious diseases (13, 16%) and other non-specified complications. First, we analyzed the overall survival/mortality rate in the cohort (all-cause mortality), 80 *exitus*.

Bivariate analysis showed that the variables significantly ($p<0.05$) associated with higher mortality were age, immunosuppression, comorbidity, number of liver segments and treatment strategy (**Table 4**).

Multivariate logistic regression analysis confirmed that age is a risk factor ($p=0.003$), and the clinical variables that most significantly influenced the overall cohort mortality were the presence of comorbidity [Exp(B)=7.06; 95%CI, 1.56-31.92; $p=0.011$] associated with the *Watch & Wait* strategy [Exp(B)=3.01; 95%CI, 1.01-9.02; $p=0.050$]. Later, we analyzed the clinical variables that influenced mortality in CE disease, 14 *exitus*. *Bivariate analysis* showed that the variables significantly ($p<0.05$) associated with higher mortality by CE were comorbidity, clinical symptoms *vs* asymptomatic-casual finding, *Watch & Wait* strategy and treatment complications. *Multivariate logistic regression analysis* confirmed that the clinical variables that most significantly influenced CE disease mortality were the presence of comorbidity [Exp(B)=10.42; CI 95%, 1.22-88.59; $p=0.032$] associated with surgical treatment complications [Exp(B)=5.85; CI 95%, 1.24-27.52; $p=0.025$].

DISCUSSION

Over decades the clinical management of echinococcosis has evolved without adequate evaluation of efficacy and the current management and treatment of CE is still largely based on expert opinion and moderate to poor quality of evidence[8,11,15,19]. Despite these limitations, standard of treatment in CE today, is based in the use of different surgical techniques with or

without chemotherapy. Nevertheless, there are a high percentage of patients who are not suitable candidates for surgical treatment, and their treatment consists of other types of therapies such as PAIR, anthelmintics or "*Watch & Wait*" strategy.

During two decades, we have attended to patients with CE without having a previously established treatment protocol in our hospital. The aim of this study was to determine the most frequently applied treatment in our cohort, the factors involved in the treatment selection and the complications regarding each type of treatment applied. Thus, we have attended to more than 500 patients with CE in our hospital, with surgical treatment being the main treatment used. We detected that factors such as age, co-morbidity or clinical setting were involved in selecting the type of treatment applied to the same patient and the highest comorbidity were the collective most frequently directed to an alternative treatment based on "*Watch & Wait*" strategy.

Regarding surgical methods, we found that factors such as the cyst location, size and number were involved. Therefore, we detected a higher proportion of surgical interventions in thoracic CE than in liver CE. These differences could be explained because thoracic CE is more frequently symptomatic than other locations. However, a selection bias is also possible due to the fact that the Service of Thoracic Surgery involves a referral of several areas of health of other regions, from which many patients were referred for surgical procedure.

Other characteristics such as large size or a solitary CE were also factors associated with the use of a surgical procedure. In this sense, larger cysts are usually active cyst with a higher growth capacity and, consequently, a higher possibility of complication. Moreover, because of the high failure rate of treatment, multiples cyst in different locations are a classic factor that results in the patient not being recommended for surgical resection.

In our work, we also detected that the anthelmintics used were somewhat associated with surgical treatment. Although there are studies that showed the utility of benzimidazole only

as a treatment for CE patients with response rates ranging from 28.5% to 73%, there was a high relapse rate after the completion of treatment that limited its use. The use of combined benzimidazoles and praziquantel could be an alternative treatment; however, despite the safety[11] of this combination, their clinical use is not still well characterized. Thus, medical treatment for CE is usually limited to decrease the relapse after of surgical treatment.

Another aim of our work was to evaluate the complications associated with different types of treatment used. Between the patient treated with surgical treatment, approximately 20% had surgical complications, with fistula being more frequent in the liver than in other locations, especially when CE was localized in the IV and VIII segments.

The mortality rate was similar to that observed in a multi-center series study (1-2%), which revealed a lesser postoperative morbidity[20].However, other characteristics of the cysts or the patients characteristics were not associated with an increasing risk of complications. We observed a postoperative mortality rate of 2% that was clearly associated with patient age and comorbidity. In this sense, defining the clinical exclusion criteria of surgical patients is important to decrease this mortality rate.

Regarding medical treatment, anthelmintics were typically used as a complementary treatment to surgical procedure. We detected a low risk of complications, with the most frequent being digestive intolerance and hypertransaminasemia; however, both cases were resolved after drug discontinuation.

Finally, another aim of our study was to examine the global and attributable mortality in our cohort. We previously published a study in which we examined the mortality and main causes of mortality in CE patients. In our previous study, we evaluated only CE patients who died in our hospital (1998-2011), and thus, we concluded that complications of CE were one of the main causes of mortality in patients infected by *Echinococcus granulosus*. However, due the methodology used in our previous work, we could not establish other factors

associated with patient mortality. In order to evaluate these factors, in the present study we included patients with CE (1998-2015) who had at least two evaluations in our hospital. Thus, similar to our previous work, we also detected that complications of CE were one of the most important causes of global mortality after cancer and cardiovascular diseases.

Moreover, another important objective in this study was to evaluate the factors associated with mortality in our cohort. Thus, thoracic CE and CE with large-sized or increased numbers of cysts were factors associated with higher mortality. Also, depending on the host, age and comorbidity were also associated with higher mortality. Finally, we also studied if the type of treatment could be involved with mortality. Therefore, *Watch & Wait* strategy was also associated with a higher mortality. The variables that most influence the mortality caused by CE in this cohort were the presence of comorbidity [Exp(B)=10.42; CI 95%, 1.22-88.59; p=0.032] and

complications in the treatment. To our knowledge, there are no other studies that evaluate the factors involved with mortality in patients with CE.

Although our work has some limitations and bias due to the retrospective nature of the study, we believe that this study can contribute to selecting the best treatment for patients with CE. However, future studies involving other multi-center randomized clinical trials could provide us with insight to develop treatments for this neglected disease.

Conclusions

Characteristics of cysts and patients are factors involved in the selection of different treatments for CE patients. Surgical complications were frequent but were accompanied by a low mortality rate. Complications of CE are one of the most common causes of mortality in CE patients, with size, location, and number of cysts and "*Watch & Wait*" treatment strategy being the main factors associated with mortality.

Authors contribution

MBG and JPL conceived the study;

MBG and MAS designed the study protocol

VVT, ALB and ACP carried out the revision of records

MBG, MII, AIG, JQS, MAS carried out the analysis and interpretation of data

ARA, MBG and JPL drafted the manuscript

JLMB, LMB, AM and MFJL critically revised the manuscript for intellectual content

All authors read and approved the final manuscript

MBG and JPL are guarantors of the paper.

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Competing interests

None declared

Ethical approval

Not required

Legends

Figure 1. Temporal evolution of the different strategies during the study period

Figure 2. Complications associated to medical and surgical treatment

Figure 3. Kaplan-Meier Survival Curve

Table 1. Main epidemiological and clinical data in 491 patients included in the study.

Table 2. Surgical techniques performed in the first intervention.

Table 3. Variables *(risk factors)* that influence mortality of the cohort (*Bivariate analysis*).

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Figure 1

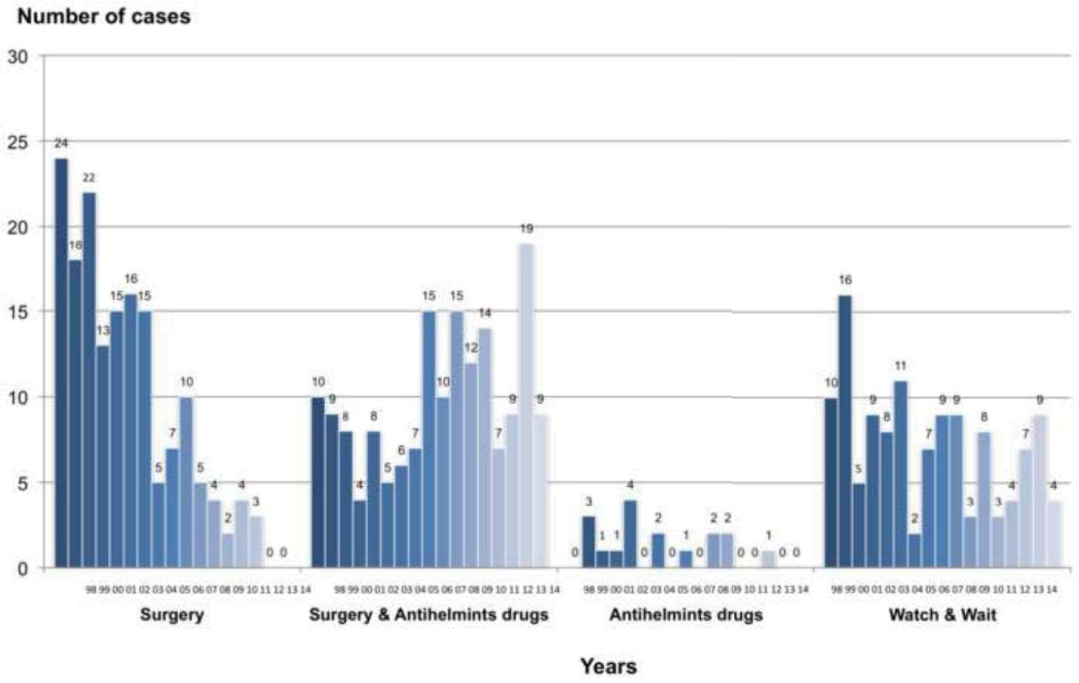
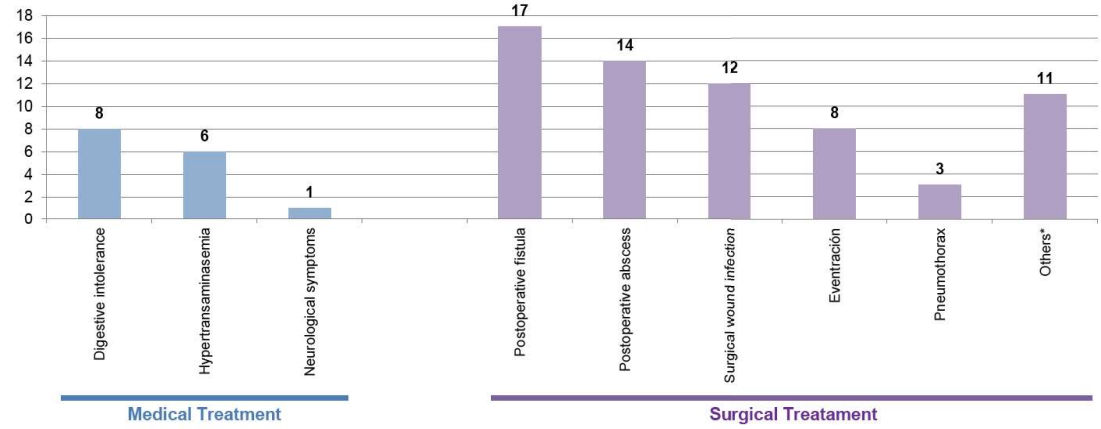


Figure 2: Complications associated to medical and surgical treatment



***Others:** one of each septic shock, intestinal ischemia, hypernatremia, nosocomial pneumonia, acute pulmonary edema, anaemia, hemoperitoneum, hemothorax, splenic bleeding, incisional wound, multiorgan failure.

Figure 3. Kaplan-Meier Survival Curve

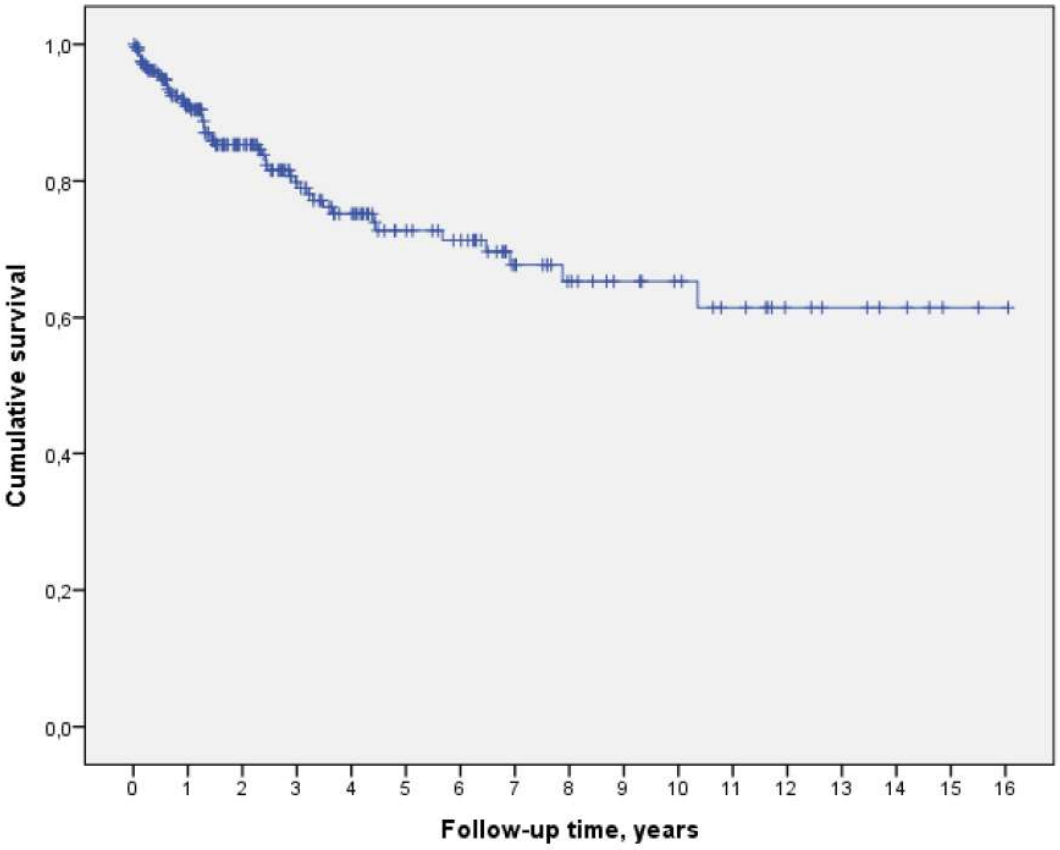


Table 1. Main epidemiological and clinical data in 491 patients included in the study.

	All patients n (%) 491 (100)	Surgery & drugs n (%) 176 (35.8)	Surgery alone n (%) 166 (33.8)	Drugs alone n (%) 17 (3.5)	Wach & Wait n (%) 131 (26.7)	PAIR n (%) 1 (0.2)	p-value
Age							0.000
mean±SD, years	59.5±20.4	50.4±19.7	55.7±17.2	71.2±20.8	75.1±14.7	79.0	
<59 years	208 (42.4)	107 (60.8)	83 (50.0)	4 (23.5)	14 (10.7)	0 (0.0)	
Sex (male)	288 (58.7)	116 (65.9)	93 (56.0)	9 (52.9)	69 (52.7)	1 (100.0)	0.141
Comorbidity	231 (47.0)	56 (31.8)	71 (42.8)	11 (64.7)	92 (70.2)	1 (100.0)	0.000
Number of diseases							0.007
1 disease	136 (58.9)	33 (58.9)	53 (74.6)	4 (36.4)	46 (50.0)	0 (0.0)	
≥ 2 diseases	95 (41.1)	23 (41.1)	18 (25.4)	7 (63.6)	46 (50.0)	1 100.0)	
mean ± SD	1.6±1.1	1.6±0.9	1.3±0.7	1.9±0.8	1.9±1.3	3.0	
Immunosuppression	99 (20.2)	18 (10.2)	28 (16.9)	5 (29.4)	48 (36.6)	0 (0.0)	0.000
Diagnostic							0.000
Asyntomatic	293 (59.7)	93 (52.8)	93 (56.0)	7 (41.2)	99 (75.6)	1 (100.0)	
Mechanical	96 (19.6)	35 (19.9)	47 (28.3)	4 (23.5)	10 (7.6)	0 (0.0)	
Infectious	58 (11.8)	20 (11.4)	14 (8.4)	5 (29.4)	19 (14.5)	0 (0.0)	
Alergic	15 (3.1)	12 (6.8)	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	
Mechanical & infectious	27 (5.5)	14 (8.0)	9 (5.4)	1 (5.9)	3 (2.3)	0 (0.0)	
Mechanical &alergic	2 (0.4)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Eosinophilia >450/µL	111 (22.6)	56 (33.3)	40 (26.8)	2 (12.5)	12 (9.2)	1 (100.0)	0.000
EIA *E. granulosus* (>1/80)	162 (33.0)	96 (54.5)	48 (28.9)	6 (35.3)	12 (9.2)	0 (0.0)	0.000
Number of cyts							0.000
1	337 (68.6)	100 (56.8)	127 (76.5)	7 (41.2)	102 (78.5)	1 (100.0)	
≥2	153 (31.2)	76 (43.2)	39 (23.5)	10 (58.8)	28 (21.5)	0 (0.0)	
Size of the largest cyst							0.001
<6.9 cm	262 (53.5)	80 (45.5)	82 (49.4)	12 (70.6)	88 (67.7)	0 (0.0)	
≥7 cm	228 (46.5)	96 (54.5)	84 (50.6)	5 (29.4)	42 (32.3)	1 (100.0)	
mean±SD, cm	7.3±4.2	8.0±4.4	7.8±4.4	6.0±3.6	6.1±3.5	7.0	
Cyst location							0.000
Liver	410 (83.5)	150 (85.2)	124 (74.7)	12 (70.6)	124 (95.4)	0 (0.0)	
Lung	69 (14.1)	25 (14.2)	37 (22.3)	4 (23.5)	3 (2.3)	0 (0.0)	
Other/diseminated	61 (12.4)	24 (13.6)	23 (13.8)	3 (17.6)	10 (7.7)	1 (100.0)	
WHO stages							0.000
1	18 (4.4)	6 (4.0)	8 (6.5)	2 (16.7)	2 (1.6)	-	
2	105 (25.6)	48 (32.0)	35 (28.2)	4 (33.3)	18 (14.5)	-	
3	58 (14.1)	30 (20.0)	13 (10.5)	1 (8.3)	14 (11.3)	-	
4	72 (17.6)	29 (19.3)	21 (16.9)	0 (0.0)	22 (17.7)	-	
5	157 (30.3)	37 (24.7)	47 (37.9)	5 (41.7)	68 (54.8)	-	
Recurrences	51 (10.4)	23 (13.1)	13 (7.8)	3 (17.6)	11 (8.4)	1 (100.0)	0.013
Cohort mortality	80 (16.3)	6 (3.4)	21 (12.7)	5 (29.4)	48 (36.6)	0 (0.0)	0.000
CE disease mortality	14 (2.9)	2 (1.1)	5 (3.0)	0 (0.0)	7 (5.3)	0 (0.0)	0.045
Mean hospital stay (days)	12.8±12.6	11.7±10.1	14.3±16.9	12.0±5.6	12.5±9.8	1.0	0.290
Follow-up	247 (50.3)	141 (80.1)	76 (45.8)	12 (70.6)	18 (13.7)	---	0.000
Follow-up time (mean±SD, years)	3.36±3.50	3.49±3.30	3.29±3.87	2.67±3.67	3.20±3.43	---	0.870

Table 2. Surgical techniques performed in the first intervention.

	Patients n (%) 342 (100.0)
Partial pericystectomy+ cholecystectomy	147 (43.0)
Combined techniques	61 (17.9)
Total pericystectomy+ cholecystectomy	54 (15.8)
Segmentectomy	40 (11.8)
Cystectomy	27 (7.9)
Lobectomia	8 (2.4)
Splenectomy	4 (0.9)
Nephrectomy	1 (0.3)

Table 3. Variables *(risk factors)* that influence mortality of the cohort (*Bivariate analysis*).

Factors	All-cause mortality (N=80)			CE disease mortality (N=14)		
	n (%)	**OR (CI 95%)**	**p-value***	**n (%)**	**OR (CI 95%)**	**p-value***
Host factors						
Elderly (≥60) *vs* young	71(88.8) *vs* 9 (11.3)	7.4 (3.6-15.2)	0.000*	14 (100.0) *vs* 0	-	0.001*
Man *vs* woman	50 (62.5) *vs* 30 (37.5)	-	0,445	7 (50.0) *vs* 7 (50.0)	-	0.505
Rural habitat *vs* urban habitat	52 (65.0) *vs* 28 (35.0)	-	0.322	9 (64.3) *vs* 5 (35.7)	-	0.658
Contacting animals *vs* non-contact	20 (25.0) *vs* 60 (75.0)	-	0.785	4 (28.6) *vs* 10 (71.4)	-	0.828
Immunosuppression, yes *vs* no	31 (38.8) *vs* 49 (61.3)	3.1 (1.8-5.3)	0.000*	3 (21.4) *vs* 11 (78.6)	-	0.905
Comorbidity, yes *vs* no	61 (76.3) *vs* 19 (23.8)	4.5 (2.6-7.8)	0.000*	12 (85.7) *vs* 2 (14.3)	7.0 (1.5-31.9)	0.003*
Clinical setting						
Relapse *vs* first CE	5 (6.3) *vs* 75 (93.8)	-	0.185	1 (7.1) *vs* 13 (92.9)	-	0.686
Clinical symptoms *vs* asymptomatic-casual finding	28 (35.0) *vs* 52 (65.0)	-	0.289	12 (85.7) *vs* 2 (14.3)	9.3 (2.0-42.4)	0.000*
Cyst´s characteristics						
Single *vs* multiple cyst	59(73.8) *vs* 21 (26.3)	-	0.294	8 (57.1) *vs* 6 (42.9)	-	0.341
Pulmonary/lung localization, yes *vs* no	7 (8.8) *vs* 73 (91.2)	-	0.134	3 (21.4) *vs* 11 (78.6)	-	0.423
Hepatic/liver localization, yes *vs* no	72 (90.0) *vs* 8 (10.0)	-	0.094	13 (92.9) *vs* 1 (7.1)	-	0.346
1 segment liver *vs* ≥2 segments	51 (70.8) *vs* 21 (29.2)	1.7 (1,1-3.0);	0.048*	7 (53.8) *vs* 6 (46.2)	-	0.619
Big (>7cm) *vs* small size	31 (38.8) *vs* 49 (61.2)	-	0.127	7 (50.0) *vs* 7 (50.0)	-	0.792
Treatment strategy						
Wait and see *vs* other strategies	48 (60.0) *vs* 32 (40.0)	5.9 (3.5-9.8)	0.000*	7 (50.0) *vs* 7 (50.0)	2.8 (1.1-8.2)	0.045*
Treatment complications, yes *vs* no	7 (21.9) *vs* 25 (78.1)		0.340	4 (57.1) *vs* 3 (42.9)	5.9 (1.3-27.5)	0.009*

*Statistical significance level of 5% (p <0.05).