Horizon Scanning in Surgery: Application to Surgical Education and Practice

Single Incision Laparoscopic Surgery (SILS) for Cholecystectomy

April 2012

American College of Surgeons
Division of Education

Prepared by the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical for the American College of Surgeons

Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

This report is not intended to be used as medical advice or to diagnose, treat, cure or prevent any disease, nor should it be used for therapeutic purposes or as a substitute for a health professional's advice. The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information.

Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Acronyms

3PLC	Three-port laparoscopic cholecystectomy
4PLC	Four-port laparoscopic cholecystectomy
ASA	American Society of Anesthesiologists
BMI	Body mass index
FDA	Food and Drug Administration (United States)
GI	Gastrointestinal
LC	Laparoscopic cholecystectomy
LOS	Length of stay
NICE	National Institute for Health and Clinical Excellence (United Kingdom)
NOTES	Natural orifice transluminal endoscopic surgery
QoL	Quality of life
RCT	Randomized controlled trial
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons
SD	Standard deviation
SEM	Standard error of the mean
SF	Short-form
SILS	Single-incision laparoscopic surgery
SILC	Single-incision laparoscopic cholecystectomy
SSRC	Single-site robotic cholecystectomy
VAS	Visual analog scale

Introduction

Background

Gallstones can form when certain substances in the bile are present in concentrations that approach the limits of solubility (Heuman et al 2011). The excess solutes – primarily cholesterol and calcium bilirubinate – precipitate to form microcrystals, which may fuse together to form gallstones (Shaffer 2007). Populations at high risk of developing gallstones include females of European or Native American ancestry and the elderly. Truncal obesity, insulin resistance, type II diabetes, hypertension and hyperlipidemia (associated with increased hepatic cholesterol secretion) are major risk factors for the development of cholesterol gallstones (Heuman et al 2011), which comprise approximately 80% of all gallstones.

As gallstones are often asymptomatic, they can be present in the gallbladder for decades without causing any adverse effects (Heuman et al 2011). The symptoms of gallstones can range from biliary colic (pain due to gallstones temporarily obstructing the cystic duct of the gallbladder during a contraction) to acute cholecystitis (inflammation and infection of the gall bladder due to persistent stone impaction in the cystic duct). Chronic gallstones may cause progressive scarring of the gallbladder wall and loss of gallbladder function (chronic cholecystitis) (Heuman et al 2011).

Asymptomatic gallstones are usually managed expectantly. For patients who decline surgery or who are at high surgical risk, small stones may be dissolved through ingestion of bile acid (ursodeoxycholic acid). The best candidates for such non-surgical treatment are those with small radiolucent stones (primarily composed of cholesterol) in a functioning non-obstructed gallbladder; however, even with successful resolution of gallstones, the recurrence rate is approximately 50% within 5 years (Schaffer 2007). For symptomatic cholelithiasis (gallstones), the primary treatment involves the surgical removal of the gallbladder (cholecystectomy). For critically ill patients, creation of a stoma in the gallbladder to allow drainage of pus (cholecystostomy) may be used to stabilize the patient before cholecystectomy is performed (Heuman et al 2011).

Surgical treatment of symptomatic gallstones was initially conducted via open cholecystectomy, which was first undertaken in the 1880s and typically involved a single 10 to 18 cm incision (Keus et al 2009). However, since the 1970s small-incision open cholecystectomy has been used whereby the incision is typically less than 8 cm (Keus et al 2009). Laparoscopic cholecystectomy (LC) was first undertaken by Philippe Mouret in France in 1987 (Adachi et al 2011), and is now the standard procedure for gallbladder removal and the most commonly performed laparoscopic surgical procedure in the world (Chamberlain and Sakpal 2009). Conventional laparoscopic surgery typically uses three or four small incisions to allow the insertion of operating ports through which a camera and instruments gain entry (Keus et al 2009).

With the increased popularity of minimally invasive surgery, several new techniques have been developed to further reduce the number and size of the incisions used during LC, aimed at reducing postoperative pain and recovery time and improving cosmetic outcomes (Chamberlain and Sakpal 2009). One such technique is natural orifice transluminal endoscopic surgery (NOTES), which eliminates skin incisions by using natural body openings. The NOTES technique has been used to perform a cholecystectomy via a transvaginal approach, but the drawbacks

include difficulties with access, orientation and closure, a lack of appropriate instrumentation, and the risk of infection (Ersin et al 2010).

Another recently developed technique is single-incision laparoscopic cholecystectomy (SILC), where a single point of access for the laparoscopic camera and instruments is via the umbilicus. This technique aims to provide the benefits of NOTES, such as fewer incisions and less visible scarring, without requiring additional specialist training beyond that required for standard LC (Hodgett et al 2009).

Burden of disease

Gallstones are a major cause of morbidity in Western countries, with an estimated incidence of symptomatic cholelithiasis of 2.2 per 1,000 individuals (Keus et al 2009), or an estimated 6.3 million men and 14.2 million women aged 20 to 74 years in the United States (US) (Shaffer et al 2005). Although the majority of gallstones remain asymptomatic, approximately one third eventually cause symptoms and complications (Portincasa et al 2009). In the US, approximately 700,000 cholecystectomies are performed each year to treat symptomatic gallstones. Ninety-eight per cent of all gallbladder and biliary tract disorders are related to cholelithiasis (Shaffer et al 2005), and gallstone-related complications are responsible for 3,000 deaths per year (0.12% of all deaths) (Portincasa et al 2009). Medical expenses related to the symptoms and complications of gallstones currently exceed $6.5 billion USD per year (Stokes et al 2011).

Cholelithiasis, with cholecystitis, is the most common principle gastrointestinal diagnosis for inpatients in the US. A survey of 994 hospitals in 28 states across the US revealed that there were 262,411 hospital discharges in the year 2000 for these combined diseases, with each costing a median of $11,584 USD to treat (Russo et al 2004). Furthermore, an association exists between the incidence of cholelithiasis and gallbladder cancer. The development of gallbladder cancer is believed to be linked with the chronic irritation of the gallbladder mucosa which can result from cholelithiasis, leading to malignant transformation or promotion of carcinogenic agents (Shaffer et al 2005).

Technology

Navarra et al (1997) were the first to perform SILC, demonstrating its technical feasibility and suggesting that it may prove advantageous in selected patients. The technique involved a single incision through the umbilicus and two trocars or ports inserted through the opening with a bridge of fascia (soft connective tissue) between them (Navarra et al 1997). Two case series quickly followed (Bresadola et al 1999, Piskun and Rajpal 1999); however, there were few studies about SILC procedures reported in the literature over the next decade (Antoniou et al 2011).

More recently, a resurgence of interest in the technique has been exemplified by the publication of numerous studies on SILC (Antoniou et al 2011). These studies have involved a variety of modifications to the original method with regards to the number, type and size of the trocars, the instrumentation, and the preferred method of gallbladder anchorage and exposure of the Calot's triangle (Antoniou et al 2011). Some techniques utilize multiple fascial punctures to insert multiple ports via the same incision, whereas others use single-port access systems that allow multiple instruments to be inserted through the same port (Figure 1). According to the systematic review

by Antoniou et al (2011), the two most common methods of SILC involve the insertion of two umbilical ports and gallbladder anchorage with two or three percutaneous sutures, or three umbilical ports and gallbladder suspension with a grasper (Antoniou et al 2011).

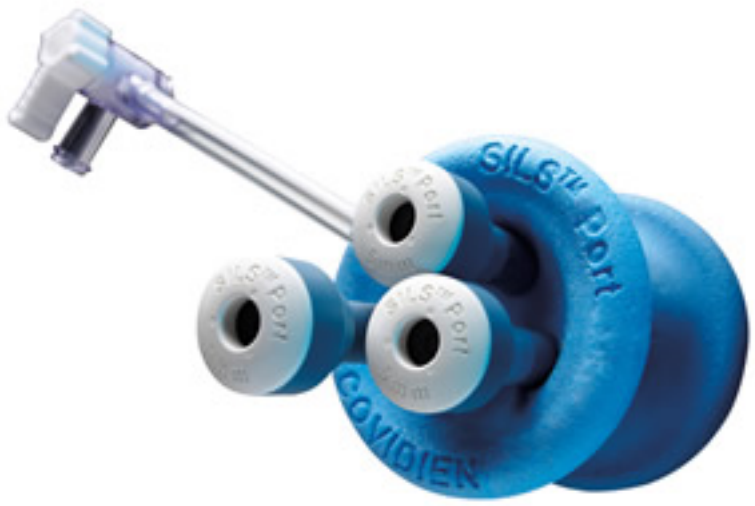

Figure 1: SILS™Port (Covidien), one of several single-port access systems available through which to perform SILC.

Stage of development

The initial SILS technique involved a single incision in the umbilicus, facilitating the placement of two ports or trocars through the opening. More recently, several variations to the technique have been developed, many utilizing single-port access systems which are inserted into a small umbilical opening, which then allow the use of multiple trocars through the single port with (Antoniou et al 2011).

Several single-port access systems have been developed for use during SILC, many of which have received US Food and Drug Administration (FDA) approval (Table 1). The Uni-X Single Port Laparoscopic System has yet to be approved by the FDA (FDA 2012).

Table 1: Single-port access systems approved by the FDA as of January 2012

Name	Company	510k number	Decision date
TriPort, TriPort+, Triport15, Quadport	Advanced Surgical Concepts, Washington, DC	K111407	18 Jan 2012
SILS Port (SILSPT5, SILSPT12, SILSPT15)	Covidien, North Haven, CT	K103253	24 Feb 2011
ASC TriPort + laparoscopic access device	Advanced Surgical Concepts, Washington, DC	K110004	26 Jan 2011
ASC TriPort (model TPRT-02-01) and Quadport (QPRT-01) laparoscopic access device	Advanced Surgical Concepts, Washington, DC	K101794	29 Nov 2010
Innovia Innoport laparoscopic access port	Innovia LLC, Miami, FL	K093783	23 Aug 2010
Innoport laparoscopic access device	Innovia LLC, Miami, FL	K090677	07 May 2009
Gelport single incision access system	Applied Medical Resources Corp, Rancho Santa Margarita, CA	K090275	18 Feb 2009
R-Port II (ASC TriPort predicate) laparoscopic access device	Advanced Surgical Concepts, North Attleboro, MA	K073170	03 Dec 2007
R-Port (R-Port II predicate) laparoscopic access device	Advanced Surgical Concepts, North Attleboro, MA	K070158	23 Aug 2007

Source: www.fda.gov

Studies investigating SILC have been performed in a number of countries, including Germany, India, China, Italy, South Korea, Turkey, The Netherlands and the US.

Several clinical trials have recently been completed, including one randomized controlled trial (RCT) comparing SILC to conventional LC (ClinicalTrials.gov identifier: NCT00981604), from which no published data are yet available. One RCT, classified as active, compares the Covidien SILS-Port with four-port laparoscopic cholecystectomy (4PLC) (NCT00832767), and a further five trials currently recruiting patients are comparing SILC to either conventional LC (NCT01278472, NCT01268748, NCT01195285, NCT01094379) or Harmonic Scalpel SILC (NCT01272505) (ClinicalTrials.gov 2012).

Current treatment and alternatives

Asymptomatic gallstones do not usually require treatment. For symptomatic gallstones, patients with small gallstones who are poor candidates for surgery may be treated medically using bile acid; however, this requires a prolonged course of treatment with suboptimal effectiveness (Leuschner 1992), and has a recurrence rate of approximately 50% at 5 years (Schaffer 2007). Extracorporeal shockwave therapy may be effective in patients with single cholesterol gallbladder stones < 20 mm in diameter; however, as long-term outcomes are unsatisfactory, this technique has limited usage (Lee and Kim 2009). In those instances where surgery for gallstones is

appropriate, there are several surgical procedures apart from SILC which can be performed. These include:

- open cholecystectomy;
- conventional LC;
- small-incision open cholecystectomy;
- NOTES.

Open cholecystectomy

Open cholecystectomy is primarily reserved for specific situations, for example when the presence of severe inflammation precludes the identification of critical anatomy during LC (McAneny 2008). Although some open cholecystectomies are performed as primary procedures, the vast majority are undertaken as a result of failed laparoscopic procedures (Visser et al 2008). Open cholecystectomy can be performed using one of two techniques: the 'antegrade' (beginning the dissection medially in the hepatoduodenal ligament) technique, or the more traditional 'retrograde' (from the fundus downward) technique, both of which have their own advantages in specific clinical settings (Visser et al 2008).

Laparoscopic cholecystectomy

First performed in 1987, LC is now the gold standard in gall bladder removal due to reduced pain and perioperative morbidity compared with open cholecystectomy (Thakur et al 2011). Conventional LC is performed using four incisions or ports (4PLC); one 10-12 mm port in the umbilicus, one 5 mm or 10-12 mm port in the subxiphoid region, and two 5 mm ports in the right subcostal area (Thakur et al 2011). Several variants on the conventional technique utilize smaller or fewer ports, and are referred to as minilaparoscopic cholecystectomy.

Small-incision open cholecystectomy

In the early 1970s, the incision size during open cholecystectomy was reduced, resulting in the technique of small incision open cholecystectomy. Initial results demonstrated superiority of this technique over standard open cholecystectomy due to a decrease in pain and surgical trauma and, as a consequence, accelerated recovery (Keus et al 2006). A recent Cochrane review demonstrated similar rates of bile duct injury and complications between small-incision open cholecystectomy and LC, with small-incision open cholecystectomy resulting in shorter operating times (Keus et al 2006).

NOTES cholecystectomy

Natural orifice transluminal endoscopic surgery involves the introduction of endoscopes into the abdominal and thoracic cavities via the mouth, urethra, vagina, and/or anus in order to perform interventions on internal organs (Moriera-Pinto et al 2011). The first NOTES cholecystectomy was performed in France in 2007 and resulted in no postoperative pain or scars and a short hospital stay (Marescaux et al 2007). Although associated with better cosmesis and reduced post-procedural pain compared with standard LC, several ethical, procedural and technological questions remain regarding NOTES (Chamberlain and Sakpal 2009). For example, the lack of sterilization and secure closure of the gastric or colonic wall remains a challenge, as the

development of gastric leaks would represent a catastrophic complication – one which rarely occurs after routine LC (Chamberlain and Sakpal 2009).

A recent systematic literature review evaluated studies on open, small-incision and laparoscopic cholecystectomy in patients with symptomatic cholelithiasis and found no significant differences in mortality or complications between the three techniques. Patients undergoing either small-incision cholecystectomy or LC had a shorter convalescence than those undergoing the open technique, but there were no clear differences between small-incision cholecystectomy and LC in terms of patient outcomes (Keus et al 2009).

Literature review

Search criteria

Keyword/MeSH terms utilized:

Cholecystectomy, single-incision laparoscopic surgery, SILS

Databases utilized:

PubMed

Inclusion criteria

Table 2: Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials; prospective non-randomized comparative studies
Patient	Patients undergoing surgical removal of the gallbladder
Intervention	Single-incision laparoscopic cholecystectomy
Comparator	Open cholecystectomy, small-incision open cholecystectomy, laparoscopic cholecystectomy, NOTES cholecystectomy
Outcome	Safety: complications Efficacy: conversion rate, operative time, blood loss, length of hospital stay, postoperative pain, cosmesis, quality of life
Language	English only

NOTES: natural orifice transluminal endoscopic surgery

Included studies

A total of eight studies, including four RCTs and four prospective non-randomized comparative studies, were selected for inclusion in this report (Table 3). Seven of the eight studies compared SILC with standard 4PLC, while one compared it with three-port LC (3PLC).

Table 3: Characteristics of included studies

Study/Location	Level of evidence (Appendix A)	Intervention and number of patients
Cao et al 2011 *China*	Level II Randomized comparative	SILC (n=57) 3PLC (n=51)
Lai et al 2011 *China*	Level II Randomized comparative	SILC (n=24) 4PLC (n=27)
Phillips et al 2011 *United States*	Level II Randomized comparative	SILC (n=117) 4PLC (n=80)
Tsimoyiannis et al 2010 *Greece*	Level II Randomized comparative	SILC (n=20) 4PLC (n=20)
Froghi et al 2011 *United Kingdom*	Level III-2 Prospective non-randomized comparative	SILC (n=16) 4PLC (n=13)
McGregor et al 2011 *United Kingdom*	Level III-2 Prospective non-randomized comparative	SILC (n=11) 4PLC (n=24)
Prasad et al 2011 *India*	Level III-2 Prospective non-randomized comparative	SILC (n=100) 4PLC (n=100)
Vidal et al 2011 *Spain*	Level III-2 Prospective non-randomized comparative	SILC (n=120) 4PLC (n=120)

3PLC: three-port laparoscopic cholecystectomy
4PLC: four-port laparoscopic cholecystectomy
SILC: single-incision laparoscopic cholecystectomy

Study profiles

RCT evidence

Cao et al (2011) compared short-term outcomes between one group of patients who underwent SILC (n=57) and another group who underwent standard 3PLC (n=51), between May and August 2010. All operations were performed by one surgeon who had previously completed more than 200 conventional LC procedures. Inclusion criteria consisted of patients who had no signs of acute choledocholithiasis or acute pancreatitis, had not undergone previous epigastric surgery, had an American Society of Anesthesiologists (ASA) grade I or II classification, were aged 70 years or less, and had a body mass index (BMI) < 30 kg/m^2. Outcomes of interest included operative time and blood loss, conversion rate, postoperative pain measured using a visual analog scale (VAS) on days 1 and 3, length of stay (LOS) in hospital and the incidence of postoperative complications at < 30 days.

Lai et al (2011) compared the outcomes of 51 patients who were randomized into either a SILC (n=24) or 4PLC group (n=27) between November 2009 and August 2010. Operations were performed by surgeons experienced in laparoscopic procedures. All patients aged 18 to 80 years who had a preoperative diagnosis of symptomatic gallstones or gallbladder polyps and were scheduled for elective cholecystectomy, were eligible for inclusion. Exclusion criteria included: patients with an ASA grade IV and V classification; patients with a contraindication for laparoscopic surgery; Mirizzi syndrome; suspected presence of common bile duct stones; suspected malignancy; previous upper abdominal surgery; long-term anticoagulant treatment; previous history of cholangitis or cholecystitis; gallstones greater than 3 cm; and an imaging

diagnosis of contracted gallbladder or chronic cholecystitis. Outcomes of interest included the incidence of complications, operative time and blood loss, rate of conversion to open cholecystectomy, LOS, VAS pain and cosmetic satisfaction scores, and time to return to usual physical activity.

The RCT by Phillips et al (2011) compared the intermediate results for one group of patients who underwent SILC (n=117) with those of another group who underwent 4PLC (n=80). Patients were drawn from 10 centers. No study dates were provided. Inclusion criteria consisted of patients aged 18 to 85 years, with a BMI < 45 kg/m^2, and a diagnosis of biliary colic with gallstones or polyps confirmed by radiographic imaging. Patients with biliary dyskinesia with an ejection fraction of < 30% were also eligible for inclusion. Exclusion criteria included pregnancy, acute cholecystitis, a previous right subcostal or upper midline incision, indication for intraoperative biliary imaging, preoperative indication for endoscopic retrograde cholangiopancreatography, an ASA grade IV and V classification, ongoing peritoneal dialysis, and an umbilical hernia or prior umbilical hernia repair. Outcomes of interest included the rate of intraoperative and postoperative complications up to one year, conversion rates, operative time and blood loss, pain and cosmetic satisfaction scores and quality of life.

Tsimoyiannis et al (2010) compared the outcomes of 40 patients who underwent SILC (n=20) or 4PLC (n=20). All procedures were performed by the same group of surgeons at one institution. No study dates were provided. Inclusion criteria consisted of a BMI < 30 kg/m^2, attacks of pain from cholelithiasis, ASA grade I or II classification, and written informed consent. Exclusion criteria included signs of acute cholecystitis or choledocholithiasis or attacks of acute pancreatitis, BMI > 30 kg/m^2, ASA grade more than II, and a lack of written informed consent. Reported outcomes included the rate of complications, operative time and blood loss, LOS, abdominal and shoulder pain scores, and postoperative analgesia use.

Non-randomized comparative evidence

Froghi et al (2011) compared perioperative outcomes and biochemical measures of systemic stress in patients who underwent either SILC (n=16) or 4PLC (n=13), between February and May 2010. Participating patients were selected from those scheduled for an elective cholecystectomy due to symptomatic gallstones. Patients were excluded if they had comorbidities or medical complications that resulted in increased baseline cytokine levels, such as acute infection, sepsis, malignancy and acute or chronic inflammation. Reported outcomes included the rate of conversion and postoperative complications, operative time, LOS, pain (measured using a VAS) and serum levels of biochemical markers of systemic stress, including C-reactive protein (CRP), white cell count (WCC), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).

The study by McGregor et al (2011) compared perioperative outcomes and biochemical measures of systemic stress in patients who underwent either SILC (n=11) or 4PLC (n=24), between February and May 2010. All procedures were performed at a single center, by one of five attending-led operative teams. All patients undergoing SILC or 4PLC during the study period were considered eligible for inclusion. Patients were excluded if they had comorbidities such as an autoimmune disease, malignancy or infection that resulted in raised inflammatory markers. Reported outcomes included the rate of conversion and intraoperative and postoperative complications, operative time, total incision size, LOS, and serum levels of biochemical markers of systemic stress, including CRP and IL-6. It is likely that there is significant patient overlap between this study and Froghi et al (2011), as both studies were conducted at the same institution during the same period of time.

Prasad et al (2011) compared postoperative pain in patients who underwent SILC (n=100) or 4PLC (n=100), between September 2009 and May 2010. All patients with symptomatic cholelithiasis, who were fit for general anesthesia, were eligible for inclusion. Exclusion criteria included patients with acute cholecystitis, abnormal liver function tests, a contracted or thickened gallbladder on ultrasound examination, and those with a suspicion of gallbladder malignancy. Outcomes of interest included operative time, rate of conversion and intraoperative and postoperative complications, and VAS pain scores. For both operative time and pain scores, the first 50 patients and the second 50 patients in each treatment group were analyzed separately.

Vidal et al (2011) compared postoperative outcomes in patients who underwent SILC (n=120) or 4PLC (n=120), between February 2009 and February 2011. Procedures were performed by two experienced laparoscopic surgeons. All patients who were referred to the center for cholecystectomy during the study period, who agreed to undergo SILS, were included. No exclusion criteria were reported. Outcomes of interest included the rate of conversion and intraoperative and postoperative complications, operative time, LOS, postoperative pain and nausea (measured using a VAS), and the incidence of incisional hernia at 24 months follow-up.

Critical appraisal

RCT evidence

Lai et al (2011) reported that randomization was achieved using computer-generated random numbers; however, the method of sequence generation was not reported in the other three studies. In three of the four included studies, sealed envelopes were used to conceal treatment allocation; however, Phillips et al (2011) did not report the method of allocation concealment. Surgeons were informed of each patient's treatment allocation in the operating room immediately prior to surgery in three studies; however, Lai et al (2011) did not report when surgeons were notified of each patient's treatment group. Phillips et al (2011) reported that patients were randomized to SILC and 4PLC in a 1.5:1 ratio.

Three studies reported that outcome assessors were blinded to treatment allocation (Cao et al 2011; Lai et al 2011; Tsimoyiannis et al 2010); however, Phillips et al (2011) did not report on blinding of outcome assessors. Lai et al (2011) reported that patients were not blinded during the study, while Phillips et al (2011) reported that patients remained blinded to the treatment to which they were randomized for the first postoperative week, following which they were informed of their treatment. The two other studies did not report on blinding of patients.

All four included studies adequately detailed their inclusion and/or exclusion criteria; however, these criteria did vary, which may limit the ability to draw comparisons between studies.

The baseline characteristics of patients, including age, gender, race, weight, height, ASA grade and indication for surgery were not significantly different between treatment groups in all four included studies. In the three studies that reported BMI at baseline, two reported no significant difference between treatment groups (Cao et al 2011; Lai et al 2011), while one study reported that patients in the 4PLC group had a significantly higher mean BMI than patients in the SILC group (*P*=0.011) (Phillips et al 2011).

Three studies provided detailed information regarding the SILC and 3PLC/4PLC operative techniques (Cao et al 2011; Lai et al 2011; Tsimoyiannis et al 2010). The fourth (Phillips et al

2011) reported only that surgery was performed in accordance with the standard of care and judgment of the surgeon.

In three studies the length of follow-up was generally short, ranging from 72 hours to three months, with data available for 100% of patients at these time-points (Cao et al 2011; Lai et al 2011; Tsimoyiannis et al 2010). Phillips et al (2011) reported that patients were followed-up for 12 months after surgery, with data available for only 28% (56/197) of patients at this time-point at the time of preparation of the article.

The statistical methodology used to compare outcomes between treatment groups was reported in all four studies. Only two studies reported using power calculations to determine adequate sample size (Lai et al 2011; Tsimoyiannis et al 2010).

Only one group of authors (Phillips et al 2011) discussed study limitations in any detail, including the lack of generalizability of the results due to the exclusion criteria used, and the considerable experience of surgeons undertaking SILC (bypassing the initial learning curve associated with the technique).

Two studies reported on the source of trial funding, one stating that the trial was not supported by any grant (Lai et al 2011), and the other stating that the trial was sponsored by Covidien, the manufacturer of the SILS Port (Phillips et al 2011). Tsimoyiannis et al (2010) declared that none of the authors had financial relationships with any pharmaceutical or device company. Similarly, Cao et al (2011) reported that the authors had no conflicts of interest to declare. However, a number of the authors in the study by Phillips et al (2011) declared financial relationships with one or more companies. No conflict of interest statement was provided by the authors of Lai et al (2011).

Non-randomized comparative evidence

Two studies reported that patients were informed of both treatment options and given the choice as to which procedure they wished to receive (Prasad et al 2011; Vidal et al 2011). McGregor et al (2011) reported that treatment allocation was at the discretion of the surgeon, while Froghi et al (2011) did not report how patients were allocated to treatment groups.

All four included studies reported their inclusion criteria, while exclusion criteria were reported in three of the four studies (Froghi et al 2011; McGregor et al 2011; Prasad et al 2011).

Where reported, the gender and height of patients at baseline were not significantly different between treatment groups. Age at baseline was reported in all four studies, with three studies reporting no significant difference between treatment groups (Froghi et al 2011; Prasad et al 2011; Vidal et al 2011), and one study reporting that patients in the 4PLC group were significantly older than those in the SILC group (P=0.0218) (McGregor et al 2011). BMI at baseline was reported in three studies, with two studies reporting no significant difference between treatment groups (Froghi et al 2011; Prasad et al 2011), and one study reporting that patients in the 4PLC group had a higher BMI than those in the SILC group (P=0.0219) (McGregor et al 2011). In the only study where it was reported, the weight of patients at baseline was significantly higher in the 4PLC group than in the SILC group (P=0.019) (McGregor et al 2011).

Three studies provided adequate information regarding the SILC and 4PLC operative techniques (Froghi et al 2011; McGregor et al 2011; Prasad et al 2011). The fourth (Vidal et al 2011) reported that the operation was performed as previously reported, and provided a reference to a publication describing the technique.

In three studies the length of follow-up was generally short, ranging from 8 hours to two months (Froghi et al 2011; McGregor et al 2011; Prasad et al 2011). Prasad et al (2011) reported that data was available for 100% of patients at 8 hours follow-up; however, it was not clear what percentage of patients were assessed at 2 months follow-up in the other two studies (Froghi et al 2011; McGregor et al 2011). Vidal et al (2011) reported that patients were followed-up for 24 months after surgery, with data available for 100% of patients at this time-point.

The statistical methodology used to compare outcomes between treatment groups was reported in all four studies. The study by Froghi et al (2011) undertook an intention-to-treat analysis, in addition to the standard analysis, in order to determine whether the results would change if patients who converted from SILC to 4PLC remained in the SILC group.

Only two of the four studies discussed study limitations in any detail (Froghi et al 2011; McGregor et al 2011). Both studies suggested that their small sample sizes may have led to a type II error. In addition, McGregor et al (2011) suggested that the lack of randomization may have led to the trial being open to selection bias, as demonstrated by the significant differences in baseline age, weight and BMI between the treatment groups. This study also suggested that the learning curve of surgeons may have introduced procedural bias (McGregor et al 2011).

Three studies reported on the source of trial funding or support, one stating that there was no source of funding for the trial (Prasad et al 2011), another stating that logistic support was provided by Covidien (Vidal et al 2011), and a third stating that funding was provided by the Imperial College NHS Trust (Froghi et al 2011). No statement regarding trial funding was provided by McGregor et al (2011). Three studies provided conflict of interest statements, with all three reporting that the authors had no conflicts of interest to declare (Froghi et al 2011; Prasad et al 2011; Vidal et al 2011). No conflict of interest statement was provided by the authors of McGregor et al (2011).

Safety and efficacy

Safety

RCT evidence

Complications

The rate of complications was relatively low in three of the four RCTs (Table 4).

Cao et al (2011) reported bile leakage in one SILC patient (1.8%), who subsequently required endoscopic retrograde cholangiopancreatography to remove common bile duct stones. Two additional patients, one SILC patient (1.8%) and one 3PLC patient (2.0%), developed a wound infection that required wound dressing and antibiotics (Cao et al 2011).

A subumbilical port wound infection in one 4PLC patient (3.7%) was noted by Lai et al (2011), who reported that there were no instances of biliary injury, bleeding, bile leakage, or intra-abdominal collection in either treatment group.

Phillips et al (2011) reported that the total rate of adverse events was not significantly different between the SILC (45/117, 38%) and 4PLC (27/80, 34%) groups (*P*=0.55); however, the majority of complications were unspecified. The incidence of wound complications was significantly higher in SILC patients compared with 4PLC patients (*P*=0.047); however, the rates of retained choledocholithiasis (*P*=1.0) and postoperative hernia recurrence (*P*=0.65) were not significantly different between the two groups (Phillips et al 2011).

Tsimoyiannis et al (2010) reported that three patients, one SILC patient (5.3%) and two 4PLC patients (11.1%) (*P*=0.54), experienced mild bile leakage for 2-4 days, and were treated conservatively through a closed subhepatic drain, placed due to difficult dissection of the bed of the gallbladder. At 72 hours follow-up, no SILC or 4PLC patients experienced vomiting, while no SILC patients and one (5%) 4PLC patient experienced nausea at this time point (*P*=0.31) (Tsimoyiannis et al 2010).

No deaths were reported in any of the RCTs.

Table 4: Complication rates in RCT studies

Study	Complication	SILC n (%)	3/4PLC n (%)	*P*-value
Cao et al (2011)	Bile leakage	1 (1.8)	-	-
	Wound infection	1 (1.8)	1 (2.0)	NR
Lai et al (2011)	Wound infection	-	1 (3.7)	-
Phillips et al (2011)	Wound complications	12 (10.3)*	2 (2.5)	0.047
	Erythema	5 (4.3)	0 (0)	0.08
	Cellulitis	2 (1.7)	0 (0)	0.52
	Inflammation	1 (0.9)	0 (0)	1.0
	Postoperative wound infection	3 (2.6)	2 (2.5)	1.0
	Suture-related complication	2 (1.7)	0 (0)	0.52
	Seroma	1 (0.9)	0 (0)	1.0
	Retained choledocholithiasis	1 (0.9)	1 (1.3)	1.0
	Postoperative hernia recurrence	4 (3.4)	1 (1.3)	0.65
Tsimoyiannis et al 2010	Bile leakage	1 (5.3)	2 (11.1)	0.54
	Nausea 72 hours after surgery	0 (0)	1 (5)	0.31
	Vomiting 72 hours after surgery	0 (0)	0 (0)	-

3PLC: three-port laparoscopic cholecystectomy
4PLC: four-port laparoscopic cholecystectomy
NR: not reported
SILC: single-incision laparoscopic cholecystectomy
*Total of 14 adverse events in 12 patients

Non-randomized comparative evidence

Complications

Froghi et al (2011) reported minor intraoperative bleeding in one SILC patient (6.3%) and one 4PLC patient (7.7%); however, at the 2-week and 2-month follow-up telephone interviews, no infections, inflammation or visits to the general practitioner for postoperative complications were reported in either group.

Vidal et al (2011) reported that intraoperative complications occurred in three SILC patients (2.5%) (due to an incomplete clipage of the cystic duct), and two 4PLC patients (1.7%) (*P*>0.05). Postoperative complications occurred in five SILC patients (4.2%) (two wound infections and three umbilical hematoma) and five 4PLC patients (4.2%) (*P*>0.05) (Vidal et al 2011). At 24 months follow-up, none of the SILC patients had an incisional hernia, compared with two 4PLC patients (1.7%) (*P*=0.036) (Vidal et al 2011).The median VAS score for postoperative nausea was 1 (range 1-2) in both the SILC and 4PLC groups (*P*=0.923) (Vidal et al 2011).

McGregor et al (2011) reported that there were no intraoperative complications in either group. Seven SILC patents (64%) and 22 4PLC patients (92%) were available for follow-up at two weeks. Four SILC patients (57%) and five 4PLC patients (23%) experienced no complications at two weeks follow-up (no statistical analyses provided). A number of wound-related complications, gastrointestinal (GI) symptoms, and non-GI symptoms were experienced by SILC and 4PLC patients at two weeks follow-up; however, no statistical analyses for these comparisons were provided (Table 5).

Prasad et al (2011) reported that there were no intraoperative or postoperative complications.

No deaths were reported in any of the non-randomized comparative studies.

Table 5: Complications at 2 weeks follow-up (McGregor et al 2011)

Complication	SILC n (%)	4PLC n (%)	*P*-value
Wound – infection	0 (0)	1 (5)	NR
Wound – bleeding	0 (0)	2 (9)	NR
Wound – scarring	1 (14)	1 (5)	NR
At least one wound not healed	2 (29)	11 (50)	NR
GI symptoms	4 (57)	12 (55)	NR
Non-GI symptoms	3 (43)	8 (36)	NR

4PLC: four-port laparoscopic cholecystectomy
GI: gastrointestinal
NR: not reported
SILC: single-incision laparoscopic cholecystectomy

Efficacy

RCT evidence

Conversion rate

Three RCTs reported on the rate of conversion to other surgical procedures. Cao et al (2011) reported that two SILC patients (3.5%) required conversion, one to 3PLC as a result of a failure in trocar insertion, and the other to open cholecystectomy due to difficulty identifying anatomic landmarks because of dense adhesions. None of the patients in the 3PLC group required conversion to open cholecystectomy (Cao et al 2011). The study by Lai et al (2011) reported that there were no open conversions and no additional ports required in either treatment group. Phillips et al (2011) reported that one SILC patient (0.85%) required conversion to 4PLC; however, no patients required conversion to laparotomy.

Operative time

Operative time was reported in all four RCTs, with two studies reporting a longer operative time in the SILC group (Phillips et al 2011; Tsimoyiannis et al 2010), and two studies reporting no significant difference between the two groups (Cao et al 2011; Lai et al 2011) (Table 6). Cao et al (2011) reported that operative time decreased considerably from 100 minutes for the first SILC to less than 60 minutes after the fifth operation, then stabilized to approximately 50 minutes.

Table 6: Operative time in RCT studies

Study	SILC Operative time (minutes)	3/4PLC Operative time (minutes)	*P*-value
Cao et al (2011)	55.2 ± 12.4	46.3 ± 10.8	0.582
Lai et al (2011)	43.5 ± 15.4	46.5 ± 20.1	0.716
Phillips et al (2011)	57.2	45.2	<0.0001
Tsimoyiannis et al (2010)	49.7 ± 9.0	37.3 ± 9.16	(-18.172 to 6.528)* <0.0001

Data presented as mean ± standard deviation
3PLC: three-port laparoscopic cholecystectomy
4PLC: four-port laparoscopic cholecystectomy
SILC: single-incision laparoscopic cholecystectomy
*95% confidence interval

Blood loss

Operative blood loss was reported in all four RCTs, with no significant differences between treatment groups reported in any of the studies (Table 7).

Table 7: Operative blood loss in RCT studies

Study	SILC Blood loss (mL)	3/4PLC Blood loss (mL)	*P*-value
Cao et al (2011)	14 ± 4.5	12 ± 3.8	0.216
Lai et al (2011)	1 (1-10)*	1 (1-30)*	0.079
Phillips et al (2011)	14.9	14.2	0.80
Tsimoyiannis et al (2010)	9.9 ± 14.4	8.5 ± 6.3	(-5.710 to 8.510)** 0.69

Data presented as mean ± standard deviation
3PLC: three-port laparoscopic cholecystectomy
4PLC: four-port laparoscopic cholecystectomy
SILC: single-incision laparoscopic cholecystectomy
* Data presented as median (range)
**95% confidence interval

Length of hospital stay

Length of hospital stay (LOS) was reported in three of the four RCTs (Cao et al 2011; Lai et al 2011; Tsimoyiannis et al 2010), with no significant differences between treatment groups reported in any of the studies (Table 8).

Table 8: Length of hospital stay in RCT studies

Study	SILC LOS (days)	3/4PLC LOS (days)	*P*-value
Cao et al (2011)	2.1 ± 1.1	2.8 ± 0.8	0.361
Lai et al (2011)	1.5 ± 0.6	1.8 ± 1.2	0.20
Tsimoyiannis et al (2010)	1.25 ± 0.44	1.10 ± 0.44	(-0.135 to 0.435)* 0.29

Data presented as mean ± standard deviation
3PLC: three-port laparoscopic cholecystectomy
4PLC: four-port laparoscopic cholecystectomy
LOS: length of hospital stay
SILC: single-incision laparoscopic cholecystectomy
*95% confidence interval

Postoperative pain

Postoperative pain was assessed in all four RCTs. Cao et al (2011) reported that mean VAS pain scores were not significantly different between the SILC (2.3 ± 0.9) and 3PLC (2.6 ± 1.2) groups (*P*=0.435) on the first postoperative day. Similarly, mean VAS pain scores were not significantly different between the SILC (1.3 ± 0.7) and 3PLC (1.5 ± 0.5) groups (*P*=0.417) on the third postoperative day (Cao et al 2011). The study by Lai et al (2011) reported that median VAS pain scores were not significantly different between the SILC (4.5, range 2-8) and 4PLC (4.0, range 2-7) groups (*P*=0.203) six hours after surgery; however, pain was significantly higher in the SILC group (1, range 0-3) compared with the 4PLC group (0, range 0-2) (*P*=0.048) on the seventh postoperative day (Lai et al 2011). Phillips et al (2011) reported that average VAS pain scores were higher in SILC patients compared with 4PLC patients at 3, 5 and 30 days after surgery; however, no significant differences between the groups were observed at any other time points (Table 9). Similarly, worst VAS pain scores were higher in SILC patients compared with 4PLC patients 3 and 5 days after surgery; however, no significant differences between the groups were observed at any other time points (Phillips et al 2011) (Table 9). Despite the differences in pain scores, no significant differences in pain medication use between the two groups were observed immediately following surgery, or at 1, 3 or 5 days or 1 or 2 weeks after surgery (Phillips et al 2011).

Table 9: Average and worst VAS pain scores after surgery (Phillips et al 2011)

	Average VAS pain scores			**Worst VAS pain scores**		
Time	**SILC**	**4PLC**	***P*-value**	**SILC**	**4PLC**	***P*-value**
Preoperative	2.5	2.5	0.711	3.1	3.3	0.450
Postoperative	4.8	4.5	0.350	6.3	6.4	0.914
Day 1	4.9	4.4	0.120	6.6	6.2	0.123
Day 3	4.0	3.3	0.026	5.4	4.6	0.012
Day 5	3.2	2.5	0.009	4.2	3.5	0.017
Day 7	2.8	2.3	0.066	3.5	2.9	0.090
Day 14	1.6	1.6	0.435	2.0	1.9	0.541
Day 30	1.6	1.3	0.028	1.9	1.5	0.089

Data presented as mean scores from a 10-point Likert scale
4PLC: four-port laparoscopic cholecystectomy
SILC: single-incision laparoscopic cholecystectomy
VAS: visual analog scale

Tsimoyiannis et al (2010) reported that abdominal pain was significantly higher in 4PLC patients compared with SILC patients at 12, 24, 48 and 72 hours after surgery, while shoulder pain was significantly higher in 4PLC patients compared with SILC patients at 6, 24, 48 and 72 hours after surgery (Table 10). The increased postoperative pain observed in 4PLC patients, was reflected in the higher number of analgesic medications requested following surgery. Specifically, 4PLC patients requested significantly more Lonarid at 4, 6, 12, 48 and 72 hours after surgery, and significantly more Ketoprofen at 4, 6, 12 and 24 hours after surgery, compared with SILC patients (Table 11).

Table 10: VAS abdominal and shoulder pain scores after surgery (Tsimoyiannis et al 2010)

	VAS abdominal pain scores			VAS shoulder pain scores		
Time	**SILC**	**4PLC**	**95% CI (*P*-value)**	**SILC**	**4PLC**	**95% CI (*P*-value)**
2 hr	0.75 ± 0.63	0.55 ± 0.51	0.68–0.70 (NS)	1.90 ± 0.78	1.80 ± 0.83	0.40-0.42 (NS)
4 hr	0.75 ± 0.63	0.95 ± 0.75	0.183-0.198 (NS)	2.05 ± 0.68	2.30 ± 0.73	0.47-0.49 (NS)
6 hr	1.00 ± 0.85	1.60 ± 0.88	0.64-0.74 (NS)	3.25 ± 1.07	3.90 ± 0.96	0.23-0.30 (0.026)
12 hr	1.65 ± 0.67	1.80 ± 0.95	0.0001-0.002 (0.001)	2.85 ± 1.08	4.05 ± 0.94	0.33-0.34 (NS)
24 hr	0.50 ± 0.60	1.55 ± 0.94	0.0001-0.0001 (<0.0001)	1.75 ± 0.63	3.40 ± 0.68	0.0001-0.001 (0.001)
48 hr	0.20 ± 0.41	1.35 ± 0.74	0.0001-0.0001 (<0.0001)	0.40 ± 0.59	2.10 ± 0.55	0.0001-0.0001 (<0.0001)
72 hr	0.05 ± 0.22	0.85 ± 0.67	0.0001-0.0001 (<0.0001)	0.10 ± 0.30	1.20 ± 0.61	0.0001-0.0001 (<0.0001)

Data presented as mean ± standard deviation
4PLC: four-port laparoscopic cholecystectomy
CI: confidence interval
NS: not significant
SILC: single-incision laparoscopic cholecystectomy
VAS: visual analog scale

Table 11: Analgesic requests after surgery (Tsimoyiannis et al 2010)

	Number of Lonarid			Number of Ketoprofen		
Time	**SILC**	**4PLC**	**95% CI (*P*-value)**	**SILC**	**4PLC**	**95% CI (*P*-value)**
2 hr	1 (0.05 ± 0.22)	2 (0.10 ± 0.30)	0.12-0.22 (NS)	1 (0.05 ± 0.22)	2 (0.10 ± 0.30)	0.12-0.22 (NS)
4 hr	3 (0.15 ± 0.36)	11 (0.55 ± 0.51)	0.11-0.68 (0.007)	0 (0.00 ± 0.00)	4 (0.20 ± 0.41)	0.01-0.38 (0.036)
6 hr	4 (0.20 ± 0.41)	10 (0.50 ± 0.51)	0.003-0.59 (0.048)	0 (0.00 ± 0.00)	5 (0.25 ± 0.44)	0.04-0.45 (0.016)
12 hr	4 (0.20 ± 0.41)	13 (0.65 ± 0.48)	0.16-0.73 (0.003)	0 (0.00 ± 0.00)	4 (0.20 ± 0.41)	0.01-0.38 (0.036)
24 hr	9 (0.45 ± 0.51)	16 (0.80 ± 0.61)	0.12-0.71 (NS)	0 (0.00 ± 0.00)	4 (0.20 ± 0.41)	0.01-0.38 (0.036)
48 hr	0 (0.00 ± 0.00)	4 (0.20 ± 0.41)	0.14-0.38 (0.036)	0 (0.00 ± 0.00)	0 (0.00 ± 0.00)	0.00-0.00 (NS)
72 hr	0 (0.00 ± 0.00)	5 (0.30 ± 0.47)	0.08-0.51 (0.007)	0 (0.00 ± 0.00)	0 (0.00 ± 0.00)	0.00-0.00 (NS)

Data presented as number of analgesics, mean ± standard deviation
4PLC: four-port laparoscopic cholecystectomy
CI: confidence interval
NS: not significant
SILC: single-incision laparoscopic cholecystectomy

Cosmetic scores

Two RCTs reported on cosmetic scores following surgery (Lai et al 2011; Phillips et al 2011). The study by Lai et al (2011) reported that the median cosmetic score (1 is worst, 10 is best) three months after surgery, as assessed by patients, was significantly higher for SILC patients (7, range 4-8) compared with 4PLC patients (6, range 3-8) (*P*=0.023). Phillips et al (2011) reported that the results of the Body Image Questionnaire demonstrated that SILC (mean score 5.5) was preferred over 4PLC (mean score 5.8) (*P*=0.04) at 2 weeks after surgery; however, no significant differences between the groups were observed at 1 week, 1 month, 3 months or 1 year after

surgery. In addition, Confidence scores and physician-evaluated Modified Hollander scores were not significantly different between the two groups at 1 week, 2 weeks, 1 month, 3 months or 1 year after surgery (Phillips et al 2011). The Photo Series 10-point questionnaire demonstrated that patients in both groups rated their scars quite highly prior to viewing standardized photos at the first evaluation session; however, when self-evaluated scores were adjusted using the standardized photos of 4PLC as an internal control, SILC patients demonstrated higher scores at 1 week, 2 weeks, 1 month, 3 months and 1 year after surgery (Table 12).

Table 12: Cosmesis self-evaluation after surgery (Phillips et al 2011)

Time	SILC Cosmetic score	4PLC Cosmetic score	*P*-value
Prior to viewing photos	8.7	8.1	0.0224
1 week	20.4 ± 3.6	18.6 ± 3.9	0.001
2 weeks	21.4 ± 3.1	18.5 ± 3.9	<0.0001
1 month	21.9 ± 2.8	19.2 ± 3.8	<0.0001
3 months	22.4 ± 2.7	20.0 ± 3.3	<0.0001
1 year	22.3 ± 2.5	19.9 ± 4.1	0.003

Scores are presented as mean ± standard deviation, ranging from 3 (worst) to 24 (best)
4PLC: four-port laparoscopic cholecystectomy
SILC: single-incision laparoscopic cholecystectomy

Quality of life

Only one RCT assessed quality of life following surgery (Phillips et al 2011). This study reported that physical quality of life scores were significantly better for 4PLC patients three days and two weeks after surgery; however, no significant differences between the two groups were observed at any other time points (Table 13). The authors reported that mental quality of life scores were not significantly different between the two groups; however, no data were provided.

Table 13: Physical quality of life* scores after surgery (Phillips et al 2011)

Time	SILC Quality of life score	4PLC Quality of life score	*P*-value
Preoperative	49.1 ± 10.3	50.3 ± 9.1	0.46
Day 1	31.2 ± 9.9	31.9 ± 8.3	0.43
Day 3	37.0 ± 9.2	40.1 ± 8.8	0.02
Day 5	42.1 ± 8.7	44.1 ± 9.1	0.13
1 week	44.7 ± 9.1	47.2 ± 6.8	0.08
2 weeks	51.5 ± 8.3	54.2 ± 6.7	0.03
1 month	48.0 ± 9.8	49.8 ± 7.5	0.46

Scores are presented as mean ± standard deviation
4PLC: four-port laparoscopic cholecystectomy
SILC: single-incision laparoscopic cholecystectomy
*Using Short Form-8 for preoperative through week 1 and Short Form-12 at >1 week

Other efficacy outcomes

Two RCTs reported on length of incision (Cao et al 2011; Lai et al 2011). The study by Cao et al (2011) reported that the incision was significantly shorter in SILC patients (21.6 ± 2.4 mm) compared with 3PLC patients (30.8 ± 2.6 mm) (*P*=0.035). Similarly, Lai et al (2011) reported that

the total wound length was significantly shorter in SILC patients (17.6 ± 2.9 mm) compared with 4PLC patients (22.5 ± 0.5 mm) (*P*=0.001).

Cao et al (2011) reported that all patients in both treatment groups resumed an oral diet within 24 hours of surgery. Lai et al (2011) reported that the time to return to usual physical activity was not significantly different between SILC patients (5.6 ± 1.6 days) and 4PLC patients (5.0 ± 1.6 days) (*P*=0.193).

Non-randomized comparative evidence

Conversion rate

All four comparative studies reported on the rate of conversion to other surgical procedures. Froghi et al (2011) reported that one SILC patient (6.3%) required conversion to 4PLC by placement of an additional abdominal port, due to extensive adhesions and technical difficulties; however, no 4PLC patients were converted to open surgery. McGregor et al (2011) reported that three SILC patients (27.2%) required conversion to 4PLC, due to either poor visibility or unclear anatomy; however, no 4PLC patients were converted to open surgery. Both Prasad et al (2011) and Vidal et al (2011) reported that all surgeries were successfully completed and there were no conversions to other procedures in either treatment group.

Operating time

Operative time was reported in all four comparative studies, with three studies reporting that there was no significant difference between the two treatment groups (Froghi et al 2011; McGregor et al 2011; Vidal et al 2011), and one study reporting that operative time was significantly higher in SILC group compared with the 4PLC group (Prasad et al 2011) (Table 14). Prasad et al (2011) reported that the mean operative time for the first 50 SILC cases (79.2 minutes) was significantly higher when compared to the operative time for the second 50 cases (54.32 minutes) (*P*<0.05).

Table 14: Operative time in comparative studies

Study	SILC Operative time (minutes)	4PLC Operative time (minutes)	*P*-value
Froghi et al (2011)	113.3 ± 33.7	89.29 ± 19.0	0.139
McGregor et al (2011)	86.91 ± 8.97*	79.08 ± 4.24*	0.3108
Prasad et al (2011)	66.76	28.08	<0.05
Vidal et al (2011)	45 (25-95)**	40 (30-70)**	NS

Data presented as mean ± standard deviation
4PLC: four-port laparoscopic cholecystectomy
NS: not significant
SILC: single-incision laparoscopic cholecystectomy
*Data are presented as mean ± standard error of the mean
**Data are presented as median (range)

Length of hospital stay

LOS was reported in three comparative studies, with all three reporting no significant differences between the SILC and 4PLC groups (Froghi et al 2011; McGregor et al 2011; Vidal et al 2011) (Table 15). McGregor et al (2011) reported that there was one readmission in the SILC group due to erythema and pain at the umbilicus, and that this readmission may have skewed the mean LOS for this group.

Table 15: Length of hospital stay in comparative studies

Study	SILC LOS (days)	4PLC LOS (days)	*P*-value
Froghi et al (2011)	1.4 ± 0.4	1.7 ± 0.6	0.573
McGregor et al (2011)	0.97 ± 0.35*	0.86 ± 0.11*	0.4238
Vidal et al (2011)	1 (1-4)**	1 (1-9)**	NS

Data presented as mean ± standard deviation
4PLC: four-port laparoscopic cholecystectomy
LOS: length of hospital stay
NS: not significant
SILC: single-incision laparoscopic cholecystectomy
*Data are presented as mean ± standard error of the mean
**Data are presented as median (range)

Postoperative pain

Three of the four comparative studies reported on postoperative pain (Froghi et al 2011; Prasad et al 2011; Vidal et al 2011). Froghi et al (2011) reported that mean VAS pain scores six hours after surgery were not significantly different in the SILC (4.4 ± 2.3) and 4PLC (5.1 ± 2.7) groups (*P*=0.115). Similarly, mean VAS pain scores 24 hours after surgery were not significantly different in the SILC (2.8 ± 2.1) and 4PLC (3.8 ± 2.0) groups (*P*=1.0) (Froghi et al 2011). At the 2-week and 2-month follow-up telephone interview, patients in both groups reported slight pain at the umbilical incision site (Froghi et al 2011). The study by Prasad et al (2011) reported that mean VAS pain scores eight hours after surgery were not significantly different in the SILC (2.62) and 4PLC (2.78) groups (*P*=0.176). The mean VAS pain score for the first 50 SILC cases (2.84) was significantly higher when compared to the mean pain score for the second 50 cases (2.58) (*P*=0.026) (Prasad et al 2011). Vidal et al (2011) reported that the median VAS pain score one day after surgery was not significantly different in the SILC group (3, range 1-5) compared with the 4PLC group (4, range 1-8) (*P*=0.311).

Other efficacy outcomes

The study by McGregor et al (2011) reported that the total incision size was significantly shorter in the SILC group (13.64 ± 1.26 mm) compared with the 4PLC group (33.0 ± 1.29 mm) (*P*<0.0001).

Two studies compared the surgical stress response in SILC and 4PLC patients by measuring biochemical stress markers including IL-6, TNF-α, CRP, and WCC, six and 24 hours after surgery (Froghi et al 2011; McGregor et al 2011). Froghi et al (2011) reported that serum IL-6, TNF-α, CRP, and WCC levels were not significantly different in the SILC and 4PLC groups at baseline and at six and 24 hours after surgery (*P*>0.05 for all). Similarly, McGregor et al (2011) reported that serum IL-6 and CRP levels were not significantly different in the SILC and 4PLC groups at baseline and at six hours after surgery (*P*>0.05 for all).

Vidal et al (2011) reported that 120 SILC patients (100%) resumed oral intake within the first 24 hours after surgery, compared with 119 4PLC patients (99%) (*P*>0.05).

Cost impact

Two studies were identified that compared the cost of SILC to that of 4PLC (Love et al 2011; Chandler and Danielson 2011).

Love et al (2011) performed a retrospective cost comparison of SILC and 4PLC undertaken in a single institution by a single surgeon. The study took place over a period of 19 months and included 116 cases of minimally invasive cholecystectomy (48 4PLC cases undertaken during the first half of the study period and 68 SILC cases undertaken during the second half of the study period). A total of nine (13.2%) SILC procedures were converted to 4PLC. The analysis considered total operating room (OR) cost (actual cost to the hospital for equipment, time and personnel), total OR charges (OR cost plus a margin to cover overheads), total hospital charges (OR charges plus hospital charges accrued in the perioperative period) and total payments (total amount received by the hospital on patients' bills). This study demonstrated that when all attempted SILC procedures, including converted procedures, were compared with 4PLC procedures, no significant difference in the cost category totals of SILC and 4PLC were observed (Table 16). However, SILC procedures that required conversion were significantly more costly than completed SILC procedures and 4PLC procedures. Of interest, the 68 patients who underwent SILC represented the surgeon's first experience with the technique. In the six months following study completion, the conversion rate fell to 3%, suggesting that the learning curve is likely to impact on the costs associated with SILC.

Table 16: Cost comparison of SILC and 4PLC (Love et al 2011)

Study	**SILC ($USD)**	**4PLC ($USD)**	***P*-value**
Total OR cost	2,109.10 ± 87.83	2,068.70 ± 76.77	0.74
Total OR charges	9,402.00 ± 214.23	8,961.50 ± 336.65	0.25
Total hospital charges	14,459.00 ± 528.00	15,412.00 ± 1,095.00	0.39
Total payments	5,601.70 ± 595.99	6,402.80 ± 593.86	0.36

Data presented as mean ± standard deviation
4PLC: four-port laparoscopic cholecystectomy
OR: operating room
SILC: single-incision laparoscopic cholecystectomy
USD: US dollars

The study by Chandler and Danielson (2011) performed a retrospective review of pediatric LC procedures completed between January 2009 and October 2010. A total of 69 LC procedures, including 42 SILC procedures and 27 4PLC procedures, were undertaken during this period. No significant differences in operative time, LOS or the number of doses of intravenous analgesia between the two groups were reported.The average operative costs, including operative supplies, operating room services, pathologic evaluation, and anesthesia services, were assessed for both groups. This study showed that the average cost for patients undergoing SILC ($USD 7,766) was not significantly different to the average cost for patients undergoing 4PLC ($USD 8,382) (*P*=0.26).

Clinical practice guidelines and consensus statements

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) have developed guidelines for the clinical application of laparoscopic biliary tract surgery (SAGES 2010). Within these guidelines, the following recommendations relate specifically to SILC:

- The indications, contra-indications and preoperative preparation for reduced port and single incision approaches are the same as those for multi port cholecystectomy.
- Access to the abdominal cavity in reduced port and single incision approaches should follow accepted standards for safe entry including avoidance and recognition of complications.
- Introduction of new instruments, access devices or new techniques should be done with caution and/or under study protocol, and, prior to the addition of any new instrument or device, it should, to the extent possible, be proven safe, and not limit adherence to established guidelines for safe performance of laparoscopic cholecystectomy.
- During initial procedures, a low threshold for using additional port sites should be maintained so as to not jeopardize a safe dissection and result.

Training and education impact

The United Kingdom (UK) National Institute for Health and Clinical Excellence (NICE) has published a clinical guidance document on SILC (NICE 2010). This guidance suggests that the procedure should only be undertaken with special arrangements for clinical governance, consent and audit or research. Specifically, it is recommended that clinicians wishing to perform SILC ensure that patients and their carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information (NICE 2010). In addition, it is suggested that clinicians audit and review the clinical outcomes of all patients undergoing SILC. Finally, as SILC is a technically challenging technique, it is recommended that it should only be carried out by experienced laparoscopic surgeons who have received specific training in the procedure (NICE 2010).

A study by Khandelwal et al (2011) described the development of a training paradigm for SILS. This program was comprised of a number of components, including attendance at a formal course (didactic lectures and observation of live cases in humans), development of a simulation model (a SILS simulator based on the 'Fundamentals of Laparoscopic Surgery' training program), and animal laboratory training (live nonsurvival porcine models). Graduated clinical adoption of the technique followed, initially involving the selection of patients who were expected to be simpler. The surgeon started with a standard LC technique which was gradually modified through the progressive elimination of ports and the introduction of new retraction techniques, while applying a low threshold for conversion. Following this training program, the analysis of the first human cases performed by trainees demonstrated that four of 19 (21%) SILC operations required conversion to standard laparoscopy or open surgery, with one patient sustaining a common bile duct injury following conversion to open cholecystectomy. The authors concluded that, due to the difficulty of the SILS technique, extensive preclinical training and participation in a formal training course are recommended, in addition to graduated, careful clinical adoption of the procedure. It is

also important that early postoperative outcomes are assessed and compared with historical controls (Khandelwal et al 2011).

Summary

Gallstones can form when certain substances in the bile are present in concentrations that approach the limits of solubility. Asymptomatic gallstones are usually managed expectantly, while cholecystectomy is the primary treatment for symptomatic gallstones. LC is the gold standard procedure for cholecystectomy; however, several minimally invasive surgical techniques have been developed to reduce the number and size of the incisions used during LC, with the aim of reducing postoperative pain and recovery time and improving cosmetic outcomes. One such technique is SILC, which involves the introduction of laparoscopic instruments via the umbilicus. Several FDA-approved single-port access systems have been developed for use during SILC.

Eight studies (four RCTs and four non-randomized comparative studies) detailed in this report compared the safety and effectiveness of SILC and 3/4PLC.

- Safety outcomes were reported in all eight studies. The rate of complications was generally low, and appeared similar in both treatment groups. One study reported that the rate of wound-related complications was significantly higher following SILC compared with 4PLC. Another study reported that the rate of incisional hernia was significantly higher following 4PLC compared with SILC at 24 months follow-up. No deaths were reported in any studies.
- The rate of conversion of SILC to either 3/4PLC or open cholecystectomy was low, and no conversions of 3/4PLC to open cholecystectomy were reported in any studies. Three studies reported that operative time was significantly longer during SILC compared with 4PLC, while five studies reported that it did not differ significantly between the two groups. Blood loss and LOS did not differ significantly between the treatment groups in any of the studies that reported these outcomes. Postoperative pain was significantly higher following SILC in two studies, significantly higher following 4PLC in one study, and did not differ significantly between the two groups in four studies. Cosmetic scores were significantly better following SILC compared with 4PLC in both of the studies that reported this outcome.

The ability to draw firm conclusions was limited by the fact that not all outcomes were reported in all studies, as well as by the fact that outcomes of interest were measured using different instruments across studies. Patient reported outcomes including cosmetic scores and quality of life were only reported in two of the eight studies. This is particularly important as the main potential advantage of the SILC procedure for patients is improved cosmetic outcome. In addition, none of the studies in the report were able to assess the long-term safety and efficacy of the SILC procedure, as the length of follow-up was limited to three months or less in the majority of studies.

Recommendations

Based on the comparative evidence presented in this report, SILC appears to be as safe and effective as traditional LC. Although SILC produces better cosmetic outcomes, additional long-term data from good quality RCTs are required in order to confirm the safety and efficacy of the procedure. The costs associated with SILC and traditional LC procedures appear similar, although this is based on limited evidence. Importantly, considerable theoretical and practical training is recommended for any surgeon wishing to add SILC to their repertoire. Ultimately, the decision as to whether to perform SILC or traditional LC will be dependent on the preferences of individual surgeons and patients.

References

Adachi T, Okamoto T, Ono S, Kanematsu T, Kuroki T. Technical Progress in Single-Incision Laparoscopic Cholecystectomy in Our Initial Experience. *Minimally Invasive Surgery* 2011; [Epub ahead of print].

Antoniou SA, Pointner R, Granderath FA. Single-incision laparoscopic cholecystectomy: a systematic review. *Surgical Endoscopy* 2011; 25(2): 367-377.

Bresadola F, Pasqualucci A, Donini A, Chiarandini P, Anania G, Terrosu G, Sistu MA, Pasetto A. Elective transumbilical compared with standard laparoscopic cholecystectomy. *European Journal of Surgery* 1999; 165(1): 29-34.

Cao ZG, Cai W, Qin MF, Zhao HZ, Yue P, Li Y. Randomized Clinical Trial of Single-incision Versus Conventional Laparoscopic Cholecystectomy: Short-term Operative Outcomes. *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques* 2011; 21(5): 311-313.

Chamberlain RS, Sakpal SV. A comprehensive review of single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES) techniques for cholecystectomy. *Journal of Gastrointestinal Surgery* 2009; 13(9): 1733-1740.

Chandler NM, Danielson PD. Single-incision laparoscopic cholecystectomy in children: a retrospective comparison with traditional laparoscopic cholecystectomy. *Journal of Pediatric Surgery* 2011; 46(9): 1695-1699.

ClinicalTrials.gov 2012. http://clinicaltrials.gov/ [Accessed February 2012].

Ersin S, Firat O, Sozbilen M. Single-incision laparoscopic cholecystectomy: is it more than a challenge? *Surgical Endoscopy* 2010; 24(1): 68-71.

Food and Drug Administration (FDA) 2012. Medical Devices. Last Updated 2012. http://www.fda.gov/MedicalDevices/default.htm [Accessed February 2012].

Froghi F, Sodergren MK, Wright VJ, Coomber R, Courtney AP, Darzi A, Paraskeva P. Single-Center Experience in Systemic Stress and Short-Term Morbidity of Single-Incision Cholecystectomy. *Surgical Innovation* 2011; [Epub ahead of print].

Heuman DM, Mihas AA, Allen J, Cuschieri A. Cholelithiasis. eMedicine Last Updated 2011. http://emedicine.medscape.com/article/175667-overview [Accessed February 2012].

Hodgett SE, Hernandez JM, Morton CA, Ross SB, Albrink M, Rosemurgy AS. Laparoendoscopic single site (LESS) cholecystectomy. *Journal of Gastrointestinal Surgery* 2009; 13(2): 188-192.

Keus F, Gooszen HG, Van Laarhoven CJ. Systematic review: open, small-incision or laparoscopic cholecystectomy for symptomatic cholecystolithiasis. *Alimentary Pharmacology and Therapeutics* 2009; 29(4): 359-378.

Keus F, de Jong J, Gooszen HG, van Laarhoven CHJM. Laparoscopic versus small-incision cholecystectomy for patients with symptomatic cholecystolithiasis. Cochrane Database of Systematic Reviews 2006; Issue 4. Art. No.: CD006229. DOI: 10.1002/14651858.CD006229.

Khandelwal S, Wright AS, Figueredo E, Pellegrini CA, Oelschlager BK. Single-Incision Laparoscopy: Training, Techniques, and Safe Introduction to Clinical Practice. *Journal of Laparoendoscopic and Advanced Surgical Techniques* 2011; 21(8): 687-693.

Lai ECH, Yang GPC, Tang CN, Yih PCL, Chan OCY, Li MKW. Prospective randomized comparative study of single incision laparoscopic cholecystectomy versus conventional four-port laparoscopic cholecystectomy. *The American Journal of Surgery* 2011; 202(3): 254-258.

Lee SK, Kim MH. Updates in the treatment of gallstones. *Expert Review of Gastroenterology and Hepatology* 2009; 3(6): 649-660.

Leuschner U. Oral bile acid treatment of biliary cholesterol stones. *Recenti Progressi in Medicina* 1992; 83(7-8): 392-399.

Love KM, Durham CA, Meara MP, Mays AC, Bower CE. Single-incision laparoscopic cholecystectomy: a cost comparison. *Surgical Endoscopy* 2011; 25(5): 1553-1558.

Marescaux J, Dallemagne B, Perretta S, Wattiez A, Mutter D, Coumaros D. Surgery without scars: report of transluminal cholecystectomy in a human being. *Archives of Surgery* 2007; 142(9): 823-826.

McAneny D. Open cholecystectomy. *Surgical Clinics of North America* 2008; 88(6): 1273-1294.

McGregor CGC, Sodergren MH, Aslanyan A, Wright VJ, Purkayastha S, Darzi A, Paraskeva P. Evaluating Systemic Stress Response in Single Port vs. Multi-Port Laparoscopic Cholecystectomy. *Journal of Gastrointestinal Surgery* 2011; 15(4): 614-622.

Moriera-Pinto J, Lima E, Correia-Pinto J, Rolanda C. Natural orifice transluminal endoscopy surgery: a review. *World Journal of Gastroenterology* 2011; 17(33): 3795-3801.

National Institute for Health and Clinical Excellence (NICE). Single-incision laparoscopic cholecystectomy (Interventional procedure guidance 346), May 2010. http://www.nice.org.uk/nicemedia/live/12237/48780/48780.pdf [Accessed February 2012].

Navarra G, Pozza E, Occhionorelli S, Carcoforo P, Donini I. One-wound laparoscopic cholecystectomy. *British Journal of Surgery* 1997; 84(5): 695.

Phillips MS, Marks JM, Roberts K, Tacchino R, Onders R, DeNoto G, Rivas H, Islam A, Soper N, Gecelter G, Rubach E, Paraskeva P, Shah S. Intermediate results of a prospective randomized controlled trial of traditional four-port laparoscopic cholecystectomy versus single-incision laparoscopic cholecystectomy. *Surgical Endoscopy* 2011; [Epub ahead of print].

Piskun G, Rajpal S. Transumbilical laparoscopic cholecystectomy utilizes no incisions outside the umbilicus. *Journal of Laparoendoscopic and Advanced Surgical Techniques A* 1999; 9(4): 361-364.

Portincasa P, Di Ciaula A, Wang HH, Moschetta A, Wang DQ. Medicinal treatments of cholesterol gallstones: old, current and new perspectives. *Current Medicinal Chemistry* 2009; 16(12): 1531-1542.

Prasad A, Mukherjee KA, Kaul S, Kaur M. Postoperative pain after cholecystectomy: Conventional laparoscopy versus single-incision laparoscopic surgery. *Journal of Minimal Access Surgery* 2011; 7(1): 24-27.

Russo MW, Wei JT, Thiny MT, Gangarosa LM, Brown A, Ringel Y, Shaheen NJ, Sandler RS. Digestive and liver diseases statistics, 2004. *Gastroenterology* 2004; 126(5): 1448-1453.

SAGES: SAGES Guidelines for the Clinical Application of Laparoscopic Biliary Tract Surgery. January 2010. http://www.sages.org/publication/id/06/ [Accessed February 2012].

Shaffer EA. Epidemiology and risk factors for gallstone disease: has the paradigm changed in the 21st century? *Current Gastroenterology Reports* 2005; 7(2): 132-140.

Shaffer EA. Cholelithiasis. The Merck Manual for Healthcare Professionals. Last Updated 2007. http://www.merck.com/mmpe/sec03/ch030/ch030b.html [Accessed February 2011].

Stokes CS, Krawczyk M, Lammert F. Gallstones: environment, lifestyle and genes. *Digestive Diseases* 2011; 29(2): 191-201.

Thakur V, Schlachta CM, Jayaraman S. Minilaparoscopic versus conventional laparoscopic cholecystectomy: a systematic review and meta-analysis. *Annals of Surgery* 2011; 253(2): 244-258.

Tsimoyiannis EC, Tsimogiannis KE, Pappas-Gogos G, Farantos C, Benetatos N, Mavridou P, Manataki A. Different pain scores in single transumbilical incision laparoscopic cholecystectomy versus classic laparoscopic cholecystectomy: a randomized controlled trial. *Surgical Endoscopy* 2010; 24(8): 1842-1848.

Vidal O, Valentini M, Ginesta C, Espert JJ, Martinez A, Benarroch G, Anglada MT, Garcia-Valdecasas JC. Single-Incision Versus Standard Laparoscopic Cholecystectomy: Comparison of Surgical Outcomes from a Single Institution. *Journal of Laparoendoscopic and Advanced Surgical Techniques* 2011; 21(8): 683-686.

Visser BC, Parks RW, Garden OJ. Open cholecystectomy in the laparoendoscopic era. *American Journal of Surgery* 2008; 195(1): 108-114.

Appendix A

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.