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Polycystic liver in the adult (PLA) in Spain: Analysis of a structured survey analysing the experience and attitude of gastroenterologists in Spain

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ABSTRACT

Background: Polycystic liver in the adult (PLA) is a rare disease characterized by chronic liver enlargement.

Objective: To analyse gastroenterologists' involvement in, experience with, and attitude toward diagnosing, monitoring, and treating patients with PLA in Spain.

Methods: Each of seven study coordinators contacted 15 specialists in their geographic area about participating in the study via an online structured survey.

Results: Of the 105 clinics contacted, 88 completed the questionnaire, with a mean of 3 patients being followed per practice, although 6 clinics were following more than 20 patients with PLA. Patients were being followed mainly by the Department of Hepatology (81 %) and/or the Department of Gastroenterology (33 %). The majority of patients were diagnosed (98 %) and monitored (97 %) using liver ultrasound. When diagnosed, 76 % of patients were under 50 years of age, females predominating. The primary treatment objective for the patients was symptomatic management. Pharmacotherapy was prescribed by 28 % of physicians: Somatostatin analogues, primarily, followed by mTOR inhibitors. One-third of the clinics indicated that they had patients who had undergone liver transplant and/or surgery.

Conclusions: Ultrasound is the diagnosing and monitoring method of choice. Among the clinics using pharmacotherapy for symptomatic management, somatostatin analogues were the drugs of choice. These clinics' infrequent use of invasive procedures suggests that they perceive the various invasive techniques as not very effective.

Key words: Multiple hepatic cysts. Polycystic kidney disease. Polycystic liver disease. Somatostatin analogues. mTOR inhibitors. Liver transplant. Fenestration via laparotomy or laparoscopy. Autosomal-dominant polycistic liver-disease (PCLD). Autosomal-dominant polycistic kidney disease (PCKD)

INTRODUCTION

Multiple hepatic cysts in the adult (MHCA) is an autosomal-dominant hereditary disease characterized by the presence of multiple cystic lesions of biliary origin over more than 50 % of the liver parenchyma, ranging from large masses of 20-30 cm to small microscopic nodules (1,2). It is an uncommon disease with an estimated incidence of less than 0.01 % (3) and a prevalence of 0.05 %-0.53 %, although the prevalence of the mutations affects 1:600 (4). The liver cysts often present for the first time in the fourth decade of life; however, the natural history of the disease suggests a continuous growth, for the number and size of the cysts steadily increases with age (5). On the other hand, there is an autosomal-recessive variant, ARPKD (autosomal-recessive polycystic kidney disease), characterized by non-obstructive fusiform dilatations of the renal collecting tubules and malformations of the biliary tract, with bile duct ectasia and periportal fibrosis.

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PLA is a disease common to two autosomal-dominant hereditary disorders. It is associated primarily with polycystic kidney disease, which is known as autosomal-dominant polycystic kidney disease (PCKD) (2,6). It may also present as an isolated condition not associated with PCKD, a disease known as autosomal-dominant polycystic liver disease (PCLD). PLA may also be associated with multiple cysts in other organs, such as the pancreas or lung, but in a much lower percentage.

Although various articles have been published on clinical cases of patients and families with PLA in Spain (7-20), the epidemiology has not been well defined, nor are there well-developed protocols for managing patients with PLA in our country. The objective of this study, backed by the *Sociedad Española de Patología Digestiva*, was to analyse gastroenterologists' involvement in and experience with diagnosing, monitoring, and treating patients with PLA in Spain, with the aim of defining how these patients are managed in Spain and determining whether this could be improved and/or a consensus could be reached.

PATIENTS AND METHODS

Information on the attitude and experience of gastroenterologists in Spain with regard to managing multiple hepatic cysts was obtained via a structured survey that took approximately 15 minutes to complete *online*. The 49-question survey was divided into 6 sections with several questions in each section. The section on *incidence, prevalence, and patient referrals* consisted of 12 questions about patients with PLA treated in the surveyee's practice to estimate the number of patients and how the different specialists managed them. The *patient profiles* section consisted of 10 questions designed to elicit further detail on patients with PLA in Spain; these questions asked for characterization of the PLA and its associated symptomatology. The section on *surgical treatment of polycystic liver*, with its 4 questions, asked about the surveyee's experience with different surgical techniques in the treatment of PLA. The *pharmacotherapy in polycystic liver cysts* section had 7 questions for describing the surveyee's familiarity with the available pharmacotherapies, including new therapies. The last two sections, *sources of information* and *classification information*, with 5 and 11 questions, respectively, were designed to categorize the surveyees. The survey was conducted by 7 coordinators, each of whom contacted 15 physicians in their geographic area. The survey itself is included as an Annex to this article.

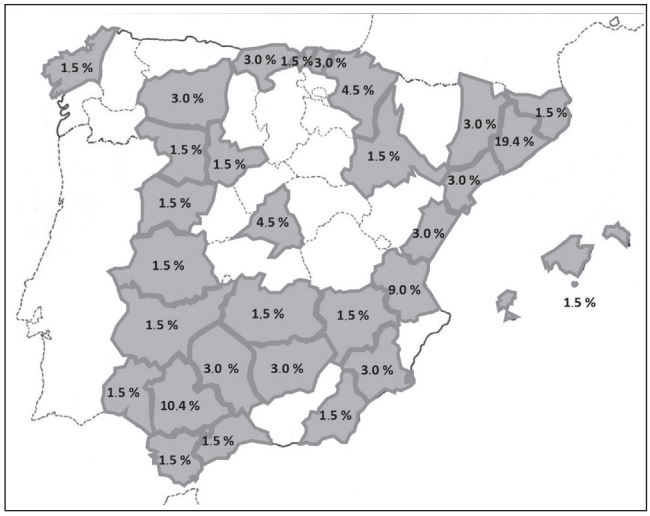

Fig. 1. Map of Spain highlighting the provinces of the 15 Autonomous Communities that participated in the survey and the percentage of participation in each province.

RESULTS

Survey

Almost all of the 105 clinics contacted (104; 99 %) agreed to participate, and 88 of them (85 %) completed the survey. Half of the surveyees identified themselves as hepatologists (45; 51 %); the rest were gastroenterologists (34; 39 %) and internists, surgeons, or specialists in other areas (9; 10 %). Approximately half of the surveyees had been treating liver diseases for more than 15 years, and 31 % of them had more than 20 years in this practice. Study participants represented most of the Autonomous Communities, the strongest participation being physicians from the province of Barcelona, followed by the provinces of Sevilla and Valencia (Fig. 1).

Demographics

Of the 88 clinics surveyed, 72 were following patients with PLA in their practice. A median of 3 patients per practice were being followed, although 6 of the 88 clinics were following more than 20 patients with PLA. Of the specialists surveyed, 28 % saw 1 new patient per year; 16 % saw 2 new patients per year; and 15 % saw more than 2 new patients per year. The percentage of patients with PCLD was 44 % compared to 56 % with PCKD. PLA was usually diagnosed prior to 50 years of age, two-thirds (65 %) of patients being female, with no difference in age at diagnosis between patients with PCLD and patients with PCKD. Few patients had an immediate family member with a clinical history of PLA. The most common phenotype was multiple small cysts. Among the hepatologists, 18 % reported that, in the last 10 years, fewer than 5 patients had died from the disease or PLA-related complications. The remaining 82 % reported no PLA-related deaths.

Table I. The different hospital units following patients with PCLD and PCKD

Department	*Following*
Patients with PCLD	
Hepatology	81 %
Gastroenterology	33 %
Internal Medicine	8 %
Surgery	6 %
Patients with PCKD	
Hepatology and Nephrology	41 %
Gastroenterology and Nephrology	16 %
Nephrology only	23 %
Nephrology with other services (Internal Medicine, Urology, Surgery)	23 %

Table II. Most common symptoms and complications in patients with PLA

Symptom or complication	*Frequency*
Back pain, abdominal distension and discomfort	73 %
Bleeding, infection, biliary obstruction or cyst rupture	26 %
Hypertension, dyspnoea	11 %
Patient asymptomatic	5 %
Malnutrition	2 %
Portal hypertension	2 %
Ascites	2 %
Dyspepsia	2 %

Patient flow

Patients with PLA usually came to the hepatologist, already diagnosed (73 % of cases), as referrals from other clinical departments -primarily from nephrology (35 %), primary care centres (33 %), and the Department of Gastroenterology (17 %). In 75 % of cases, patients who were diagnosed with PLA by the hepatologist were not referred to any other specialist for disease management. The majority of patients diagnosed with PCLD also were followed clinically by the hepatology unit (81 %) and/or gastroenterology unit (33 %). It was less clear how patients with PCKD are followed clinically, but in 28 % of cases, they were followed by both the nephrology and hepatology services. It is also worth mentioning that 23 % of the patients with PCKD were being seen only by the nephrology service (Table I).

Symptoms

Back pain, abdominal distension and discomfort constituted the most common symptomatology (73 %), followed by complications such as bleeding, infections, biliary obstructions, and cyst rupture (26 % of cases). Most of the clinics (82.3 %) had not experienced any of their patients dying of PLA-related complications (Table II).

Diagnosis and monitoring techniques

The technique of choice for diagnosing and monitoring patients with PLA was liver ultrasound, used for diagnosis in 98 % of cases and, for monitoring, in 97 %. Other techniques included computerized tomography (CT), used for diagnosing in 89 % and, for monitoring, in 49 % and, less commonly, magnetic resonance imaging (MRI), used for diagnosing in 58 % and, for monitoring, in 30 %.

Treatment

Overall, the primary treatment objective for patients with PLA was symptomatic management (78 %), followed by improvement in quality of life (12 %), and hepatic volume reduction (6.8 %) and stabilization (3.4 %).

Pharmacotherapy

As with surgical treatment, one of the primary objectives of pharmacotherapy is symptomatic management (Table III). In the last year, 28 % of the clinics had used pharmacotherapy, the most common therapy being somatostatin analogues, followed by mammalian target of rapamycin (mTOR) inhibitors. Although some clinics had not prescribed any drugs, they still recognized that treatment with octreotide, lanreotide, everolimus, and sirolimus could be of value in the management of patients with

Table III. Primary objectives of pharmacotherapy and drugs administered in the last year to patients with MHCA

Pharmacotherapy objectives	*Frequency*
Symptomatic management	88 %
Quality of life	49 %
Stabilization of liver volume	32 %
Reduction of liver volume	19 %
Others	12 %
Pharmacotherapy	
Octreotide	22 %
Lanreotide	13 %
Everolimus	7 %
Sirolimus	6 %
Tolvaptan	4 %
Others	4 %
None	72 %

PCLD. Of the 18 % of clinics that had no direct experience with pharmacotherapy, 40 % reported that they did not believe it was appropriate to prescribe drug treatment for their patients with PLA because of the significant number of adverse effects, and 30 % stated, as the reason for not recommending drug treatment, that their patients were currently asymptomatic.

Surgical treatment

At 40 % of the clinics reporting, their patients with PLA had undergone an orthotopic liver transplant (OLT) within the last 10 years. End-stage liver disease was the primary reason for these patients undergoing OLT in the context of PLA. At 14.8 % of the clinics, one patient from their practice had undergone a transplant, while at 4.9 % of the clinics it was two patients and, at 16.4 %, it was more than two. One-third (33.8 %) of the clinics indicated that they had patients under their care who had been treated surgically; 13.1 % of the clinics had one patient, 14.8 % had two patients, and 4.9 % had more than two patients who had undergone surgery. Laparoscopic fenestration was the invasive technique most commonly reported (75 %), this being perceived as the technique with the best risk/benefit ratio (Table IV).

DISCUSSION

In Spain, PLA is perceived as a rare disease, with the majority of hepatologists and gastroenterologists treating fewer than 5 patients with this pathology. This fact lends great importance to the survey conducted, for it reflects the reality and daily clinical practice of physicians in Spain. It is important to bear in mind, however, that these results are an approximation –not derived from a national registry of patients– and that the majority of surveyees were from the provinces of Barcelona, Sevilla, and Valencia.

Females have a greater predisposition than males to developing massive PLA (> 15 cysts) and to having larger cysts. There is a hormonal component to the disease being more prevalent in females: pregnancy and the number of pregnancies correlates with a more severe phenotype (6), and the use of oestrogen therapies in postmenopausal women is associated with an increase in liver volume (21). PLA is a disease common to two autosomal-dominant hereditary disorders: PCKD and PCLD. PCKD has its origin in mutations of two genes: *PKD1* (85 % of cases) and *PKD2* (15 % of cases) (22), which code for two proteins called polycystine 1 and 2, respectively. These genes are located on chromosomes 16 and 4 (23). In PCKD, the most common extrarenal manifestation is a polycystic liver. The prevalence of PLA in patients with PCKD is 58 % in patients 15-24 years old, 85 % in patients 25-34 years old, and 94 % in patients 35-46 years old (24). The mutations associated with PCLD are unknown in 80 % of patients, and in the remaining 20 %, they have their origin in the mutation of two other genes: *PRKSCH* and *SEC63*. The first gene codes for a protein called hepatocystine, which is expressed in the endoplasmic reticulum (25-27). In our study, there were similar percentages of patients with PCLD and patients with PCKD. In Spain, the specialist who treats most of the patients with PCLD is the hepatologist, whereas patients with PCKD are treated by various services –nephrology and hepatology, in particular– who work together on the majority of cases. Most patients come to the hepatologist already diagnosed, as referrals from the nephrologist or the patient's primary care physician. The diagnosis is made using imaging studies, such as ultrasound, CT (which best defines the extent of liver disease and the involvement of adjacent organs), and MRI –ultrasound being the technique of choice for diagnosis and monitoring.

The majority of patients are asymptomatic with normal liver function (both its synthesis and its excretion functions); thus, the diagnosis is usually a chance finding. Generally, the cysts cause no symptoms unless they become large or are complicated by bleeding, infection, rupture, or malignity (28). When hepatic cysts do become symptomatic, the clinical picture is characterized by painful hepatomegaly, abdominal distension, a feeling of fullness, or lumbar pain (13). In our study, the predominant symptoms (73 %) were those stemming from the cysts compressing

Table IV. Frequency of different surgical techniques in patients with PLA and physicians' experience with these techniques

	Laparoscopic fenestration	*Sclerosing of dominant cyst*	*Partial liver resection*	*Percutaneous aspiration of dominant cyst*	*Orthotopic liver transplant*
Frequency	75 %	60 %	50 %	35 %	40 %
Good benefit / morbidity ratio	40 %	36 %	38 %	0 %	NE
Poor benefit / morbidity ratio	20 %	9 %	13 %	0 %	NE
Very transitory effect	20 %	27 %	13 %	100 %	NE
No experience in the technique	20 %	27 %	38 %	0 %	NE

NE: Not evaluated.

adjacent hepatic parenchyma and neighbouring structures: back pain and abdominal distension and discomfort.

The primary objective of pharmacotherapy was symptomatic management, although the total number of patients receiving this was rather low. Only about one-third of the physicians surveyed for this study recommended pharmacotherapy for their patients, somatostatin analogues being the drug of choice. In patients with PCKD and PCLD, it has been shown that the renal and hepatic cysts grow in response to cAMP and that reducing cAMP levels limits the progression of nephropathy and hepatopathy, which suggests that inhibiting these mechanisms could be an effective therapy. The somatostatin analogues (such as octreotide and lanreotide) reduce intracellular cAMP and could limit fluid accumulation in hepatic cysts (29,30). In a recent study with 54 symptomatic patients with PCLD and PCKD, 6 months of lanreotide therapy resulted in a significant reduction in liver volume of 2.9 %, compared to a 1.6 % increase in patients who received a placebo (31). Despite this evidence, many of the physicians surveyed do not prescribe these drugs because of the side effects. On the other hand, the interaction between mTOR and the secretion of VEGF mediated by HIF-1 suggests that the use of mTOR inhibitors could be effective in the treatment of PCKD (32). Furthermore, the hepatic cyst epithelium expresses high levels of mTOR, which suggests that mTOR inhibitors could be effective in limiting the growth of hepatic cysts (33). Studies of multiple renal cysts conducted with numerous experimental models have shown that rapamycin and everolimus (mTOR inhibitors) slow cyst growth and protect renal function (33,34). A recent meta-analysis of the efficacy and safety of mTOR inhibitor therapy in patients with PCKD concluded that it may decrease renal volume with no great improvement in renal function (35); in patients with PLA, however, there was no effect on liver volume. In this survey, mTOR inhibitors were second to somatostatin analogues, in terms of the types of drugs recognized and administered by the surveyees.

As for surgical treatment of patients with PLA, the various invasive surgical techniques were perceived as not very effective, mainly because the benefits are transitory. Even so, one-third of the clinics surveyed indicated that their patients had undergone liver transplant and/or surgical treatment. In PLA, the objective of treatment is to reduce the size of the cysts without compromising liver function and to keep the patient asymptomatic for as long as possible (3). Treatment of these patients consists of reducing cyst volume using a percutaneous approach (aspiration and alcoholisation) or a surgical approach (fenestration via laparotomy or laparoscopy and/or hepatic resection) (36,37). Generally speaking, an attempt is made to reserve surgery for those cases where medical treatment has not been effective, although it appears that surgical intervention is the treatment of choice in our country. Partial hepatic resection with cyst fenestration is somewhat successful in certain patients with massive symptomatic cysts (30). Even though several research projects have recently been conducted, the results so far do not indicate whether laparotomy or laparoscopy is the best choice for fenestration (3). These treatments are aggressive, expensive, and only partially effective, however, because the symptoms usually recur due to the growth of new cysts or of the cysts already treated. Sometimes, in the most severe cases, a liver transplant or combined liver and kidney transplant must be done (36). The survival rate –for both transplanted organ and patient– is very high in patients with PCLD who have undergone liver transplant (38).

In conclusion –and acknowledging the possible limitations of the survey– PLA is an uncommon pathology in our country, which means there is little clinical experience. Moreover, because of its association with other organs, management of the disease would be shared by various specialists, with the hepatologist playing the leading role. The objective to be achieved with these patients is monitoring cyst size (ultrasound being the technique of choice) and keeping them asymptomatic. To do this, various pharmacotherapies, such as the somatostatin analogues and mTOR inhibitors, are used, while surgery is an option for patients who are refractory to medical treatment.

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ANNEX. COPY OF THE QUESTIONNAIRE AVAILABLE ONLINE FOR CONDUCTING THE STUDY

INTERVIEW AND PRESENTATION INFORMATION
Questionnaire

INCIDENCE, PREVALENCE, AND REFERRAL OF PATIENTS

P.1. Let's talk about Prevalence. How many patients with multiple hepatic cysts are you following in your practice?

I have no experience with this pathology → **INTERVIEW OVER**
Patients with multiple hepatic cysts you are following in your practice **patients**

P.2. Of the patients with multiple hepatic cysts you are following in your practice:

How many have pure polycystic liver disease? patients
How many have polycystic liver-kidney disease? patients

P.3. And from the standpoint of Incidence, how many new patients with multiple hepatic cysts do you see every year, on average?

I do not diagnose new patients → **GO TO P.9.**
Patients with multiple hepatic cysts diagnosed per year patients

P.4. Of the new patients with multiple hepatic cysts you see in your practice every year:

How many have pure polycystic liver disease? patients
How many have polycystic liver-kidney disease? patients

P.5. Of these new patients you see who have multiple hepatic cysts (P.3.), could you indicate how many patients fit each of the following statements?

1. They come by referral, already diagnosed with multiple hepatic cysts patients
2. They come by referral, not diagnosed, and I diagnose them patients
They do not come by referral, and I diagnose them patients
Other (specify) _____ patients

(IF P.5. "Referred" > 0 DO P.6.)

P.6. Thinking of the patients who come to you by referral (per responses P.5.1. P.5.2.) (diagnosed or not), could you tell me where they are referred from?

From family doctor / general medicine practitioner patients
From a surgery practitioner patients
From a nephrology practitioner patients
From a gastroenterology practitioner patients
From another hepatologist's practitioner patients
Other (specify) _____ patients

P.7. Of these new patients diagnosed in one year (P.3.), how many do you refer to another specialist?

Number of patients with multiple hepatic cysts referred patients
No patients patients

(ONLY IF P.7. > 0 %)

P.8. And of these patients you referred, could you tell me to whom you referred them?

To another hepatologist patients referred
To a nephrologist patients referred
To a gastroenterologist patients referred
Other (specify) _____ patients referred

P.9. What service follows the patients with PURE multiple hepatic cysts at your hospital? **(MULTI-RESPONSE)**

I don't know	1
Gastroenterology	2
Surgery	3
Hepatology	4
Internal Medicine	5
Other (specify) _____	98

P.10 At your hospital, what service follows the patients with multiple RENAL cysts who also have multiple hepatic cysts? **(MULTI-RESPONSE)**

I don't know	1
Nephrology only	2
When there is liver involvement, Nephrology and (STATE RESPONSE P.6.) jointly	3
When there is liver involvement, Nephrology and (STATE RESPONSE P.6.) but separately	4
Other (specify) _____	98

P.11. What methods do you use to diagnose multiple hepatic cysts?

_____	1
_____	2
_____	3
_____	4
Other (specify) _____	98

P.12. What imaging techniques do you use for monitoring patients with multiple hepatic cysts? **(MULTI-RESPONSE)**

Ultrasound	1
CT	1
MRI	1
Other (specify) _____	98

PATIENT PROFILES

P.13. Thinking of the patients with multiple renal cysts and liver involvement you are currently treating, could you tell me their mean age at diagnosis?

Under 30 years	1
30-40 years	2
40-50 years	3
50-60 years	4
Over 60 years	5

P.14. What would you say was the mean age of these patients with PURE multiple hepatic cysts when they were diagnosed by the clinician?

Under 30 years	1
30-40 years	2
40-50 years	3
50-60 years	4
Over 60 years	5

P.15. And could you tell me how many patients of each gender you are treating?

Male	___	patients
Female	___	patients

P.16. What percentage of patients has an immediate family member with a history of multiple cysts?

Less than 25 % [1]
Approximately 50 % [2]
Approximately 75 % [3]
100 % [4]

P.17. What percentage of patients with multiple hepatic cysts develops fibrosis?

Less than 25 % [1]
Approximately 50 % [2]
Approximately 75 % [3]
100 % [4]

P.18. What percentage of patients shows multiple small cysts in the liver?

Less than 25 % [1]
Approximately 50 % [2]
Approximately 75 % [3]
100 % [4]

P.19. What percentage of patients shows few but large cysts in the liver?

Less than 25 % [1]
Approximately 50 % [2]
Approximately 75 % [3]
100 % [4]

P.20. Have you identified potentially prognostic factors in the patients you are treating who have multiple hepatic cysts? **(UP TO TWO RESPONSES POSSIBLE)**

No, none [1]
Oestrogens: An improvement / stabilization of the disease occurs after menopause [2]
Renal function: In patients with multiple renal cysts, the less renal function is affected, the greater the hepatic manifestation [3]
Renal function: In patients with multiple renal cysts, the more renal function is affected, the greater the hepatic manifestation, also [4]
Others (specify) _____ [98]

P.21. What are the most common symptoms and complications seen in patients with multiple hepatic cysts? **(MULTI-RESPONSE)**

Hypertension / dyspnoea [1]
Back pain / abdominal distension and discomfort [2]
Bleeding, infection, cyst rupture, or biliary obstruction [3]
Bone involvement (fractures, etc.) [4]
Others (specify) _____ [98]

P.22. How many patients have died in the last 10 years from complications of multiple hepatic cysts?

None [1]
Fewer than 5 patients [2]
5-10 patients [3]
More than 10 patients [4]
Other (specify) _____ [5]

MULTIPLE HEPATIC CYSTS SURGICAL TREATMENT

P.23. How many patients with multiple hepatic cysts have undergone transplant (liver) on your service or unit in the last 10 years?

Patients with surgical treatment ☐ ☐ ☐

P.24. How many of the patients with multiple hepatic cysts you are currently treating have undergone a surgical treatment? **CHECK THAT NUMBER EQUAL OR LESS THAN P.1.**
Patients with surgical treatment ☐☐☐

P.25. Which of the following surgical techniques have you ordered on your patients? **(MULTI-RESPONSE)**

A. I have never ordered surgery	1
B. Percutaneous aspiration of dominant cyst	2
C. Sclerosing of dominant cyst	3
D. Laparoscopic fenestration	4
E. Partial liver resection	5
F. Liver transplant	6

P.26. Of the surgical techniques selected in the previous question, what is your experience with each of the surgical techniques used? **(ASK FOR EACH OF THE OPTIONS MENTIONED IN P.25.)**

Surgical techniques you have ordered on your patients	B	C	D	E	F
Good benefit / morbidity ratio	1	1	1	1	1
Poor benefit / morbidity ratio	2	2	2	2	2
Very transitory	3	3	3	3	3
Others (specify) _____	98	98	98	98	98

MULTIPLE HEPATIC CYSTS PHARMACOTHERAPY
Now we'll talk about pharmacotherapy for patients with multiple hepatic cysts.

P.27. Thinking about pharmacotherapy for multiple hepatic cysts, what are your primary treatment objectives for these patients?

	1st	2nd
Symptomatic management	1	1
Improvement in quality of life	2	2
Reduction of liver volume	3	3
Stabilization of liver volume	4	4
Other (specify) _____	98	98

P.28. Could you tell me which drugs you're familiar with (even if you've never prescribed them) for the treatment of *multiple hepatic cysts?* **(SPONT.)**

P.29. Which of the therapies listed below are you familiar with? **(SHOW OPTIONS)**

P.30. Which have you used in the last year? **(SHOW OPTIONS)**

	P.28. Spontaneous	P.29. Suggested	P.30. Last year
Everolimus / Afinitor®	1	1	1
Lanreotide / Somatuline Autogel®	2	2	2
Octreotide / Sandostatin Lar®	5	5	5
Sirolimus / Rapamure®	5	5	5
Tolvaptan / Smsca®	5	5	5
Other (specify)_____	98	98	98

P.31. All in all, how many patients with multiple hepatic cysts do you have on pharmacotherapy currently and with which drug?
Patients on pharmacotherapy ☐☐☐
None on pharmacotherapy 1 → **SKIP TO P.33.**

P.32. Of the patients you have on pharmacotherapy, how many are you treating with each of the following drugs? **(ⓘ SHOW OPTIONS) (THE PRODUCTS MENTIONED IN RESPONSE P.30. WILL APPEAR.)**

	P.32. No. patients
Everolimus / Afinitor®	☐
Lanreotide / Somatuline Autogel®	☐
Octreotide / Sandostatin Lar®	☐
Sirolimus / Rapamure®	☐
Tolvaptan / Smsca®	☐
Other (specify)_____	☐

(DO P.33. IF YOU HAVE NO PATIENTS ON PHARMACOTHERAPY PER P.31.)

P.33. Given that you have no pharmacological experience with these patients, and considering the articles published **(ENABLE LINK TO PUBMED WITH THE APPROPRIATE SEARCH)** on these drugs in recent years, are you considering the option of using this type of treatment?

Yes 1
No. Briefly explain the reason for this decision: _____ 2

SOURCES OF INFORMATION

P.34. What sources do you use to get information about the treatment of multiple hepatic cysts?

Experience of other hepatologists whom I know personally 1
Experience of other nephrologists whom I know personally 2
Experience of other gastroenterologists whom I know personally 3
Experience of other hepatologists who are known experts in the treatment of multiple cysts 4
Experience of other nephrologists who are known experts in the treatment of multiple cysts 5
Experience of other gastroenterologists who are known experts in the treatment of multiple cysts 6
Asociación Española para el Estudio del hígado [Spanish Association for Liver Studies] 7
Others (specify) _____ 98

P.35. Would you say that the survey has helped you to be more aware of the pathology?

Very much more aware 1
Much more aware 2
Somewhat more aware 3
It has not changed my perception of the pathology 4 → **SKIP TO P.37.**

P.36. In what sense are you now more aware of the pathology?

_____ ☐

P.37. To what extent would you say the survey has made you change your perspective on the pathology?

Very much 1
A lot 2
Somewhat 3
Not much 4 → **SKIP TO K.1.**
Not at all 5 → **SKIP TO K.1.**

P.38. In what sense have you changed your perspective on the pathology?

_____ ☐

CLASSIFICATION INFORMATION

K.1. Are you a member of some medical association?

Yes 1
No 2 → **SKIP TO K.3.**

K.2. Of which medical associations are you a member? **(MULTI-RESPONSE)**

Asociación Española para el Estudio del hígado [Spanish Association for Liver Studies] 1
Sociedad Española de Patología Digestiva 2
Other 1 (specify) _____ 1
Other 2 (specify) _____ 2
Other 3 (specify) _____ 3
Other 4 (specify) _____ 4
Other 5 (specify) _____ 5

K.3. How often are you accustomed to reading medical specialty journals? (you may answer in times per week or per month or per year, whichever is easier for you)

Times per week ☐
Times per month ☐
Times per year ☐

K.4. Which medical specialty journals, specifically, do you usually read?

_____ 1
_____ 2
_____ 3
_____ 4

K.5. How many years have you been treating liver diseases?

☐☐☐ years

K.6. Please, indicate your specialty

Gastroenterologist 1
Surgeon 2
Hepatologist 3
Internist 4
Others (specify) _)_____ 98

K.7. What level hospital do you work in?

Primary 1
Secondary 2
Tertiary 2

K.8. Your hospital is located in the province of

_____ ☐

K.9. The reference population for your hospital is

< 200,000 inhabitants 1
200,000-500,000 inhabitants 2
> 500,000 inhabitants 3

K.10. Could you tell me what year you were born?

☐☐

K.11. You are

Male	1
Female	2

THANK YOU VERY MUCH FOR YOUR COLLABORATION

Date of interview	Day	Month	Length of interview	minutes
Date of supervision	Day	Month		