Gall Bladder Surgery: A Journey Of The Restless Human Mind

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Abstract:

Gall bladder surgery has come a long way from completely conservative measures to a no-scar technique (notes). Every new technique brought a new change, especially in the size of the incision, and has attained the safest possible level. Cholecystectomy is the standard treatment for symptomatic gallstones, and it has been performed for over 100 years. The standard treatment for gall bladder diseases in the past was open surgery, which was a full laparotomy from the xhiphi sternum to the pubic symphysis. This was then reduced to standard laparotomy i.e., below the umbilicus, then to kocher's incision and later to minilap. In this long journey, the principle of gallbladder surgery remained the same. Despite the fact that the complications following cholecystectomy are few, most patients still have trouble because of reasons such as postoperative pain, ileus, infection, wound dehiscence, incisional hernias, chronic pain, discomfort, disability, and long convalescence, even leading to nonresolution of symptoms. This had led to several methods of dealing with gallstones including gallstone dissolution, extracorporeal shock-wave lithotripsy, and various techniques of cholecystectomy. Laparoscopic cholecystectomy came as the right procedure at the right time, it almost abolished the long post-operative recovery period and brough the procedure to day case level. This technique proved the test of time and is now the gold standard treatment for symptomatic gall stone disease. To reach to this pinnacle of success, mankind has had to go through a lot and as technology is progressing, the new techniques and resources will continue to proceed. The aim of the article is to look back in history, reflect at the difficult path travelled, the bridges that were made and journey ahead, to let the next generation of surgeons and doctors know the history of cholecystectomy.

Keywords; laparotomy, cholecystitis, cholecystectomy, calot's triangle, laparoscopy

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I. Historical Background

For the first time in history, it was in 1420 by florentine pathologist antonio benevieni, who mentioned about a woman who died of abdominal pain.^[1] biliary colic with this description continued to be part of medical literature for years to come, with numerous physicians and surgeons, including francis glisson in 1658,^[1] reporting similar cases. The first gallstone surgery dates back to 1687 when stal pert von der wiel found accidental gallstones while operating on a patient with purulent peritonitis.^[2] regardless, the treatment of symptomatic gallstone disease was primitive and ineffective until the 18th century. Jean-louis petit, the founder of gall bladder surgery in 1733, suggested the removal of gallstones and drainage of the gall bladder, thus creating a fistula in patients with empyema, which he successfully performed in 1743.^[2] pettit's rigid criteria of surgical intervention were modified over the years; it included skin stimulants to provoke adhesion of the gall bladder to the abdominal wall and subsequent introduction of the indwelling trocar to remove stones and bile from the adhered gallbladder to minimize peritonitis. Thus, gall bladder surgery continued till 1859, when j.l.w thudichum proposed a twostage elective cholecystostomy.^[1,3] in the first stage, the inflamed gall bladder was sewn to the anterior abdominal wall through a small incision, which served as a route for the removal of gall stone at a later date. Around the same time, on july 15, 1867, dr john stough bobbs from indianopolis, indiana, whilst operating on a patient with a suspected ovarian cyst, found an inflamed and adhered sac containing "several solid ordinary rifle bullet" like structures. He opened the sac (which incidentally happened to be the gall bladder packed with multiple gallstones), removed the gallstones and left the gall bladder in the abdomen after closing the defect in the gall bladder (i.e., he performed a cholecystostomy). The patient recovered and outlived dr bobbs. Marion simms must be credited with designing, perfecting and performing the first cholecystostomy on a 45-year-old woman with obstructive jaundice in 1878.^[4] though the patient died on the eighth postoperative day due to a massive internal haemorrhage, it paved the way for theodor kocher to perform the first successful cholecystostomy in june 1878.^[1,2,3,4] whilst

others had busied themselves with the product of the disease, it was carl johann august langenbuch^[4] who observed that these measures were only temporary and rallied to find a definite solution for the disease.

At that time, biliary colic was a more medical problem and ordinary surgeons were inadequately exposed to the problem. Langenbuch, at the age of twenty-seven, was appointed director of the lazarus hospital in berlin.^[4] it was here that he came across many such patients because of his unique position. Two animal experiments by zambecarri in 1630 and teckoff in 1667 had shown that the gall bladder was not essential to life.^[4] moreover, physicians believed that the gall bladder itself gave rise to stones. Langenbuch kept pondering over these ideas. He developed the technique of cholecystectomy through cadaveric dissection and on july 15, 1882, he successfully removed the gall bladder of a 43-year-old man who was suffering from the disease for 16 years.^[4]

Langenbuch found two gallstones in a chronically inflamed and thickened gall bladder. The patient was discharged uneventfully from the hospital after six weeks. His initial report appeared in 1882, but it was ignored. This recent version of cholecystectomy was debated against the already-established cholecystostomy. An audit performed in 1886 showed thirty-nine cholecystectomies with a mortality of 27% against 8 cholecystectomies with a mortality of 12%.^[4] by now, langenbuch's cholecystectomy had convinced more and more surgeons worldwide and by 1897 nearly 100 operations with a mortality rate of less than 20 per cent were performed. By the turn of the century, it was established that cholecystectomy could guarantee permanent relief from pain whereas cholecystostomy gave a permanent fistula and not a pain-free state. Langenbuch died on june 9, 1901, due to neglected appendicitis, but the path shown by him led to further advancement and modification in biliary surgery.^[4]

Laparoscopic Era

Langenbuch's open cholecystectomy remained the gold standard for symptomatic cholelithiasis for over a century. The only major change in the operation was the introduction of operative cholangiography for the detection of common bile duct stone by mirizzi over 60 years ago.^[5] however, in the last decade, the introduction of laparoscopic techniques to perform cholecystectomy has revolutionized this procedure. The revolutionary nature of this procedure has been unprecedented in surgical history and has been compared to other surgical mileposts such as the development of vascular surgery and organ transplantation.^[6]

The earliest reference to laparoscopy dates back to biblical history.^[6] at that time, classical galenic medical tradition was based on the concept of maintaining homeostasis by balanced production and excretion of bodily wastes. Imbalance led to disease states and thus classical restoration to normal balance was by means of purgatives and cathartics. Alternatively, surgically draining the abdomen of "bad humours" by means of trocar insertion was in vogue as described by ezekiel and celsus (25 bc ad 50).^[6]

The term trocar, coined in 1706, was thought to be derived from "trocarter troise-quarts", a three-faced perforator enclosed in a metal canula.^[7] laparoscopic trocar-like instruments have been recovered from roman ruins. Dimitri oh, a german gynaecologist, performed the first endoscopic examination (ventroscopy) in 1901 through an incision in the posterior vaginal fornix. He also wore a head mirror to reflect light and augment visualization. In addition, in 1901, george kelling, a german surgeon, described "celioscopy" in a dog after peritoneal insufflation with air. Jacobeus of sweden performed the first human celioscopy in 1910, on a patient with ascites. Bernheim from the united states was the first surgeon to publish his experience in laparoscopy entitled "organoscopy" in the annals of surgery 1911.^[8,9,10]

World war i halted the laparoscopic march until the mid-1920s when kelling rejuvenated "organoscopy" in 1923. He presented before the german surgical society his 22 years' experience with diagnostic laparoscopy.^[11] thus began the era of minimally invasive surgery. The pioneers of laparoscopy believed that this technique was an important adjunct to surgical practice. Nonetheless, inadequate technology limited their vision, both literally and figuratively. Light sources, danger of thermal burns to intra-abdominal organs, bowel perforation and vascular injuries posed genuine risks and significantly limited the use of laparoscopy.

In 1929, kalk, the "father of modern laparoscopy", advocated refinement in the technique through the introduction of the faroblique (135 degrees) lens system, a separate pneumoperitoneum needle and a second puncture site.^[12] in 1938, veress developed a needle with a spring-loaded obturator that allowed safe insertion and insufflation of the peritoneal cavity.^[12] despite such advances in laparoscopic imaging and techniques, the troublesome problem of increased intra-abdominal pressure and thermal injury to the bowel associated with unipolar cautery severely restricted the use of the laparoscope. In 1952, fourestier, gladu and valmiere revolutionized laparoscopy with the introduction of a quartz rod to transmit an intense light beam distally along the telescope enabling photographic images.^[8,9,12] closed circuit television was added in 1959.^[8,9,12] another decade was required to overcome the dangers of the insufflation of the abdomen. In 1966, kurt semm introduced an automatic insufflator device capable of monitoring intra-abdominal pressure; he also developed thermo coagulation, designed a high-volume irrigation aspiration system, perfected the endo loop applicator along with knot-tying techniques and instruments. He adapted numerous gynaecologic procedures to laparoscopic techniques. Beyond the realm of gynaecologic surgery, he performed omental adhesiolysis, bowel suturing,

tumour biopsy and staging and, notably, incidental appendicectomy.^[8,12,13] although interest was piqued, general surgeons still considered laparoscopy a "blind" procedure and thus did not incorporate it into the practice of general surgery.

By the late 1970s, gynaecologic surgeons had embraced laparoscopy thoroughly. General surgeons remained sceptical and staunchly supported traditional open surgery. Hasson's introduction of trocar placement under direct vision in 1978 cleared much of the doubts among general surgeons who became more receptive to laparoscopic surgery.^[13] liver biopsies were the first laparoscopic procedures attempted by general surgeons in 1982.^[14] warshaw, tepper and shipley applied laparoscopy to the staging of pancreatic cancer in 1986, with a reported accuracy rate of 93%.^[15]

Mouret from france claimed to have performed first human laparoscopic cholecystectomy. On that day in march 1987, as he was completing a gynaecologic laparoscopy on a woman who was also suffering from symptomatic gallstones, he shifted his laparoscope to the subhepatic area. Upon finding a comparatively free and supple gall bladder, he decided to remove it laparoscopically instead of opening it up. He performed the procedure successfully and the patient recovered without complications.^[16] within two years, in the usa, the procedure was being adopted and because of the massive demand from the patients, standard traditional stages of scientific evaluation were bypassed. Finally, in september 1992, an nih consensus conference held in bethesda concluded that laparoscopic cholecystectomy was the treatment of choice for gall bladder lithiasis.^[17]

Controversies Of First Laparascopic Cholecystectomy

Professor dr med erich mühe from böblingen, germany, performed the first laparoscopic cholecystectomy on september 12, 1985. The german surgical society rejected mühe in 1986 after he reported that he had performed the first laparoscopic cholecystectomy yet in 1992 he received their highest award, the german surgical society anniversary award. In 1990, at the society of american gastrointestinal surgeons (sages) convention in atlanta, perissat, berci, cuschieri, dubois, and mouret were recognized by sages for performing early laparoscopic cholecystectomies, but mühe was not. However, in 1999, he was recognized by sages for having performed the first laparoscopic cholecystectomy; sages invited mühe to present the storz lecture. In mühe's presentation, titled "the first laparoscopic cholecystectomy", which he gave in march 1999 in san antonio, texas, he described the first procedure. Finally, mühe had received the worldwide acclaim that he deserved for his pioneering work. One purpose of this article is to give mühe the recognition he deserves for being the developer of the laparoscopic cholecystectomy procedure and lastly our future generation of surgeons should know the history of the most commonly performed procedure.^[18]

Review Of Methods Of Treating Gallstones

Cholecystectomy has been performed for over 100 years and is the standard treatment for gallbladder stones, with proven safety and efficacy.^[19] despite the fact that the complications following cholecystectomy are few, most patients still have trouble because of postoperative ileus, pain, discomfort, disability, and long convalescence^[20]. Because of fear of an operation, the lengthy recovery period and their dislike of a 'large' scar, there is always a demand by many patients for non-operative treatment of their gallstones.

However, all non-operative treatments leave an intact gallbladder, which almost always leads to gallstone recurrence and does not eliminate the risk of developing gallbladder carcinoma.^[21] arguments had led to the development of many new therapies for the management of gallstones including methods that are non-invasive, minimally invasive, and newer surgical techniques like laparoscopic cholecystectomy and mini cholecystectomy. The revolution in minimally invasive surgery, specifically laparoscopic cholecystectomy, was still in progress. The rapid acceptance and increase in demand for the procedure remain to be fully evaluated. It was not known at the beginning if the laparoscopic method can match the safety of the "gold standard" of open cholecystectomy.

Oral Bile Acid Therapy:

Administration of the bile acids leads to the production of bile that is less saturated with cholesterol, which then leads to the dissolution of gallstones. Treatment of gallstones by prolonged administration of bile salts was reported by rewbridge in 1937^[21], but his success largely went unnoticed. Interest in bile acid therapy with chenodeoxycholic acid was renewed in the early 1970s, but because of concerns about its side effects like diarrhoea, skin rash, change in liver function tests, and potential for hepatotoxicity and atherogenicity, it has largely been replaced by ursodeoxycholic acid.^[23,24,25,26] this is largely free from side effects but is expensive and because these two agents appear to work by slightly different mechanisms, the two are commonly used in combination.

The bile acids are more effective most in small (i.e., 5-10mm), floating, radiolucent, cholesterol stones in a functioning gallbladder. ^[21,26,27] using these selection criteria, approximately 15-20% of patients are suitable for bile acid therapy.^[28] the treatment is prolonged, and the time required for dissolution ranges from 6 months to

2 years. Regular monitoring is required till dissolution is achieved. Dissolution rates are higher and recurrence rates are lower in young, non-obese individuals with a single stone.^[26] the estimated success rate is around 60% and nearly half of these patients develop stone recurrence at the end of 5 years.^[24,25,28] the percentage of recurrent stones which will give rise to symptoms is not yet known.

At present the indications for bile acid therapy are limited to patients who cannot safety undergo an operation and to patients who choose to avoid an operation.^[26]

Contact Dissolution Therapy:

The most commonly used agents were methyl tert-butyl ether (mtbe) and monoctanoin, but mtbe is more potent and was preferred for gallbladder stone dissolution. It is an alkyl ether with a high capacity for dissolving the cholesterol in a matter of hours. As with bile acid therapy, mtbe is ineffective against pigment stones but can dissolve the cholesterol in mixed stones, leaving a residue of mud or gravel which is cleared in hours or days.^[21]

Methyl tert-butyl ether (mtbe) is usually administered via a percutaneous transhepatic catheter into the gallbladder. It is manually injected and aspirated continuously 4-6 times each minute for an average of 5 hours per day for 1-3 days.^[29] this is necessary because the rate of dissolution is dependent upon prolonged contact of the solvent with the maximal stone surface area. It is also important to do this so as not to allow the absorption of mtbe from the gut, which may result in nausea, vomiting and sedation. Haemolysis, abnormalities of liver function, duodenitis and renal failure are other less common complications of methyl tret-butyl ether absorption.^[29] the odour of mtbe in the patient's breath is an early sign that absorption is occurring.

The largest reported study has been conducted at mayo clinic, with successful treatments in seventy-two out of seventy-five high-risk surgical patients. Four patients developed stone recurrence at 6-16 months and four required cholecystectomy for persistent symptoms.^[30]

This technique was in its evolutionary stage and required considerable skill and care. There was definite potential for complications.^[21,26]

Percutaneous Cholecystostomy:

Direct percutaneous access to the gallbladder is being pursued, particularly in elderly and high-risk patients, for the treatment of acute cholecystitis, empyema, and perforated gallbladder with localized abscess formation.^[21] drainage of the gallbladder under these conditions produces immediate relief of symptoms. The procedure is performed under local anaesthesia, using ultrasound and fluoroscopic guidance, with minimal morbidity and mortality.^[31] the few complications that may occur following this procedure are catheter dislodgment, bile leakage and vasovagal reaction during instrumentation of the gallbladder.^[29,31]

After percutaneous drainage of the gallbladder, under these conditions when the acute illness has resolved, the access route can be used for other therapeutic options including contact dissolution of gallstones with solvents and mechanical stone removal from the gallbladder ^[21, 29] this mode of treatment is reserved only for critically ill patients with acute cholecystitis. ^[31]

Percutaneous Cholecystolithotomy:

Percutaneous cholecystolithotomy was originally described in 1983 in poor risks patients with acute cholecystitis treated by percutaneous cholecystostomy.^[21] after dilatation of the cholecystostomy tract, stones were removed using baskets or forceps. The method and instruments have been adapted from percutaneous nephrolithotomy.^[32]

Although the standard approach is transhepatic, large cannula, which make extraction easier, cause unnecessary trauma to the liver. The transperitoneal approach is avoided because risk of bowel puncture and intraperitoneal bile leakage. Despite these risks, chiverton et al 1990, and cheslyn-curtis and russell 1991, have reported a 94% success rate of transperitoneal punctures of the fundus of the gallbladder, without any complications.^[21,33]

The procedure is performed under general anaesthesia or local anaesthesia with intravenous sedation. After percutaneous cholecystography, a needle puncture of the gallbladder is made using a combination of fluoroscopic and ultrasonographic guidance. A guide wire is placed in the gallbladder and the tract is dilated to introduce the cholecsytoscope. Stones are removed with forceps or disintegrated with intracorporeal lithotripsy and removed piecemeal. After all, fragments have been extracted a foley catheter is left in the gallbladder for about 10 days and a contrast study is done before catheter removal. ^[21,32]

There are no specific selection criteria for this procedure. The only patients who are unsuitable for this procedure are those with contracted thin-walled gallbladders, not only because the gallbladder is diseased, but also for technical reasons.^[21] the result of large series of one hundred cases at middlesex hospital shows an 89% success rate^[21]; smaller studies have also shown similar success rates.^[21,32]

The complications reported with this procedure are bile leakage, subhepatic bile collection, pancreatitis and transient cholangitis; immediate cholecystectomy may also be required as a result of one of the complications of the procedure ^[21,33]

Extracorporeal Shock-Wave Lithotripsy:

The use of extracorporeal shock-wave lithotripsy for the fragmentation of gallbladder stones in 1985 was a natural advance after the successful extra-corporeal treatment of renal calculi in 1980.^[35] unlike the treatment of renal calculi, where they are cleared by spontaneous fragment passage down the water, in the gallbladder, the stone fragments have to negotiate the cystic duct, common bile duct, and finally the ampulla of vater. Although the gallbladder can contract, it does not undergo peristalsis and therefore passage of fragments does not occur as readily as in the urinary tract. The gallbladder emptying, unlike the urinary tract, may be impaired by the effects of chronic inflammatory disease.^[35]

Effective extracorporeal shock-wave lithotripsy requires adjuvant bile acid therapy.^[26,35] the patients liable to benefit from extracorporeal gallstone lithotripsy are those with a history of biliary pain having radiolucent stones less than 3cm in diameter, not more than three in number, with a functioning gallbladder.^[36,37] a functioning gallbladder is necessary as to allow bile acid to reach the stones and for the spontaneous passage of stone fragments.

An estimated 10-25% of all patients with symptomatic gallstones are suitable for extracorporeal shockwave lithotripsy treatment depending upon selection criteria.^[26,37,38] fragmentation rates of 75 to 95 per cent have been achieved by different centres followed by complete stone clearance in about 90% of cases at 12-18 months. [21,35,36,37,38]

Complications observed in these patients range from cutaneous petechiae or ecchymosis, transient haematuria, biliary colic, acute pancreatitis and acute cholecystitis. Biliary colic is the most frequent complication occurring in approximately half of the patients undergoing therapy.^[37,38] recurrence after extracorporeal biliary lithotripsy for a single small stone is infrequent but common for multiple stones.^[26] the best results are achieved with solitary stones less than 20mm in diameter, the value of lithotripsy for treating multiple stones is less certain.^[21] extracorporeal shock-wave lithotripsy is not a definitive treatment for gallstones but may offer a temporary solution.^[26]

Mini-Cholecystostomy With Interventional Radiologic Stone Removal:

The aim of the procedure is to decompress the biliary tract and to create a strong wide tract for subsequent radiologic stone removal.^[39] this technique is beneficial for high-risk cholecystectomy patients presenting with acute cholecystitis or severe biliary colic. Under sedation and local anaesthesia, ultrasound-guided surgical cholecystectomy is done. Through a small incision over the marked gallbladder fundus, a 24f foley catheter is placed in the gallbladder and the fundus is sutured around the catheter. The peritoneum and the rectus sheet are also stitched to the fundus to ensure a strong tract and prevent the chances of bile leakage.^[40] stone extraction is attempted after the seventh to tenth post-operative day via the cholecystectomy tract using radiologic techniques.

In the study of thirty-six elderly high-risk patients, stones were successfully removed in 95% of cases (35 patients) without mortality. This safety of mini cholecystectomy is due to minimal operative stress.^[40]

Mini Cholecystectomy:

Cholecystectomy may be safely performed through a small transverse subcostal incision of 5-8 cm. The operative technique is generally similar to conventional cholecystectomy with different modifications being used by different authors. Some split the abdominal muscles rather than divide them, some used headlights while others use special retractors with lights and diathermy scissors. ^[41,42,43] at no stage of the operation does the surgeon's hand enters the abdominal cavity. All the dissection is conducted with the help of instruments.

The only exclusion criteria mentioned by most of the series is clinical evidence of common duct stone.^[42, 43, 44] the average length of hospitalization was 3.5 days and the operation was completed without enlarging the incision in 84% of cases.^[42] the method of cholecystectomy called as mini cholecystectomy was described as early as 1982 by dubious and berthelot.^[44] it is claimed to have many benefits of laparoscopic cholecystectomy without the large initial cost.^[44] this procedure had the potential to be the gold standard for gall bladder surgery and was gaining popularity, but the big boss was waiting at the dawn of the new era in surgery, the laparoscopic cholecystectomy.

Laparoscopic Cholecystectomy:

Laparoscopic cholecystectomy took the field of surgery by surprise; it magnified views, utilised better hand instruments, showed quick recovery, had high demand from patients and most importantly the principles of gall bladder surgery remained the same. Surgeons had nothing new to learn other than hand-eye coordination, for it was the same calot's triangle, the same common bile duct (cbd) and the same cystic duct ligation.

The technique became popular with a standard of four ports. People attempted with three ports, two ports, a single port (sils), and natural orifice surgery (notes) but the standard to date is four ports. It gave freedom to the surgeons to access cbd and perform common bile duct explorations, and intraoperative cholangiograms (ioc), either trans-cystic or through cbd removal of stones. Now the interesting topic of discussion in the surgical fraternity is the selective vs routine use of intraoperative cholangiograms. Indigo cyanin green (icg) is used for knowing the biliary anatomy and the results are great. Icg images are dynamic and are seen in real-time, which means that structures like cbd can be identified and kept under constant vision until after clipping the cystic duct. Unlike ioc, where the cbd is identified through x-ray, images are not in real-time and cbd injury can still happen even after ioc. It has been seen that bile duct injuries happen after ioc has been done, not before.

Regarding instrument evolution, better sealing (i.e., cutting and sealing) devices like ligasure and harmonic, with which no clips or ligation are required, have been successfully introduced. Dual cameras, which can switch from normal mode to icg mode with the press of a button, have become commonplace. In addition, robotic learning modules and lap mentors have been established where patients are replaced by augmented reality (ar) and various variants of surgeries can be learnt without putting patients at risk.

Laparoscopic cholecystectomy, since induction, has rendered the non-operative methods for gallstones such as oral dissolution, extracorporeal shock-wave lithotripsy and other "minimally invasive" procedures obsolete as predicted by macintyre and wilson in 1993.^[45] this reminds me of the story of "the bridge builder" which i would love to share here

An old man going a lone highway, Came, at the evening cold and gray, To a chasm vast and deep and wide. Through which was flowing a sullen tide The old man crossed in the twilight dim, The sullen stream had no fear for him. But he turned when safe on the other side And built a bridge to span the tide.

"old man," said a fellow pilgrim near, "you are wasting your strength with building here; Your journey will end with the ending day, You never again will pass this way; You've crossed the chasm, deep and wide, Why build this bridge at evening tide?"

The builder lifted his old gray head; "good friend, in the path i have come," he said, "there followed after me to-day A youth whose feet must pass this way. This chasm that has been as naught to me To that fair-haired youth may a pitfall be; He, too, must cross in the twilight dim; Good friend, i am building this bridge for him!" ⁽⁴⁶⁾

All these people from langenbuch, cuschieri, dubois, mouret and to erich mühe were those bridge builders who contributed their bit to the broader vision of surgical progression and patient safety. They built those difficult bridges, which we are crossing daily without realising the hurdles that were there before when there was no road.

II. Conclusion:

The journey of gall bladder surgery continues as technological development goes on. The latest innovations like endo eye, flexible hand instruments, 3d vision, 4k, 5g robotic telesurgery, hd views, sils, notes, use of indigo cyanin green (icg) for biliary anatomy and colonic anastomotic blood supply, robotic surgery and the last but not the least needle-o-scopic surgery where the port size will be 0.25cm and hand instruments will be needles. This journey of our restless mind has brought us from a very barbaric operative technique to a safe minimal invasive technique. Sometimes we wonder that this restlessness may take us to a newer dimension of unsafe areas where human touch or human factors are completely taken away from us and replaced by machines (which may happen sooner than we think) but at the same time, we are optimistic that we have a robust system

of analysis and review which will ultimately take us to the new higher level of safety as various other techniques are proving to be.

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