New Technologies

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The evolution towards mini-invasiveness in surgery has opened new strategies in the way of performing laparoscopic cholecystectomy (LC), which have recently gained attention. Cholecystectomy has often been the field for the initial application of new technologies, since it remains the most common operation in abdominal surgery, mostly performed in the elective setting. Still, even if nowadays laparoscopic cholecystectomy is considered the "gold standard" since 1992, its indubitable advantages are still burdened by a slight but significant rise in the rate of major biliary injuries, which is certified around 0.42 % [1], which consists of a two- to fourfold rise in the rate reported in the literature for open cholecystectomy. Major concerns regarding the widespread of new technologies in LC should consider these data, and the university, the scientific societies, and the health providers

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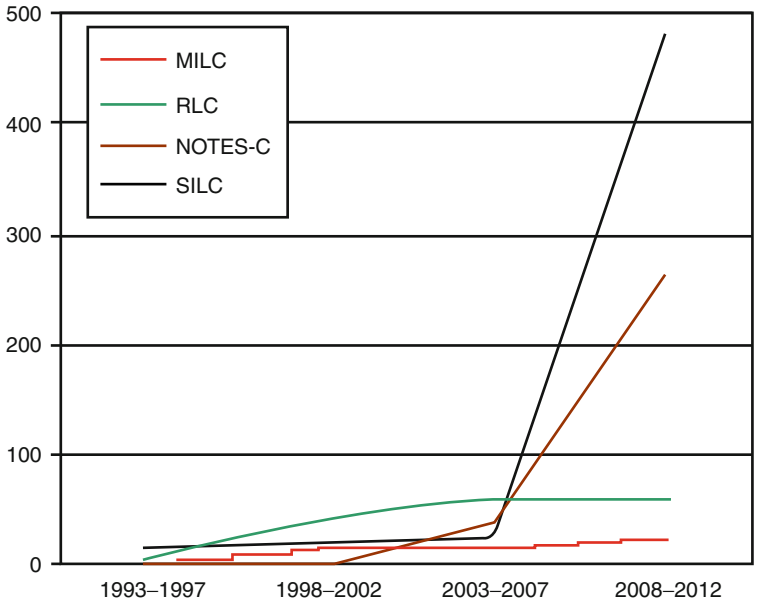

Fig. 8.1 Number of articles retrieved in PubMed concerning the new technologies for laparoscopic cholecystectomy

should ascertain the safety issues before considering a new surgical operation to be done outside clinical trials. This concept has not always been fulfilled, and some of the operations that we consider in this chapter have gained spread between surgeons, mostly due to a strong pressure by the industry of new surgical devices and instruments [2]. Also, reports on cost-effectiveness should be part of a surgical health policy, and the relatively few papers and health technology assessment reports on the subject are not the most cited references when analyzing a new technology [3].

We have taken into consideration four alternatives to standard 4-port LC, one strictly regarding the technological aspect (robotics) and three other aspects focused on reduced port surgery (mini-laparoscopy, single-access laparoscopy, and surgery through natural orifices). A literature search has been done in PubMed, Cochrane Library and Tripdatabase starting from 1994 through March 2013 and the papers have been classified for evidence strength following the Oxford CEBM 2011 scheme. The results in terms of quantity of studies published in PubMed are summarized in Fig. 8.1; the major interest in single-incision access for cholecystectomy is directly followed by studies in the field of natural orifice surgery, where the curves are still in the rising area, while the number of articles concerning mini-laparoscopy and robotics is slowly growing, but their number is far lower than the former.

8.1 Robotic Laparoscopic Cholecystectomy (RLC)

The question if a robotic assistant (RLC) could ameliorate the standard 4-port laparoscopic cholecystectomy (LC) has been highlighted by a recent meta-analysis of randomized controlled trials, where the authors put together both "camera only robotic assistants" (EndoAssist, Aesop, Passist) and fully robotic remote systems (Zeus, da Vinci). A detailed and systematic review of the literature revealed that there were six randomized clinical trials including 560 patients. One trial involving 129 patients did not state the number of patients randomized to the two groups. Of the remaining 431 patients in the remaining five trials, 212 patients underwent laparoscopic cholecystectomy with the help of robot assistant, and 219 patients underwent the same procedure with the help of a human assistant. All the trials were at high risk of bias and errors due to play of chance. Mortality and surgical complications were reported in only one trial with 40 patients. There was no mortality or surgical complications in either group in this trial. Mortality and morbidity were not reported in the remaining trials. Quality of life or the proportion of patients who were discharged as day-patient laparoscopic cholecystectomy patients were not reported in any trial. There was no significant difference in the proportion of patients who underwent conversion to open cholecystectomy or in the operating time between the two groups. Since the presumed lowering of errors due to a robotic assistant was not demonstrated, we can state that no significant advantage comes from a RLC over standard LC [4] (LE2).

The main drawback of advanced robotic surgery is the associated cost. Obviously, from the perspective of the cost requirements, an investment in this technology can only be justified if the costs are reasonable and a significant benefit is demonstrated regarding patient outcome. A prospective case-matched study was conducted on 50 consecutive patients, who underwent RLC (da Vinci robot, Intuitive Surgical) between December 2004 and February 2006. These patients were matched 1:1–50 patients with conventional laparoscopic cholecystectomy, according to age, gender, American Society of Anesthesiologists score, histology, and surgical experience. End points were complications after surgery, conversion rates, operative time, and hospital costs. No minor, but 1 major complication occurred in each group (2 %). No conversion to open surgery was needed in either group. Operation time (skin to skin, 55 min vs. 50 min, $p = 0.85$) and hospital stay (2.6 days vs. 2.8 days) were similar. Overall hospital costs were significantly higher for robotic-assisted cholecystectomy $7,985.4 (SD 1,760.9) versus $6,255.3 (SD 1,956.4), $p < 0.001$, with a raw difference of $1,730.1(95 % CI 991.4 –2,468.7) and a difference adjusted for confounders of $1,606.4 (95 % CI 1,076.7–2,136.2). This difference was mainly related to the amortization and consumables of the robotic system. In conclusion, RLC showed no benefits in clinical outcome over LC. The costs for RLC were significantly higher than for LC because of extensive expenses for the robotic system itself and its consumables and is, therefore, not justifiable [5] (LE3).

The role of RLC as a start-up for more difficult tasks in robotics was studied by Jayaraman et al. [6]. There were 16 procedures in the robotic arm and 20 in the laparoscopic arm. Two complications (da Vinci port-site hernia, transient elevation

of liver enzymes) occurred in the robotic arm, whereas only one laparoscopic patient (slow to awaken from anesthetic) experienced a complication. None was significant. The mean time required to perform robotic cholecystectomy was significantly longer than laparoscopic surgery (91 vs. 41 min, $p<0.001$). The mean time to clear the operating room was significantly longer for robotic procedures (14 vs. 11 min, $p=0.015$). They observed a trend showing longer mean anesthesia time for robotic procedures (23 vs.15 min). Regarding learning curve, the mean operative time needed for the first 3 robotic procedures was longer than for the last 3 (101 v. 80 min); however, this difference was not significant. They concluded that RLC can be performed reliably, but, owing to the significant increase in operating room resources, it cannot be justified for routine use. Their experience, however, was far to demonstrate that RLC is one means by which general surgeons may gain confidence in performing advanced robotic procedures (LE3).

Vidovszky et al. [7] investigated the learning curve of the procedure. Interestingly, they did not experience a significant change in robotic operative time, changing from 38.2 ± 22.9 min for the first 16 cases (stage 1) to 32.5 ± 12.7 min for the last 16 cases (stage 3). These data suggested that the learning curve to master the robotic technique is short for a relatively simple procedure, such as cholecystectomy. The total robotic operative time was influenced primarily by the difficulty of the dissection, which varied from patient to patient. They found, however, that the total operating time ("skin to skin") improved from their initial 16 cases (85.6 ± 25.7 min) to the final 16 cases (68.2 ± 17.1 min), but this improvement represented primarily the improvement in setup time(LE4).

All the robotic trials available in literature have been performed in elective, non-inflamed cases: the role of RLC in acute cholecystitis is still to be studied.

Single-site surgery might reveal as a fascinating application for robotics: in fact the technical possibilities might bypass the limitations of a single-entry site. Since Desai's first operation in cadavers [8], Intuitive Surgical International (Sunnyvale, CA, USA) has developed a single-site platform for the da Vinci robot in 2010 [9]. Technical problems are still present, but studies have established its feasibility in urology, gynecology, and digestive surgery [10] (LE2).

The largest series about single-site robot-assisted laparoscopic cholecystectomy (SSRLC) was published by Pietrabissa et al. [11]. The primary goal of the study from an efficacy standpoint was completion of the procedure without conversion. The primary goal in terms of safety was freedom from major adverse events such as serious intraoperative injury or death. Other goals and focal points included measuring the times required to complete the procedure and analyzing the effect of the learning curve on the different recorded times. In addition to collecting data about the procedure, at the completion of the study, an 11-item questionnaire was administered to each of the 5 operating surgeons to gather their technical and clinical opinions about robotic single-site technology. Two patients underwent conversion. No major intraoperative complications occurred, but there were 12 minor incidents (7 ruptures of the gallbladder and 5 cases of minor bleeding from the gallbladder bed). Mean total operative time was 71 (±19) min, with a mean console time of 32 (±13) min. No significant reduction in the operative times was observed with

the increasing of each surgeon's experience. The technique was judged more complex than standard 4-port laparoscopy but easier than single-incision laparoscopy as the robotic view, exchange of left-right hands, and triangulation allow an operation more comparable to standard LC(LE 4).

A reduction in the SSRLC operative time has been demonstrated in more recent case–control studies but still not comparable to standard LC times, due to docking and robot assembly [12, 13] (LE3).

Future implications of research should better study the role of RLC in the setting of costs, while randomized controlled trials to compare SSRLC to LC are awaited in order to establish a role for this procedure in selected patients especially in those centers where robotic surgery is routinely performed and that carry a great expertise.

8.2 Mini-Laparoscopic Cholecystectomy (MILC)

Mini-laparoscopic cholecystectomy (MILC) is a safe and technically feasible procedure for the treatment of gallstone disease and an alternative to single-port surgery (SPS). LC made through reduced 2- to 5-mm ports has gained a wide attention at the end of 1990s and at the beginning of 2000, as soon as the industries put new instruments in commerce especially for 2–5-mm trocars, including devices like scissors, forceps, and clip appliers. The three 5-mm trocar MLC allows the same surgical procedures to be undertaken as for the conventional approach.

The main goal was to achieve, with the use of reduced ports, less pain and a better cosmesis while keeping the same standards of work as in standard LC. It has regained attention after the onset of SILC, which carries the same goals in reducing mini-invasiveness, as an alternative method [14]. To this regard, in a meta-analysis of MILC versus LC, mini-laparoscopic cholecystectomy without intraoperative cholangiography (IOC) was successfully performed in a number of studies using a combination of three 3-mm ports with either 10-mm or 12-mm ports in study populations with variable exclusion criteria (LE2). Consistently with these observations, McCormack et al. successfully performed MILC with routine IOC using one 5-mm and three 3-mm ports in 89 % of consecutive elective cases of cholecystectomy, eliminating the likelihood of selection bias and demonstrating that IOC can be sufficiently performed as an adjuvant to the MILC technique when deemed appropriate based on surgeon judgment or preference. Most of the cases are described as using the standard trocar positions and keeping the larger trocar at the umbilical level (which serves for the extraction): the combinations in the articles retrieved vary from 3 to 4 trocars and various combinations of 2-, 3-, and 5-mm trocars, 5–10-mm cameras, and so on. Indeed a standardization of MILC has not yet been reached. A recent Cochrane review [15] (LE1) summarizes 13 RCTs comparing MILC to LC and finds a high rate of success (87 %). Pain was significantly lower in MILC and there was a better cosmetic satisfaction. Alas, the analyzed RCTs lack primary information on safety issues and are all at high risk of bias (incomplete blinding, outcome data and selective reporting). So, although morbidity and mortality are not significantly different in the two arms, its application outside selected trials is not

recommended. Some criteria for selection of the patients and costs are eligible from the largest case series on MILC on 932 patients [16] (LE4); most patients reduced the operative trocar from 10/12 to 5 mm and the umbilical trocar to 5 mm, such as to have a 5-mm 3-port LC. A selection of 45 patients (elective cases, women with a low BMI) have undergone a 3-mm 3-port LC, and the fragility of instruments is enhanced as a costly issue.

From a financial perspective, previous studies [14] showed that there was no cost difference associated with the use of 3-mm ports and other MILC instruments compared to conventional instrumentation based on our accounting and cost allocation records. Further advantages of the proposed technique consist of cosmesis and also in a decrease of operative trauma. The latter might result in a reduced incidence of incisional hernias and possible complications (hemorrhages) at the site of trocars' insertion.

Lately, MILC has regained interest in the literature, as a possible alternative to single-incision technique, which is associated with loss of triangulation and decreased maneuverability, making the procedure technically demanding [17]; future randomized trials are welcome for a comparison of outcomes between the two methods.

The lack of standardization of the technique (how many 5-mm or 3-mm ports) is still a concern and further studies should aim at standardizing the operation. On the basis of the literature data, an all three 5-mm trocar MLC is feasible, effective, and easy to perform (without any increase in technical difficulties). The technique provides acceptable and comparable results concerning the operative time, the postoperative morbidity, and hospitalization as those already reported for conventional laparoscopy. Instead, the 3-mm MLC should only be considered in a small group of selected patients (young, thin, scheduled) and mainly for cosmetic reason. Sparing patients a wider skin incision at the trocar sites might reduce postoperative pain, increase prompt recovery of gastrointestinal functions, shorten hospitalization, help contain health-care costs, and increase cosmesis [18]. Still these benefits are not considered as primary without a strong information on its safety and clinical and economic benefits. This would also permit a more precise calculation of the costs of MILC and of the instruments required. The selection of a subgroup of patients which would mostly benefit from this approach is also an important issue to be studied in future trials.

8.3 Single-Incision Laparoscopic Cholecystectomy (SILC)

Single-incision laparoscopic surgery (SILS) is so called as it reduces to one skin incision the entry port to the abdomen. SILS is a step forward in the direction of mini-invasive surgery, and in recent years, its efficacy and security have been proved in operations on humans. The most "surgical" alternative to NOTES has started in 1997 [19] but had a boost starting from 2008 to 2010, together with the commercialization of new port devices, which allowed to solve the main problems of the single access: the creation of a stable transabdominal platform and the triangulation of instruments in the operating field. New articulated or curved instruments and new

access devices were created in order to perform LC with the instruments passing through a single incision (or, in the beginning, multiple contiguous incisions) generally placed in the umbilicus. The umbilicus is the most used access point in this kind of surgery, because of the presence of a natural scar, which makes the procedure virtually scarless. Cholecystectomy, as it is the most frequent elective operation in surgery, was the mainstay of the technique, which has nowadays interested many surgical operations. There is a lot of literature on this subject, and it's the only new technology which has clinical guidelines [20] and a health technology assessment [21] written back in 2010. Then, the evidence was low and the advisors' committee suggested its use only in controlled clinical trials and by experienced laparoscopic surgeons who had received specific training in the procedure. Since then numerous randomized controlled trials have been conducted, and at least 5 meta-analyses of RCTs have been written in 2012 comparing SILC to LC and collecting 200–400 patients per arm [22–26] (LE1). The only ascertained significance, in accordance to all the studies, regards the time required to perform an SILC, which always results significantly longer with a weighted mean difference of 9–17 min. This parameter is often used as an index of an increased difficulty of the procedure, and its stabilization serves as a proxy to determine the learning curve: a pilot study from China [27] done by a single experienced surgeon showed a normalization of the operating time after 20 procedures (LE4), and another study from the USA evidenced the cutoff after 10 procedures [28] (LE4). Another claim of SILC was a better perceived cosmesis: the results of the meta-analyses seem to confirm it, but the evaluation scales and times were very heterogeneous in the analyzed trials, thus requiring confirmation in future studies. Another hope of the surgeons was a lowering of the postoperative pain in SILC, but no significant difference has ever been evidenced in the cited reviews. An interesting survey [29] (LE 4) asked 281 young women about their laparoscopic cholecystectomy (done in the previous 2 years); fewer than 50 % of patients recalled the number of incisions they had, and the more painful site was reported to be the umbilical incision by 2/3 of the patients. This puts some questions concerning the hypotheses of SILC benefits. The two operations have also no statistical differences regarding hospital stay or return to normal activity, morbidity, incisional hernias, or conversion to open surgery. The RCTs did not, alas, have the appropriate power to investigate differences in complications, as biliary injuries (which are the most feared and serious adverse effects of cholecystectomy) have very low rates in LC (0.4 %) [1]. A systematic review has been dedicated specifically to the calculation of bile duct injuries in a pool of 2,626 patients from 45 different studies [30] (LE2) and found a 0.72 % rate, significantly higher than LC. We concern, although, that the majority of the case series comprehended the learning curves. More definite data are awaited from large multicentric randomized trials, like the European MUSIC (MUlti-port vs. Single-port Cholecystectomy – http://music.world.it/). The costs of SILC can be higher and are especially related to single-port devices and operating room subcharges [31] (LE 2) by means of 2,000 $ (on 79 pts), even if this data is not confirmed by lower evidence studies [32] (LE 3). Costs might be reduced with the use of "home-made" devices for single-port entry [33] (LE 4), like the glove port, as shown in Fig. 8.2.

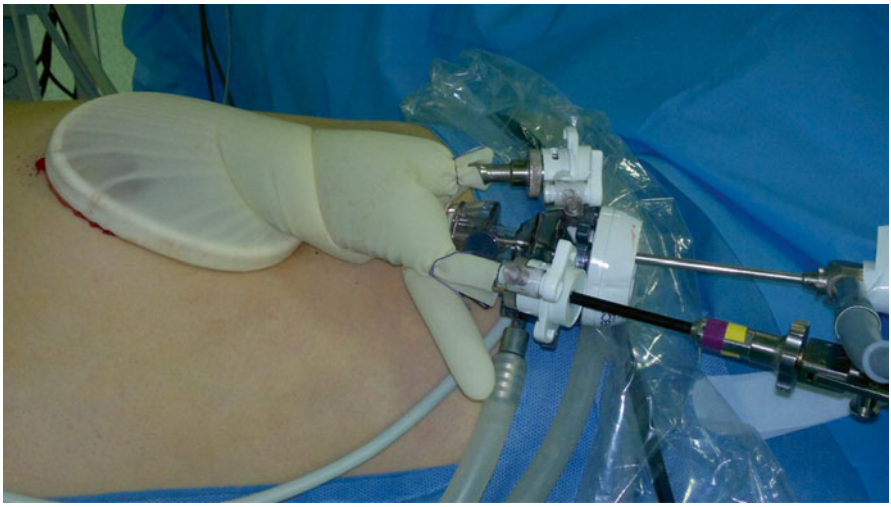

Fig. 8.2 Glove port for single-site surgery

Implications for research will need to focus on standardized and well-designed RCTs, in order to assess any advantage in terms of quality of life and cosmesis, which seem to be the only real advantages of SILC in order to select patients who would benefit from it.

8.4 Natural Orifice Cholecystectomy (NOTES-C)

The concept of access to the abdominal cavity by entering through natural orifices has been called to the attention of the surgical community since the first reported clinical cases in 2007 but has been conceived since 2004 in animal studies by Kalloo in 2004 in his report of peritoneoscopy and transgastric liver biopsy in a porcine model [34]. That same year, Rao and Reddy simultaneously performed peritoneoscopies and genital organ procedures using flexible endoscopes introduced perorally and in 2007 reported the first transgastric human appendectomy, which generated widespread interest in clinical applications of NOTES [35]. As for transgastric cholecystectomy, it was also in 2005 that Swanstrom's and Parks' teams successfully performed transgastric cholecystectomy and cholecystogastrostomy using flexible endoscopes in the animal model [36, 37]. Two years went by before any interest in clinical applications arose, and it was thanks to the use of the transvaginal route. The clinical transvaginal approach for NOTES was not preceded by extensive animal experimentation, since the accessibility and safety of this access route had been proven through the use of culdoscopy in gynecology and of the vaginal route to extract surgical specimens [38]. In early March 2007, Zorron's team performed the first series of transvaginal NOTES cholecystectomies in four patients, based on the previous experimental trials [39]. A short time later, Bessler successfully performed

a hybrid transvaginal cholecystectomy with three abdominal laparoscopic entry ports [40], and in April 2007, Marescaux performed the purest NOTES cholecystectomy in a patient using a single abdominal entry port [41]. Since then clinical series of NOTES-C in humans have been published, although two distinct paradigms can be distinguished: one involving an endoscopical access to the peritoneum (EA-NOS or natural orifice surgery) and the other a more "surgeon-friendly" surgical access (SA-NOS). An analysis of the literature shows that the vast majority of human studies can be ascribed to SA surgery, whereas experimental research in animals and cadavers mostly involves EA surgery [42]. The former consists in gaining access through viscera (transgastric, colonic, rectal, vesical), with an operative endoscope that creates a controlled perforation which needs an endoscopical device to close it. It carries risks of infective contamination and the challenge of a failure of the parietal defect closure. Clinical case series are limited to few cases [43] (LE 4) in pilot and strictly controlled studies. They all used additional transabdominal mini-ports (hybrid NOTES), and a variable amount of the procedure is laparoscopically assisted (extraction of large specimens, closure of the gastrotomy). Preliminary results on morbidity in a prospective multicentric observational study counting 12 % of EA-NOS procedures (43 of 362 patients) [44] (LE4) demonstrate a 24 % complication rate, much higher than the transvaginal route (7 %). SA-NOS instead has developed relentlessly, especially the transvaginal route for NOTES-C. At the beginning of the experience, also the transumbilical surgery was considered part of the NOTES procedures as the incision was located in an embryological natural orifice (e-NOTES) [45]. The ease of creating and closing a surgical incision made in the posterior fornix of the vagina has facilitated the spread and the appeal of this operation, like European registry (EURO-NOTES) documents [46]. There is a single trial comparing transvaginal NOTES-C to LC with a third arm concerning a transumbilical cholecystectomy performed by means of hybrid NOTES (with the use of an endoscopic operative platform); results showed a success rate of 94 %, without differences in the rate of parietal complications at 1-year follow-up [47] (LE2). Postoperative pain, length of hospital stay, and time off from work were similar in the three groups. Surgical time was longer among cases in which a flexible endoscope was used (CL, 47.04 min; TV, 64.85 min; TU, 59.80 min).The largest prospective series of NOTES-C comes from the German registry [48] (LE4) on 551 patients, and the complication rate was 3.3 % with 4.7 % conversions to LA or open surgery. Intra- and postoperative complications accounted for 4 major complications requiring redo or additional surgery (bladder or intestinal perforations, bleedings, pelvic abscesses, and abdominal pain). Mean operative time was 62 min (20–211). Concerns were raised due to sexual complications (especially dyspareunia) after transvaginal approach, but observational studies have not proved it, and a prospective study on 106 female patients confirms a good quality of life after the operation [49] (LE4). When women were asked about their expectations after transvaginal hybrid NOTES, particularly young and nulliparous, women expressed concerns about sexual function and fertility [50, 51]. On the other hand, most studies addressing sexual function after transvaginal hysterectomy could not find a negative effect [52] (LE4); currently, the number of patients getting pregnant after

NOTES and particularly the number of patients seeking pregnancy after NOTES are much too small to draw any meaningful conclusions. Surveys have also proved a theoretical good acceptance of NOTES-C by 100 women [53], while 100 male partners don't justify the cosmetic benefit in front of the potential risks [54]. Reports on emergency surgery for acute cholecystitis are still sporadic [55] (LE4 on six patients). A new concept regards intralumenal surgery, in which endoscopic ultrasound-guided cholecystostomy performed via the duodenum appears promising in selected patients [46] (LE5). Future research should focus on larger randomized trials especially concerning transvaginal NOTES-C to assess safety issues. This probably is the branch of NOTES that will be the most rapidly diffused clinically in the near future while we await for a real benefit to be proved by future trials. All the other transvisceral approaches grouped in EA-NOS (transgastric, transcolonic, and transvesical) are limited by the need for significant technology improvements. Therefore, high-complexity surgical acts seem difficult to achieve under EA-NOS conditions in the near future. In this field, a consistent and continuous collaboration between industry and physicians in the area of robotics and magnetic instruments will play a substantial role in the takeoff of the technique. More research is also needed on training and learning curve. Prospective, randomized studies of large patient populations are necessary to assess the long-term results of NOTES procedures.

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