Review Article

Systematic review of laparoscopic fenestration and percutaneous sclerotherapy in the management of symptomatic nonparasitic simple liver cysts

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Abstract: In the management of symptomatic nonparasitic simple liver cysts (SN-SLC), percutaneous sclerotherapy (PS) and laparoscopic fenestration (LF) represent the treatment options of choice. Recently, European guidelines on Interventional Ultrasound indicated PS as a good alternative to LF, with similar efficacy and lower complication rates. However, the choice of the best treatment options for SN-SLC remains a debated matter. Objective of this manuscript is to review the literature and to report on the short and long-term results of PS and LF for patients affected by SN-SLC. A Medline review of articles (July 1988–July 2019) concerning the over mentioned subject was performed. Papers considering pediatric patients, patients affected uniquely by polycystic liver disease, or less than five patients were excluded from the current analysis. Overall, 62 studies met inclusion criteria: one study comparing results of PS and LF, 40 and 21 studies reporting on results following LF and PS, respectively, accounting for an overall study population of 1,658 patients (1,037 and 621, respectively). Abdominal pain, eventually associated to fullness/discomfort, was the main symptom at diagnosis. Overall morbidity rate was 8% (7.9% and 9.9% among the LF and PS groups, respectively). Mortality rate was nil among LF patients and 0.2% among PS patients. Following cyst treatment, rapid symptoms relief was observed in the majority of patients. Average follow-up duration was of 49 and 29 months among studies investigating LF and PS results, and symptoms recurrence necessitating for additional treatment was observed in 1.6% and 8.2% of patients treated with LF and PS, respectively. While PS, mainly performed using alcohol/minocycline, seems associated with a lower risk of perioperative complications and higher rate of symptoms recurrence, LF is indicated when differential diagnosis with other condition is necessary, in the presence of biliary communication, or after ineffective PS. However, a multidisciplinary decision is recommended for defining the most appropriate treatment.

Keywords: Laparoscopic fenestration (LF); percutaneous sclerotherapy (PS); symptomatic nonparasitic simple liver cyst (SN-SLC)

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Introduction

Among cystic hepatic diseases, nonparasitic simple liver cysts (N-SLC) represent a subgroup characterized by a smooth wall, covered with an epithelium secreting a fluid similar to bile. N-SLC are fluid-filled cavities that arise from malformations of the ductal plate during embryonic

development (1). N-SLC are often incidentally diagnosed at imaging and their detection is gradually increasing, paralleling the increasing use of imaging modalities, including ultrasound, computed tomography, and magnetic resonance. In the majority of cases, N-SLC are asymptomatic but, as a result of their increase in volume, in about 15% of patients (2,3) they may be associated to aspecific symptoms, like abdominal pain, early satiety, nausea, or vomiting, becoming symptomatic (S)N-SLC (4). Depending on their diameter, which can be up to 30 cm, SN-SLC can also present as a palpable abdominal mass or as hepatomegaly.

When symptoms impair quality of life, treatment of SN-SLC is advocated and aims at relieving symptoms by reducing the cyst volume and consequently the compression on close structures. In this context, laparoscopic fenestration (LF) and percutaneous sclerotherapy (PS) represent the treatment options of choice. LF consists of a combination of cyst fluid aspiration, followed during the same operation by the excision of extra-hepatic cyst wall. PS consists in the radiologically guided placement of a pig tail drainage in the cyst cavity, followed by the aspiration of the cyst content, the injection in the cyst of a sclerosing agent in order to damage the inner epithelial layer of the cyst, and by the aspiration of the sclerosing agent by the cyst.

In 2014, Clinical American College of Gastroenterologists (ACG) guidelines suggested LF as the treatment option more effective, compared to PS, in the management of SN-SLC (5). In 2016 the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines on Interventional Ultrasound indicated, with a strong consensus, PS as a good alternative to LF, with lower complication rates and similar efficacy (6).

Given the lack of quantitative comparisons of LF versus PS results in the management of SN-SLC, we designed this systematic review of the available literature in order to assess efficacy, in terms of symptomatic relief and symptomatic recurrence, and safety of LF and PS.

Methods

Articles reporting characteristics of patients affected by SN-SLC and results following LF or PS were included in the current review. We included studies mainly focused on patients treated for solitary SN-SLC, however studies additionally including patients affected by multiple SN-SLC or symptomatic polycystic liver disease (SPLD) as a part of the study population were also included in the current review, while studies reporting uniquely on patients affected by SPLD were excluded from final analysis. Studies analyzing pediatric patients were excluded, as well as studies reporting on less than 5 patients. We systematically searched Medline (through PubMed) (7,8) for all years to August 2019 (last PubMed search was performed on August 25, 2019).

Initially, searches employing MeSH terms were performed for keywords and text (title or abstract). As shown in *Table 1*, search terms were organized in three main search groups, 4, 8, and 12, focused on patients affected by SN-SLC, patients undergoing LF treatment, and patients undergoing PS treatment, respectively. Combination of search group 4 singularly with search groups 8 and 12 led to the identification of 167 and 162 articles (search groups 9 and 13, respectively), focused on LF and on PS for SN-SLC, respectively. An additional "manual" research, using the "related articles" function, allowed to "explode" research. Further searches of reference lists of other articles supplemented the results of overmentioned research, resulting in the identification of additional 24 manuscripts (11 concerning LF and 13 concerning PS in the management of SN-SLC) and overall to the identification of 353 manuscripts, whose titles, abstracts, and full texts were independently reviewed by two authors (G Zimmitti and V Sega), in order to assess whether the studies met the eligibility criteria. Contrasting results between G Zimmitti and V Sega were discussed case by case, until an agreement was found. Included studies were classified, according to the management strategy, in two groups: LF and PS studies. An intention to treat analysis was performed, consequently cases converted to open procedures among LF studies were included in the analyses.

One author (G Zimmitti) extracted data from articles included in the study. In case of uncertainty concerning extracted data, two investigators (G Zimmitti and V Sega) discussed until resolution was achieved. Primary outcomes of the current study were relief of symptoms immediately after LF/PS, recurrence of symptoms requiring an additional treatment during follow-up, while secondary outcomes were study characteristics, patients characteristics, reintervention rates, operative time, hospital stay, conversion to laparotomy and surgical technique in case of LF, and sclerosant technique in case of PS. Morbidity following LF/PS was classified according to the Clavien-Dindo classification (9) by one investigator (G Zimmitti). Grade I and II were defined as minor complications and grade III, IV and V as major complications. The Newcastle-Ottawa scale (NOS)

Table 1 Medline search strategy

Search number	Search term	Results
1	Symptomatic liver cyst	523
2	Simple liver cyst	596
3	Nonparasitic liver cyst	243
4	1 OR 2 OR 3	1,182
5	Laparoscopic fenestration	292
6	Laparoscopic unroofing	121
7	Laparoscopic management	23,679
8	5 OR 6 OR 7	23,924
9*	4 AND 8	167
10	Aspiration sclerotherapy	370
11	Percutaneous treatment	27,716
12	10 OR 11	28,049
13#	4 AND 12	162

*, studies concerning laparoscopic fenestration of nonparasitic symptomatic liver cysts; #, studies concerning percutaneous sclerotherapy for nonparasitic symptomatic liver cysts.

was used in order to assess the risk of bias within studies included in this review (10). According to NOS, a score was given to each included study and was based on selection of study group, inclusion of a control group, comparability of groups and outcome of interest clear definition. Studies were independently scored by G Zimmitti and V Sega and disagreements were resolved through discussion between two investigators.

Results

Of 353 manuscripts identified by Medline (through PubMed) and by manual research, 253 were initially excluded by title or abstract analysis, based on overmentioned eligibility and exclusion criteria, leading to 100 articles concerning LF (n=55) and PS (n=45) for the management of SN-SLC. Such manuscripts were reviewed by full text analysis, finally leading to the identification of 62 studies, 41 focused on LF [(11-35) and (36-51)] and 22 on PS (37,52-72). One article (37), comparing results of LF and PS, was included in both the two groups of papers. The content of such manuscripts was considered relevant for the current review (*Figure 1*).

The study design of manuscripts included in this review are shown in *Table 2*. Publication dates ranged between 1988 and 2019, study periods between 1985 and 2018. Of 1,678 patients included in the 62 overmentioned studies, 1,057 underwent a LF and 642 a PS for SN-SLC. *Tables 3* and *4* respectively resumes characteristics of patients and results of studies reporting on LF and PS for patients affected by SN-SLC Among LF articles, patients affected by a solitary SN-SLC were 793 (75%), among PS articles were 425 (68%). Concerning study design of articles included in this review, in the LF and PS groups of articles retrospective studies were 40 (98%) and 14 (64%) while prospective studies were 1 (2%) and 5 (23%), respectively. In addition, in the PS group of articles 3 (14%) randomized clinical trial were observed. Mean NOS value was 5.4 for both LF and PS groups of articles. Median number of patients included in the reviewed articles was 21 both for LF (range, 5 to 66) and PS (range, 5 to 86) groups of articles. The main symptom related to SN-SLC was abdominal pain both in the two study groups. Follow-up duration following treatment was reported in 35 of 41 studies included in LF group and in 18 out of 22 studies included in the PS group. The main cyst diameter was reported in 33 studies (80%) in the LF group of articles and in 15 (68%) studies in the PS group of articles, however in 6 studies among PS articles it could be obtained by the main cyst volume, using the following formula: diameter = $\sqrt[3]{}$(main cyst volume) × (π/6). Finally, main cyst volume average diameter was 12.2 cm among LF articles (7 to 18 cm) and 9.7 among PS articles. The location of treated SN-SLC was reported in 58% and 32% of LF and PS studies, respectively, and a right liver location was observed in 49% of cases among LF articles (25% to 100%) and 64% (26% to 76%). Ethanol was the only sclerosing agent in 14 (67%) out of 21 studies analyzing results of PS, in two studies ethanol or other sclerosing agents (acetic acid and tetracycline, respectively) were used, while in the remaining 5 studies sclerosing agent was represented by minocycline hydro-chloride (n=2), hypertonic saline solution (alone, n=1; associated with bleomycin, n=1), and polidocanol (n=1).

In the group of articles reporting on LF for SN-SLC, operation duration was reported by 26 studies and accounted for a mean of 96 minutes (50 to 200 minutes). Overall, conversion rate was reported by 32 articles and 19 (2.2%) patients needed for a conversion to laparotomy during LF. Postoperative morbidity rate was reported by all included study on LF, with 78 patients out of 1,058 (7.4%) experiencing a complication following surgery. Complication rate was nil in 16 (39%) studies.

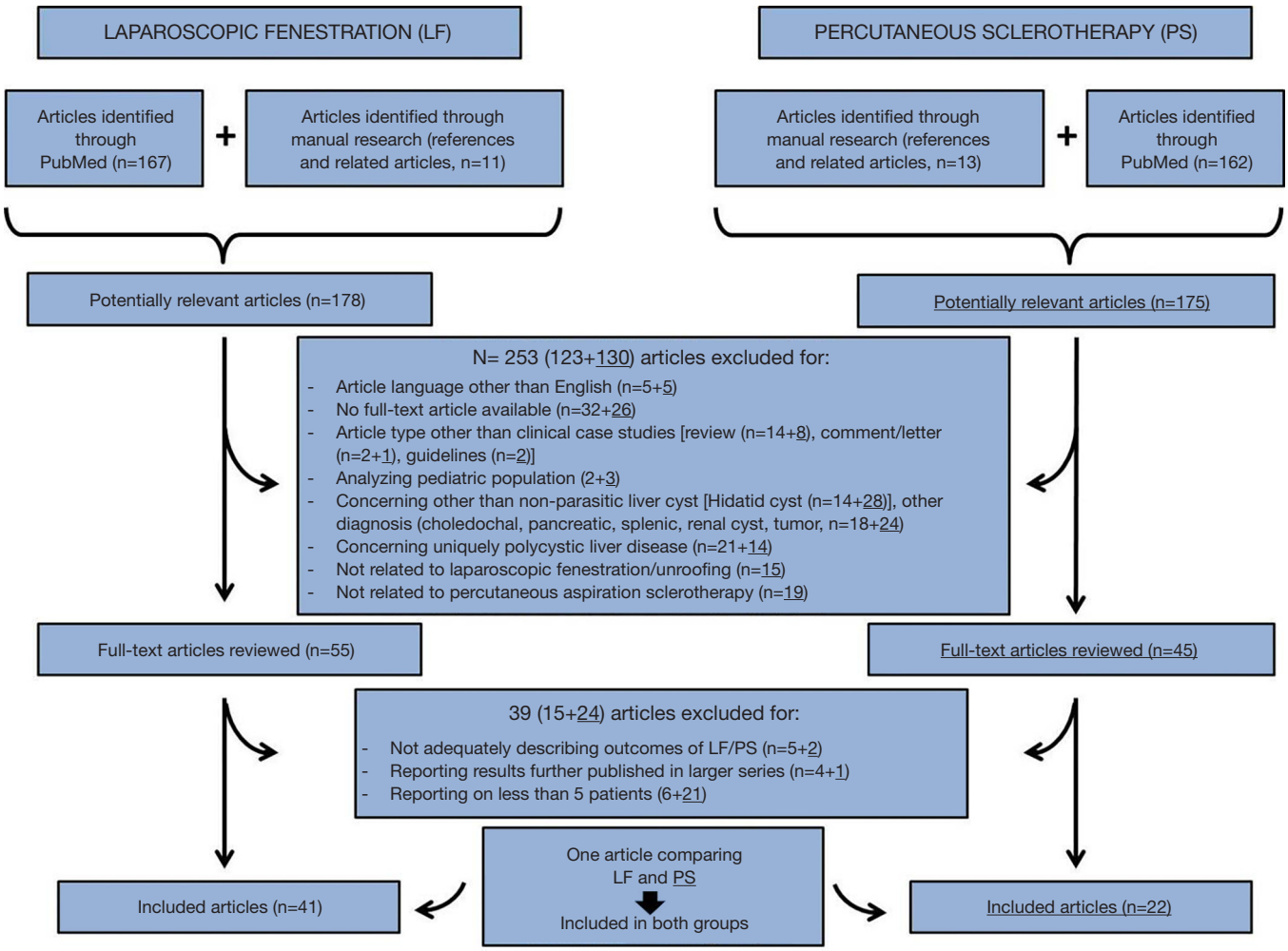

Figure 1 Strategy for article search and selection.

Table 2 Study design of articles included in this review

Study design	Laparoscopic fenestration (n=41)	Percutaneous sclerotherapy (n=22)
Retrospective study	40	14
Prospective study	1	5
Randomized clinical trial	0	3

Among 38 (93%) studies reporting on Dindo-Clavien grade of postoperative complication, at least one major complication was observed in 34% of studies, mortality being nil, and among 37 studies reporting the duration of postoperative recovery, the average length of hospital stay following LF was 4 days (0 to 9 days). Concerning PS studies, of 20 (out of 22, 91%) studies reporting on postoperative complications, 52 patients (9.3%) experienced a postoperative complication. In two (10%) studies no complications occurred following PS while in the remaining studies the most serious postoperative complication was graded as minor and major in 15 (75%) and 3 (15%) studies, respectively. Among 3 studies reporting postoperative major complications, one death due to acetic acid intoxication

Table 3 Published studies (n=41) concerning laparoscopic fenestration for symptomatic nonparasitic simple liver cyst: patients/cysts characteristics, operative details and postoperative outcomes

Author, year of publication	Study period	Study design	NOS	No. of patients (affected by SC, %)	Main symptom at diagnosis [%]	Main cyst size, cm	Right liver location	Surgery duration, minutes (conversion rate)	Morbidity (D-C, description of the most serious complication)	Symptom relief	LOS, days	Follow-up duration, months	Re-operation for symptoms recurrence (SC/MC)
Martin (11), 1998	1988–1997	RS	6	20 [65]	Abd pain [NR]	14 [8–24]	NR	81 [45–180] (nil)	25% (2, conservatively treated bile leak)	100%	3 [1–10]	31 [1–80]	30% (1/5)
Diez (12), 1998	1992–1996	RS	5	10 [80]	Abd pain [NR]	NR [5–18]	60%	NR (nil)	Nil	100%	4 [3–6]	NR [6–36]	10% (0/1)
Zacherl (13), 2000	1991–1998	RS	6	9 [100]	Abd pain/fullness [100]	NR	100%	87 [30–180] (nil)	10% (2, upper extremity vein thrombosis)	100%	5 [3–13]	NR	10%
Katkhouda (14), 2000	1990–1997	RS	6	16 [100]	Abd pain [65]	14 [7–22]	NR	48 [45–56] (nil)	6% (3A, abscess treated with CT guided drainage)	100%	1.3 [1–3]	30 [3–78]	Nil
Hansman (15), 2001	1984–2000	RS	4	6 [100]	Abd pain [NR]	11.3±4.8	53%	NR (nil)	Nil	100%	NR	42±8	Nil
Gigot (16), 2001	1984–2001	RS	6	19 [53]	Abd pain [31]	13 [8–30]	63%	NR (21%)	21% (3A, pneumothorax)	100%	6 [3–17]	38.5 [NR]	10% (0/2)
Regev (17), 2001	1984–1999	RS	5	18 [100]	Abd pain/fullness [81]	NR	NR	NR	Nil	100%	NR	63 [6–90]	5%
Schachter (18), 2001	1996–1999	RS	5	12 [83]	Abd pain/fullness [100]	NR	8%	NR	Nil	100%	5.8 [3–10]	30	Nil
Tocchi (19), 2002	1975–1999	RS	6	8 [100]	Abd pain [NR]	15±4.2	NR	78±20 (nil)	12.5% (3B, reoperation for cyst wall bleeding)	NR	6±5	50±9.3	25%
Tan (20), 2002	1993–2001	RS	6	11 [91]	Abd pain/fullness [100]	13 [6–18]	90%	68 [40–120] (nil)	Nil	100%	3 [2–4]	20 [4–46]	10%
Petri (21), 2002	1982–2001	RS	4	34 [95]	Abd pain [81]	10±3	NR	NR	9% [2]	NR	7	NR	19.4%
Tagaya (22), 2003	1993–1999	RS	6	5 [100]	Abd pain [100]	9 [7–18]	20%	200 [72–270] (nil)	Nil	100%	9 [7–12]	63 [35–102]	20%
Fiamingo (23), 2003	1996–2002	RS	6	15 [60]	Abd pain [81]	10 [7–13]	NR	80 [45–120] (7%)	27% (3A, port site bleeding)	100%	5.5 [3–12]	34 [2–72]	12% (0/2)
Hsu (24), 2005	1996–2001	RS	5	5 [20]	Abd fullness [100]	18 [10–20]	NR	150 [110–215] (nil)	Nil	80%	4 [3–5]	48 [24–72]	Nil
Fabiani (25), 2005	1989–2001	RS	5	40 [92]	Abd pain [NR]	11 [5–20]	47%	82 [15–210] (5%)	Nil	100%	5.3 [2–12]	69 [30–124]	2% (0/1)
Neri (26), 2006	1999–2003	RS	6	12 [58]	Abd pain [83]	11 [6–20]	NR	55 [40–90] (nil)	17% (2, NR)	100%	6 [4–14]	18 [3–38]	Nil
Palanivelu (27), 2006	1995–2005	RS	6	27 [100]	Abd pain/fullness [100]	16 [5–43]	74%	72 [55–104] (nil)	11% (2, prolonged ascites conservatively treated)	100%	4	74 [2–144]	Nil
Szabó (28), 2006	1995–2005	RS	5	21 [80]	NR	7 [4.5–20]	NR	NR	Nil	100%	4.7 [3–37]	49 [20–127]	5%
Bai (29), 2007	1998–2004	RS	5	44 [32]	NR	12 [6–23]	45%	NR	11% (3A, bile leak treated with percutaneous drainage)	NR	4±1.5	57 [24–103]	4% (0/2)
Gall (30), 2009	1985–2006	RS	5	48 [80]	Abd pain [87]	11 [2–30]	25%	75 [40–170] (nil)	15% (NR)	NR	3 [NR]	77 [3–250]	4%
Gamblin (31), 2008	2001–2008	RS	6	46 [13]	Abd pain [92]	13 [2–21]	NR	178 [54–380] (nil)	19% (<3B, NR)	100%	2 [1–11]	13 [1–49]	Nil
Mazza (32), 2009	1990–2007	RS	6	46 [100]	Abd pain [57]	9.2 [3–20]	55%	NR	4% (3A, bile leak treated with radiologic drainage)	100%	1.5 [1–3]	NR	4.3%
Treckman (33), 2010	1999–2007	RS	5	41 [79]	NR	11 [6–18]	59%	85 [30–145] (7.3%)	7% (3B, reoperation for bile leak)	NR	5 [2–29]	34 [6–103]	3%
Loehe (34), 2010	1995–2007	RS	6	66 [100]	Abd pain/fullness [81]	10	NR	80±53 (1.5%)	6% (3B, reoperation for cyst bleeding)	90%	5±3.7	69 [6–151]	9%
Donati (35), 2010	2002–2008	RS	4	21 [71]	Abd pain/tension [85]	9.7±2.2	38%	101 [55–165] (nil)	5% (2, resp distress)	100%	4.2±2.6	40 [6–82]	5% (0/1)
Faulds (36), 2010	2009–2010	PS	5	6 [NR]	Abd pain [NR]	11 [7–16]	60%	NR (nil)	17% (2, pneumonia)	100%	0 [0–5]	10 [3–13]	Nil
Kim (37), 2012	1997–2011	RS	4	14 [57]	NR	10.5	NR	104 (7%)	Nil	NR	3.3	NR	NR
Wahba (38), 2011	1999–2009	RS	5	23 [30]	NR	NR	NR	12.2±3.2 (4%)	4% (2, postoperative bleeding conservatively treated)	NR	NR	59±40	4%
Mazoch (39), 2011	1995–2009	RS	5	16 [NR]	Abd pain [87]	15 [6–26]	81%	NR	12% (3B, reoperation for hemorrhage)	NR	5.5	41	6%
Kamphues (40), 2011	2002–2008	RS	5	43 [84]	NR	8 [2–27]	NR	94 [30–95] (nil)	Nil	100%	5 [2–8]	49 [19–97]	4.7%
Scheuerlein (41), 2013	2000–2008	RS	6	47 [33]	Abd pain/fullness [73]	12 [6–20]	NR	80 [16–230] (6.4%)	13% (NR)	68%	5.2 [2–19]	43 [3–119]	9%
Ardito (42), 2013	2000–2010	RS	5	47 [60]	Abd pain [NR]	NR	60%	164 [50–240] (nil)	Nil	100%	5 [2–12]	67 [12–142]	2% (1/1)
Gocho (43), 2013[&]	2010–2011	RS	6	6 [100]	Abd fullness [NR]	11 [10–15]	50%	144 [100–210] (nil)	Nil	100%	3 [3]	15.5 [8–20]	Nil
Noerregaard (44), 2014	2007–2012	RS	6	29 [100]	Abd pain [87]	NR	55%	NR (6%)	6% (3A, cyst hemorrhage requiring radiologic drainage)	NR	1 [1–14]	28 [1–60]	16%
Lee (45), 2014*	2004–2014	RS	6	29 [64]	NR	9.6±4.8	NR	110 [25–525] (nil)	3% (2, pneumonia)	100%	5 [2–11]	62	3%
Wu (46), 2014	2009–2011	RS	5	30 [80]	NR	11.5±3.2	30%	58.5±6.8 (nil)	Nil	NR	5±0.6	13±8	Nil
Manterola (47), 2016	2008–2015	RS	5	41 [NR]	NR	10 [6–21]	54%	50 [35–90] (nil)	Nil	NR	1	35 [6–90]	Nil
Debs (48), 2016	2000–2012	RS	6	27 [60]	Abd pain [81]	13.6	55%	NR	Nil	NR	NR	NR	15%
Kisiel (49), 2017	2002–2012	RS	4	48 [73]	NR	NR	NR	NR	8% (3A, bile leak treated with ERCP)	96%	2 [1–7]	66 [22–173]	6%
de Reuver (50), 2018[c]	1999–2014	RS	8	34 [30]	Abd pain [66]	12 [8–20]	41%	90 [60–120] (6%)	20% (3B, reoperation for unspecified reason)	85%	5 [4–7]	64 [15–165]	9%
Tsirlis (51), 2019	2016–2018	RS	6	17 [100]	Abd pain [76]	15 [6–24]	65%	170 [97–335] (nil)	12% (3A, bile leak treated with ERCP)	100%	2 [1–10]	19	Nil

*, data concerning this manuscript refer to additional 5 patients who underwent laparoscopic liver resection (three left lateral sectionectomy, one right and one left hepatectomy); [c], data concerning this manuscript refer to additional 11 patients who underwent open cyst fenestration; [&], included patients who underwent single-port LF. NOS, Newcastle Ottawa Scale; SC, solitary cyst; D-C, Dindo-Clavien; LOS, length of stay; MC, multiple cyst; RS, retrospective study; NR, not reported; abd, abdominal.

Table 4 Published studies (n=22) concerning aspiration sclerotherapy for symptomatic nonparasitic simple liver cyst: patients/cysts characteristics, aspiration procedure details and postprocedure outcomes

Author, year of publication	Study period	Study design	NOS	No. of patients (no. of cysts, % of patients with solitary cists)	Main symptom at diagnosis (%)	Right liver cyst (%)	Cyst size at diagnosis, cm (range)	Cyst volume at diagnosis, mL	Sclerosing agent	Morbidity (D-C)	Symptom relief	Cyst volume reduction at 12 months, %	LOS, days	Follow-up Duration, months	Re-treatment for symptoms recurrence
Kairaluoma (52), 1989	1985–1987	RS	5	8 (15, 50%)	Abd pain [100]	NR	10 [6–25]	NR	Ethanol	12% (2, severe pain, procedure aborted)	88%	NR	NR	18 [12–32]	Nil
Montorsi (53), 1994	1987–1991	RS	4	21 (21, 62%)	NR	67	NR	450	Ethanol	10% [1]	100%	87.5	NR	18 [6–60]	NR
Tikkakoski (54), 1996	1985–1992	PS	5	25 (59, 44%)	Abd pain [100]	NR	9 [5–25]	520	Ethanol	16% (1, pain during ethanol injection, procedure aborted)	84%	48 [12–72]	NR	48	NR
Cellier (55), 1998	1992–1994	RS	5	7 (NR, 71%)	Abd pain [100]	NR	8.5 [5–130]	NR	Minocycline, hydrochloride	25% (1, transient pain)	71%	NR	NR	28 [24–42]	43%
Poźniczek (56), 2004	1995–2000	RS	4	19 (19, 100%)	NR	NR	10 [5–24]	NR	Ethanol	NR	58%	NR	NR	35 [6–60]	42%
Yang (57), 2006	1997–2003	RS	7	27 (31, NR)	Abd pain [78]	NR	NR	782	Ethanol	7% (2, hypotension requiring fluids/dopamine)	100%	98	1–3	29.6	NR
Erdogan (58), 2007	1997–2006	RS	5	30 (NR, 100%)	Abd pain [85]	NR	13 [3.5–25]	NR	Ethanol/tetracycline	7% (2, fever requiring readmission)	100%	NR	2 [2–23]	15 [2–35]	3%
Zerem (59), 2008	1999–2004	RCT	7	20 (23, 75%)	Abd pain [100]	NR	NR	175	Ethanol	6% (1, transient fever)	NR	92	1	24	19%
Nakaoka (60), 2009	1998–2007	PS	5	13 (17, 15%)	Abd pain [77]	NR	8 [4.3–16]	366	Ethanol, amine oleate	15% [1]	100%	93 [47–100]	NR	54 [1–95]	8%
Jusufovic (61), 2011	NR	PS	5	20 (20, 100%)	Abd pain [100]	55	NR	718	20% saline solution	Nil	100%	96.3 [75–100]	NR	24	NR
Yan-Hong (62), 2012	NR	RCT	8	67 (NR, 100%)	Abd pain/discomfort [66]	–	9 [8–13.5]	429	Ethanol	NR	86%	95 [NR]	NR	30±4.4	NR
Kim (37), 2012	1997–2011	RS	4	14 (NR. 71%)	NR	NR	11.5	NR	Ethanol, acetic acid	29% (5, death due to acetic acid intoxication)	NR	NR	6	NR	NR
Spârchez (63), 2014	2008–2013	PS	5	13 (13, 100%)	Abd/thoracic pain [77]	54	8.1 [5–10]	158	Polidocanol	15% (1, intracystic bleeding, procedure aborted)	69%	92 [3–100]	NR	1	23%
Yu (64), 2014	2006–2011	RS	7	45 (52, 68%)	Abd pain/fullness [78]	NR	8.3±1.8	319	Ethanol	7% (1, transient pain)	84%	NR	NR	12	16%
Lee (65), 2014	2009–2012	RS	5	17 (19, 88%)	Abd pain/fullness [65]	26	8.9 [7–11]	369	Ethanol	18% (2, transient fever treated with antibiotics)	100%	98 [97–100]	5 [3–8]	13 [8–22]	nil
Souftas (66), 2015	NR	PS	6	10 (14, 60%)	Discomfort [80]	60	9.1 [7–13]	408	15% saline solution and bleomycin	Nil	100%	100	1	12	NR
Akhan (67), 2016	1993–2012	RS	5	35 (39, 88%)	Abd pain [80]	NR	NR	94	Ethanol	3% (3A, liver abscess, treated with aspirated)	100%	95 [60–100]	1	38 [4–173]	nil
Larssen (68), 2016	1993–2010	RS	4	47 (51, 89%)	NR	NR	NR	520	Ethanol	2% (2, ethanol intoxication)	NR	99 [83–100]	NR	56 [24–193]	nil
Jang (69), 2016	2003–2013	RS	6	42 (43, 21%)	Abd pain/fullness [81]	76	12 [6–21]	930	Ethanol	19% (1, pain during ethanol injection, procedure aborted)	94%	95	NR	33 [12–106]	NR
Wijnands (70), 2017	2003–2014	PS/RS	6	86 (NR, 62%)	NR	70	11 [9–15]	696	Ethanol	11% (2, cyst infection treated with antibiotics)	89%	94	NR	NR	NR
Danza (71), 2017	2004/2015	RS	6	21 (24, 86%)	Abd fullness [87]	NR	NR	NR	Minocycline, hydrochloride	12% (2, intracystic hemorrhage)	100%	NR	NR	NR [24–120]	nil
Wijnands (72), 2018	2014–2016	RCT	6	34 (NR, 32%)	Abd pain [80]	NR	9.7	450	Ethanol	9% (3A, cyst re-aspiration due to symptoms persistency)	90%	NR	NR	6	NR

NOS, Newcastle Ottawa Scale; SC, solitary cyst; D-C, Dindo-Clavien; LOS, length of stay; SC, solitary cyst; MC, multiple cyst; RS, retrospective study; NR, not reported; abd, abdominal.

occurred, which represented the only death in the overall study population.

The median duration of follow-up following treatment was 43 months (10 to 77 months) and 24 months (1 to 56 months) among LF and PS articles, respectively. Among 40 LF studies (97%) analyzing long-term outcomes, the overall rate of symptoms recurrence requiring an operative management was 6% (63 out 1,043 patients) and was nil in 12 studies. Among 6 studies specifying if the symptoms recurrence occurred among patients affected by solitary versus multiple SN-SLC, of 17 patients undergoing an additional treatment (out of 218, 7.8%), 88% occurred among patients affected by multiple SN-SLC. Among 22 PS studies reporting on long-term outcomes, the overall rate of symptoms recurrence requiring an operative management was 9.7% (27 out 278 patients) and was nil in 5 studies.

Discussion

In the current review, we retrospectively analyzed and compared clinical and surgical characteristics and perioperative and long-term outcomes of 1,678 patients from 62 studies published up to August 2019 and reporting on LF and/or PS for patients affected by SN-SLC. Despite the choice of the correct treatment option for SN-SLC still represents a matter of debate, no trial comparing LF and PS have been performed and only studies comparing LF and PS in the management of SN-SLC report either on small groups of patients (37) or on outdated data referring to patients treated before 2000 (73).

According to our inclusion criteria, the number of studies reporting on LF was higher, compared to PS studies, and was paralleled by higher number of patients treated with LF, compared to PS, however comparison between studies reporting on patients treated with LF versus PS showed overall similarity in terms of study quality and risk of bias (according to means of NOS scores), of median number of patients included in the singular studies and of symptoms at the time of SN-SLC diagnosis. Cysts treated with LF were larger and more often located in the left liver, compared to cysts treated with PS. This probably reflects the trend to recommend a more invasive (and hypothetically effective) treatment to patients affected by larger cysts, as well as the relative difficulty to treat with LF cysts located in the right liver, mainly in the posterior sector.

Concerning treatment safety, despite overall rate of postoperative complication was similar between patients undergoing LF and PS, among studies reporting Dindo-Clavien grade of post-procedure complication, at least one major complication was more often observed after LF, compared to PS. Following cyst treatment, studies focusing on LF, compared to those focusing on PS, reported a slightly lower rate of cyst recurrence requiring for additional treatment. Such results parallel recommendations from ACG and EFSUMB guidelines (5,6), suggesting PS as a good alternative to LF, with lower rates of serious post-procedure complication but lower efficacy of PS, compared to LF, while reflecting different mechanisms for symptoms relief and recurrence following cyst treatment.

When considering LF, the aspiration of the cyst and the removal of its wall determine a rapid symptom relief, while an incomplete deroofing or the development of a false lumen due to adhesions with close anatomical structures and tissues are considered the main responsible for cyst recurrence (39,74). In contrast, in order to correctly report and quantify efficacy results of PS is important to know that, following evacuation of the cyst using aspiration sclerotherapy, cyst fluid will reaccumulate within some days and will subsequently and slowly disappear after at least 5 to 6 months (22), highlighting the importance of a long follow-up duration to adequately assess efficacy of PS. In this context, the average follow-up duration among PS, almost half than that of studies focusing on LF studies, may be responsible for a partial underestimation of the real rate of symptomatic recurrence following PS and as such should be carefully evaluated.

The current review has some limitations: first is the heterogeneity of outcomes following treatment, among LF and PS studies, which probably accounts for different study population, given the presence in the studies analyzed of a variable number of patients affected by multiple, other than single SN-SLC. Thus, it may be hypothesized that differences in rates of symptoms recurrence requiring additional treatment may be related to different rates of patients affected by multiple cysts among studies. Among strengths of the study, we highlight that it is based on an up-to-date Medline search, with an independent screening of found references, as well as of risk of bias assessment of finally included studies, performed by two authors (Giuseppe Zimmitti and V Sega). Exclusion of studies focused on polycystic liver disease, namely characterized by a different natural history and by different outcomes and management, as well as of studies including less than five patients and of duplicated datasets, contributed to reduce biases in reported outcomes rates.

In conclusion, both PS and LF are widely used for the

treatment of SN-SLC and are both associated with high safety and efficacy. Despite a moderate heterogeneity in outcome results among two groups of papers analyzed, PS seems to be associated, compared to LF, with a lower rate of serious post-procedure complications and a higher risk of symptomatic cyst recurrence. However, heterogeneity in study groups makes outcome results comparison between PS and LF difficult and prevents from stating definitive conclusion.

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Footnote

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