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Review

Robotic surgery in gynaecology

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Key content

- Robotic surgery has gained popularity in the last decade and the da Vinci® Surgical System has been increasingly used for complex gynaecological surgery.
- The advantages of robotic surgery over conventional laparoscopic surgery are: greater degree of movement, precise dissection, 3D vision, tremor filtration and a shorter learning curve. The disadvantages are mainly the high cost and lack of haptic feedback.
- The current role of robotics in gynaecological surgery.

Learning objectives

- To provide an overview of the advantages and drawbacks of robotic surgery over conventional open and laparoscopic surgery.
- To review the latest evidence and evaluate the role of robotics in general gynaecology and the subspecialties, including oncology and urogynaecology.
- To discuss training issues for individuals and for theatre teams.

Ethical issues

- Is it ethical to deny patients who would benefit from robotic surgery this option because of the cost?

Keywords: gynaecological / robotic / surgery

Linked resource: Single best answer questions are available for this article at https://stratog.rcog.org.uk/tutorial/tog-online-sba-resource

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Introduction

Minimally invasive techniques are becoming increasingly common for surgical procedures in gynaecology. Robotic surgery using the da Vinci® Surgery System (Intuitive Surgical Inc, Sunnyvale, California, USA) has gained popularity in the last decade for complex gynaecological surgery. The da Vinci® robotic system was initially designed with input from US defence and space programs for surgeons to remotely treat soldiers on the battlefield. However, it was successfully redeveloped and in 2001 the US Food and Drug Administration (FDA) cleared it for use in general laparoscopic surgery. Subsequently, the first FDA-approved cases of robot use in gynaecological surgery in 2005 have heralded a decade of expansion and evaluation of this relatively novel surgical technique.

The da Vinci® technology

The da Vinci® system has three components: a 3D high-definition vision system, surgeon console and a robotic platform (patient cart) with three or four robotic arms that hold the Endowrist® Instruments and the camera (Figures 1 and 2). The surgeon controls the instruments, camera and energy source remotely from hand (Figure 3) and foot controls at the console. To begin the procedure, the surgeon must establish a pneumoperitoneum and insert the ports. Then the theatre team 'dock' the robot platform by correctly positioning the platform relative to the patient and inserting the instruments into the ports. A bedside assistant is also utilised for supplemental actions such as suction, retraction and uterine manipulation.

Newer systems such as the da Vinci® Si and the da Vinci® Xi include features such as dual-console capability, enhanced high-definition 3D vision and extensibility for digital operating room integration and the ability to detect indocyanine green dyed lymphatics using near-infrared (NIR) fluorescence imaging.

Advantages of robotic surgery

Robotic surgery offers all of the advantages of minimally invasive surgery, including decreased blood loss, quicker recovery, decreased length of hospital stay, less pain and

Figure 1. Surgeon console daVinci Si ©2015 Intuitive Surgical, Inc. depicting the foot and hand controls and binocular viewer. Reproduced with permission from ©2015 Intuitive Surgical Inc.

better cosmesis. Compared with conventional laparoscopy, the robotic system movements are reduced by up to ten times, which provides tremor filtration and allows for precise movements. A stable camera with 3D vision further assists such precision and microsurgical dissection. In contrast to laparoscopic surgery, where the camera control and vision can change depending on the assistant's hand-eye coordination, patient breathing and pneumoperitoneum, the robotic camera control lies with the surgeon, providing a fixed, stable field of vision. Another important advantage is the intuitive hand movements when using the robot as the instruments move in the same direction as the surgeon's hands, whereas in straight stick laparoscopy, the hand and instrument movements are counterintuitive. The specialist Endowrist® Instruments have seven degrees of movement to mimic the movements of the surgeon's hand and wrist and to better replicate the steps of the open technique. This, together with self-control of the camera and an ergonomic console designed to reduce fatigue may contribute to the shorter learning curve for robotic surgery.[1]

Dual console systems are available to facilitate training, mentoring and collaboration during minimally invasive

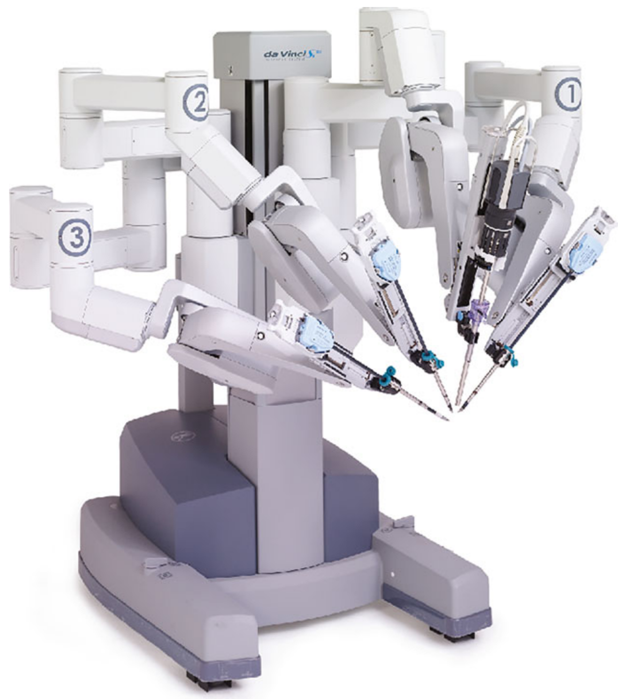

Figure 2. Patient cart depicting robot arms. Reproduced with permission from ©2015 Intuitive Surgical, Inc.

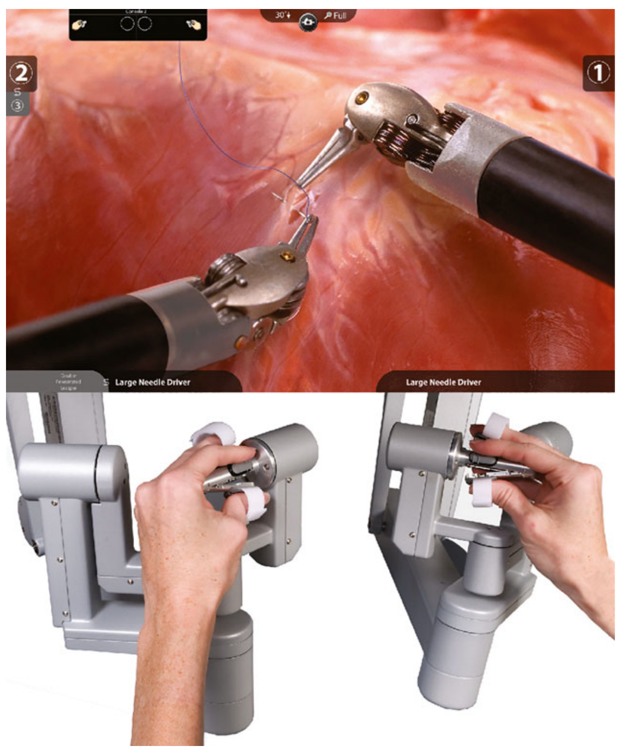

Figure 3. Master controls showing the operator's hands on the master controls of the surgeon console (below) and the corresponding view on the operative screen (above). Reproduced with permission from ©2015 Intuitive Surgical, Inc.

surgery. Telesurgery, or the ability to perform long-distance surgery, is also a theoretical possibility with the robotic system.

Disadvantages of robotic surgery

One of the main disadvantages of the robotic system is the absence of haptic or tactile feedback. The lack of tactile sensation can potentially lead to increased tissue trauma, compromised security of knots and weakening of sutures.[1] This is partially compensated by the three dimensional spatial view and visual cues.[1,2] The visual cues provide a perception of haptic feedback, which improves with experience, making 'real' haptic feedback less important.[3]

Separation of the console surgeon from the operating field can be a disadvantage.[2,4] The robotic surgeon loses control over accessory tasks such as change or removal of instruments and has to rely more on the robotic surgical assistant and scrub nurse compared with traditional laparoscopic surgery.

The capital cost associated with robotic surgery is the single most prohibitive factor in its uptake.[5] The initial outlay combined with maintenance and instrument costs makes it more expensive than conventional laparoscopy. The monopoly of Intuitive Surgical has been responsible for these high costs. With new robotic manufacturers introducing their models soon, market competition should increase and these costs are expected to come down.

Positioning, port insertion and docking

Correct positioning of the patient, appropriate trocar placement and docking are essential for safe and successful robotic surgery. This is important for maximising operative field exposure, minimising arm collisions and avoiding off-camera injuries.[2]

Patient positioning

Most robotic gynaecological procedures are done in the steep Trendelenburg position. Prolonged procedures in this position can lead to patient sliding, especially in obese patients. Therefore adequate support should be used in the form of bean bags, gel pads or shoulder pads. The legs should be placed in Allen stirrups, with knees flexed less than 60° to avoid nerve palsies and pressure points padded appropriately. A tilt test can be performed to determine the maximum Trendelenburg tolerated. Uterine manipulators should be placed prior to docking.

Port insertion and trocar placement

Port placement depends on the number of arms used. If three arms are used, then four ports are needed: one for the camera, two for the robotic instruments and one assistant port. The camera port is usually 12 mm while the robotic trocars are 8 mm. If 4 arms are used, an extra port would be needed for the third robotic instrument. The three arm models, such as the daVinci® S, are older models; the newer ones (daVinci® Si and daVinci® Xi) have four arms.

For a robotic hysterectomy, the camera port is placed about 8–10 cm cephalad to the level of the fundus; this could be above the level of the umbilicus in obese patients. For a robotic sacrocolpopexy, the camera port is placed at or cephalad to the umbilicus, depending on the size of the uterus, if present. The right and left instrument ports are placed 8–10 cm lateral and 2–3 cm caudal to the camera port.[4] The assistant port can be placed on either side, 8–10 cm lateral and 2–3 cm cephalad to the camera port. Port placement sites for hysterectomy and sacrocolpopexy are illustrated in Figures 4 and 5.

An 8 cm distance between all ports is essential in order to prevent robot arm collisions. The ports should be placed vertically with the black band on the robotic trocars at the level of the peritoneum, avoiding slipping across the rectus sheath, in order to prevent excessive stretching and pain postoperatively.

Docking the robot

The robot can be 'straight docked' with the robotic platform placed between the patient's legs or 'side docked', where the patient cart is at a 45° angle to the axis of the patient on the operating table. Side docking leaves more space for the assistant performing uterine manipulation.

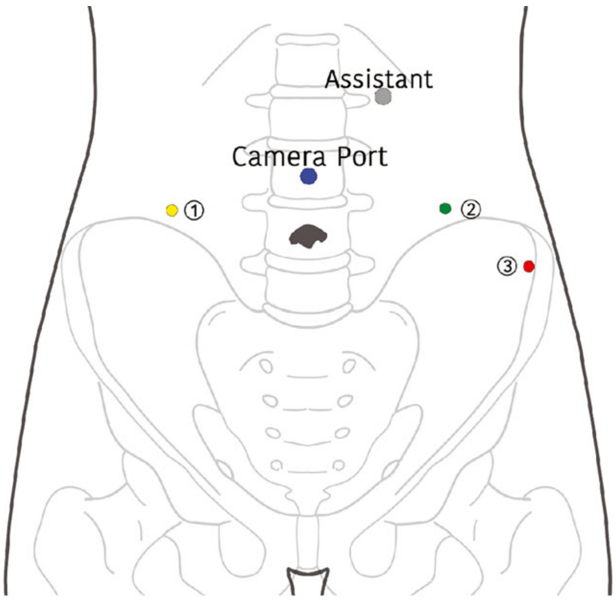

Figure 4. The four arm port placement for hysterectomy. Adapted with permission from ©2015 Intuitive Surgical, Inc.

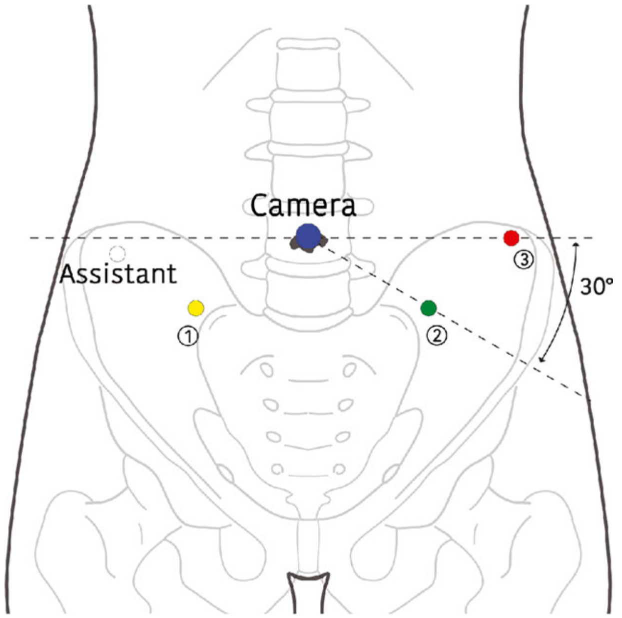

Figure 5. The four arm port placement for sacrocolpopexy. Adapted with permission from ©2015 Intuitive Surgical, Inc.

Robotic hysterectomy for benign disease

Hysterectomy is one of the most common operations in gynaecology. Traditionally, this was done by either a vaginal or open approach. A Cochrane review in published 2009 (and updated in 2015) demonstrated that the laparoscopic approach has clear advantages over open hysterectomy, including less blood loss and a smaller drop in blood count, a shorter stay in hospital, quicker return to normal activities, fewer wound infections and fewer episodes of raised temperature after surgery.[6] Despite this, only a fraction of hysterectomies are performed laparoscopically.

A 2009 cross-sectional study of 518 828 hysterectomies in the USA showed that 64% of hysterectomies were abdominal, 14% were laparoscopic and 22% vaginal.[7] The technical expertise required for laparoscopic hysterectomy, especially for suturing, a steep learning curve, longer operative time and limited degrees of motion may be responsible for this trend. It has been proposed that the robotic approach may overcome these problems and lead to an increased rate of minimally invasive hysterectomy.

Patzkowsky et al.[8] compared the perioperative outcomes of hysterectomy performed by the robotic and laparoscopic routes for benign disease and found that they appeared to be equivalent. Conversion to laparotomy rate was lower in the robotic group (1.7% versus 6.2% P=0.007). However, the rates of urinary tract infection were higher. In a randomised controlled trial comparing robotic and laparoscopic hysterectomy in 95 patients, Sarlos et al.[9] showed a better quality of life following robotic hysterectomy but this involved a longer operating time. Both surgeons had performed about 500 laparoscopic hysterectomies and 30 robotic hysterectomies before commencing the study. Their vast experience in laparoscopy combined with the impact of the learning curve, especially in handling the robot, may have contributed to the finding of longer operating times with the robot.

In another study, Rosero et al.[10] reported similar outcomes but also found that robotic hysterectomies cost on average $2489 more than traditional laparoscopic hysterectomy (95% CI $2,313–2,664). Similar conclusions were drawn by a Cochrane review in 2014 that assessed the safety and effectiveness of robot-assisted surgery in gynaecology.[11] These studies reveal that robotic hysterectomy for benign disease is feasible but takes longer and is associated with higher cost.

Conversely, Chiu et al.[12] showed that, for cases with severe adhesions, robotic surgery was associated with a shortened operation time and concluded that, compared with the laparoscopic approach, robotic surgery is a feasible alternative for performing total hysterectomy with severe adhesions.

Robotic applications in gynaecological oncology

Robotic surgery has applications in gynaecological oncology procedures that entail radical hysterectomy and pelvic and para-aortic lymph node dissection. The International Federation of Gynecology and Obstetrics (FIGO) criteria staging requires lymphadenectomy for staging in endometrial cancer. Node status is pivotal for determining adjuvant therapy.[13] Morbid obesity can be a limiting factor when performing these procedures, which were traditionally done by the open approach. Laparoscopic para-aortic lymph node dissection also needs a high degree of technical skill. The robotic platform can make this type of surgery more feasible and is becoming popular. The technology also supports NIR fluorescence imaging with indocyanine green, which can be used for intraoperative identification and mapping of sentinel nodes.

Boggess et al.[14] compared outcomes in 323 women who underwent endometrial cancer staging by the open, laparoscopic and robotic techniques. Lymph node yield was highest for robotic techniques (P<0.0001) with hospital stay (P<0.0001) and estimated blood loss (P<0.0001) the lowest for this cohort. Conversion rates were similar in both groups. They concluded that staging by the robotic technique is feasible and preferable over the open technique and may be preferable over laparoscopy in women with endometrial cancer. A recent meta-analysis by O'Neill et al.[15] concluded that for simple total hysterectomy with node staging, robot-assisted surgery is associated with improved outcomes, including reduced hospital stay, complications and blood transfusions when compared with open surgery and reduced blood loss, complications and conversions when compared with laparoscopic surgery.

A systematic review by Geetha et al.[16] comparing open, laparoscopic and robotic approaches for cervical cancer showed that the mean blood loss, postoperative infectious morbidity and the hospital stay was lower with laparoscopic and robotic approaches compared with the open method. Nodal yields were similar for all methods. Similarly, Vizza et al.[17] prospectively compared the surgical outcomes of laparoscopic and robotic radical hysterectomy with lymphadenectomy in cervical cancer and found that the mean blood loss and median length of stay were lower in the robotic group (P=0.28). Another study by Vitobello et al.[18] found robotic radical hysterectomy and pelvic lymphadenectomy to be feasible, safe and comparable in both early and advanced cervical cancer. However, the authors concluded that robotic radical hysterectomy requires longer follow-up to establish survival outcomes.

Persson et al.[19] described their experience of 80 robotic radical hysterectomies and showed that there were minimal complications. They also commented that they were able to perform minimally invasive procedures which would not have been possible without the robot, such as laparoscopic radical trachelectomy, and removal of bulky pelvic tumours and nodes.

Lonnerfors et al.[20] reported that from their case series of 1000 robotic gynaecological surgeries between 2005 and 2011, 606 women were operated on for a malignant disease. Interestingly, the proportion of minimally invasive surgery for cervical, endometrial, and early ovarian cancer increased from 26% in 2005 to 81% in 2011. Overall, there were low rates of conversions and intraoperative complications.

However, despite the clinical applications described, a Cochrane review[11] found limited evidence on the effectiveness and safety of robot-assisted surgery compared with laparoscopic and open approaches for gynaecological cancer. It has therefore been suggested that its use should be limited to clinical trials.

Robotic applications in urogynaecology

Pelvic organ prolapse (POP) is a very common problem with approximately 11% of the female population undergoing surgery for prolapse in their lifetime.[21] One type is posthysterectomy vaginal vault prolapse. Cochrane reviews in 2008, 2011 and 2013 concluded that abdominal sacrocolpopexy was the gold standard for the treatment of vault prolapse and had superior outcomes compared with vaginal procedures.[22] However, it is important to note that the sacrocolpopexy studies had heterogeneous surgical types as comparators, including vaginal uterosacral colpopexy, sacrospinous colpopexy and transvaginal mesh.

Numerous studies comparing laparoscopic and abdominal sacrocolpopexy have found comparable clinical outcomes but a shorter length of stay and reduced blood loss with the laparoscopic approach.[23] However, laparoscopic sacrocolpopexy has not been rapidly adopted because of the technical difficulties associated with this procedure.[23] As a result, there has been much interest in robotic sacrocolpopexy.

Akl et al.[24] described their series of robotic-assisted sacrocolpopexy in 80 patients. Mean operative time was 197.9 minutes, which decreased by 25.4% after the first 10 cases. The complication rates were low and the authors concluded that robotic sacrocolpopexy was feasible with a short learning curve. A systematic review by Hallock et al.,[25] which included eight studies, evaluated the outcomes and costs of robotic sacrocolpopexy versus laparoscopic sacrocolpopexy and found that they both resulted in similar objective (anatomical cure or improvement, operating times, blood loss and hospital stay) and subjective (postoperative pain and functional activity) success rates, quality of life outcomes and overall perioperative complication rates. Robotic sacrocolpopexy had similar or longer operative times, caused similar or less blood loss and resulted in more short-term postoperative pain. Robotic sacrocolpopexy was associated with higher costs compared with laparoscopic sacrocolpopexy but, when initial purchase and set up costs were excluded, this difference was minimal. Hallock et al.[25] concluded that robotic sacrocolpopexy is an acceptable alternative to laparoscopic sacrocolpopexy for the management of apical vaginal prolapse, but longer follow-up is needed. Another systematic review supported the use of robotic sacrocolpopexy over laparoscopic sacrocolpopexy but at a higher cost.[26] Thus, the evidence suggests that robotic sacrocolpopexy is a comparable, safe and effective procedure compared with laparoscopic and open sacrocolpopexy.

In patients with POP who desire fertility, hysteropexy is an option and has been described by both open and laparoscopic routes. Some authors have also described robotic hysteropexy. A prospective cohort study of 50 women in the Netherlands[27] undergoing robotic sacrohysteropexy showed that operative times were comparable with the open and laparoscopic approaches, average blood loss was less than 50 ml and 95.2% were very satisfied with the results.

Robotic myomectomy

A retrospective study of 322 patients by Gobern et al.[28] comparing the outcomes of open, laparoscopic and robotic myomectomies found that though robotic myomectomies were associated with a longer operative time (robotic = 140 minutes, laparoscopic = 70 minutes, open =

72 minutes, $P<0.005$), laparoscopic and robotic myomectomies were associated with less blood loss, fewer transfusions and shorter hospital stays. Another retrospective review of 86 women undergoing robotic or laparoscopic myomectomy showed no difference in operating time or hospital stay between the two groups; however, blood loss was less in the robotic group.[29] An important point to be considered during robotic myomectomy is the need for morcellation for specimen retrieval. There have been recent concerns about dissemination of malignant material from occult leiomyosarcomas; various statements have been issued in this regard. A detailed discussion of this is beyond the scope of this review.

Robotic surgery for endometriosis

Robotic surgery can facilitate difficult surgery in one quadrant and therefore can be used to excise deep, infiltrating endometriosis. In a study of 78 women comparing standard laparoscopy with robotic surgery for the treatment of endometriosis, there were no significant differences in time in hospital, blood loss or intraoperative and postoperative complications between the two groups. However, the robot group required significantly longer operating times.[30]

Robotic tubal anastomosis

A prospective cohort study[31] of robotic tubal anastomosis compared with the open approach showed that the procedure was feasible but operative times were higher in the robotic group. Pregnancy rates were comparable between groups (robot 62.5%; open 50%), yet the rate of abnormal pregnancy was higher in the robotic group. However, there is a paucity of literature in this area and more studies are needed.

Robotic cerclage

There have been reports of robotic assisted transabdominal cerclage during pregnancy with successful pregnancy outcomes.[32] One study by Moore et al.,[33] describing robotic transabdominal cerclage in 24 nonpregnant women, showed that though the operative time was longer, recovery time and blood loss were lower. They concluded that robotic cerclage was a safe alternative to the traditional laparotomy approach and is associated with quicker recovery. Cronin et al.[34] describe two cases of robotic interval cerclage in women with cervical insufficiency followed by pregnancies and term deliveries of two healthy infants. Further studies are needed to determine pregnancy and delivery rates in this group of women.

Training in robotic surgery

Learning curve

A number of studies have evaluated the integration of robotic surgery into training programs and the associated learning curve. It is generally proposed that there is a faster learning curve when developing robotic laparoscopic skills compared with traditional laparoscopy for both benign and oncology procedures.[24,35–37] This may in part be because of the proposed ergonomic benefits of robotic surgery.[36,38,39] One study comparing the learning curves for robotic and laparoscopic skills concluded that the robot allowed a quicker improvement in surgical skills compared with laparoscopy. Moreover, this effect was greater in the novice laparoscopic surgeon and was less noticeable in the experienced laparoscopic surgeon.[36]

A large single-centre prospective trial analysed the operative times for 1035 robotic-assisted total laparoscopic hysterectomies over a 5-year period; this included the training of 11 fellows in clinical gynaecologic oncology. The authors concluded that participation in a minimum of 50 cases should be sufficient to overcome the learning curve.[35] The learning curves for different robotic gynaecological surgeries vary from 20 cases for hysterectomy and pelvic lymphadenectomy for endometrial cancer, to 50 cases for benign hysterectomies and 10 cases for sacrocolpopexy.[24,40] As a comparison, traditional laparoscopic sacrocolpopexy was shown to have a learning curve between 18–24 cases.[41]

Individual credentialing

There are no national guidelines on credentialing for individual surgeons. However, Intuitive Surgical Inc have provided recommendations based on which institutions have developed training pathways. The initial phase of training should include robotic simulators. The da Vinci® skills simulator by Intuitive Surgical Inc is a virtual reality skills simulator; various other simulators are commercially available. After simulation training, training courses on animal or cadaveric models help enhance performance and shorten the learning curve. Dual console training can also facilitate training and collaboration between the mentor and trainee. Finally, live surgery under the guidance of a proctor for the first few robotic courses allows direct supervision and familiarisation with the new technique.[40] All cases performed should be reviewed for outcomes and complications.[3]

Training of theatre teams and robotic safety

Setting up a robotic program usually needs a planning phase, implementation phase and evolving programme phase.[3] In the planning phase, training of the surgeons and theatre teams takes place. Theatre teams should include specialist anaesthetists, surgeons, technicians and scrub nurses. In the implementation phase, the first few cases are performed by the team followed by the evolving programme phase where maintenance of skills and expansion takes place.

Robotic technology has the potential to malfunction, with a reported failure rate of 0.2–0.4%. Potential problems include equipment malfunction, instrument failure or port problems. The surgical team must therefore be familiar with troubleshooting common problems.[40] Patients should be counselled about this risk and operators should maintain laparoscopic skills to minimise the need to convert to open surgery in these cases. Operative checklists, such as the World Health Organization (WHO) checklist, promote focused team working; they should be considered for implementation in robotic surgery.

Cost

The initial setup and maintenance costs of the robot are very high. Intuitive Surgical Inc have a market monopoly and the purchase prices are in the range of $1–2.5 million.[42] The life of a robot is around 10 years but the robotic instruments can only be used up to 10 times. An increased operating time when compared with laparotomy also adds to the cost. The additional cost for a robotic hysterectomy compared with laparoscopic hysterectomy has been quoted as approximately $2600;[43] this difference is lower for oncological procedures.[44] Comparative figures between different countries cannot be used as the reimbursement rates are calculated differently in different areas.

Some studies have actually shown a cost saving.[45,46] A UK study demonstrated that robotic surgery for endometrial cancer was associated with the shortest stay in hospital, least high-dependency usage, significantly lower conversion rates, lower complication rates and an overall cost saving.[45] Some of the cost of robotic surgery is offset by the reduced length of hospital stay and earlier return to normal activities and work, especially where the procedures were done by laparotomy.[42,45] Overall, most studies demonstrate that open laparotomy is associated with higher costs than the robotic approach, mainly because of the length of hospital stay but the robotic approach is more expensive than the laparoscopic approach.[44–47] Thus, if the availability of a robot would lead to more minimal access surgeries being performed in an institution, there would be an overall benefit. A sufficient caseload is needed to justify the use of the robot in any institution so that it is cost effective and this can be achieved by sharing the robot between specialties.

Preowned systems can also be considered where cost is a major factor. As centres upgrade to newer systems, the older systems could be purchased by smaller centres at around 75% lower price points.[5] This would enable robotic surgery, with its associated benefits, to become more widely available.

Newer platforms

The da Vinci® robotic platform has replaced all the older platforms, such as Aesop, Amadeus and Zeus systems. Newer platforms will be available soon, one of which is the SPORT™ (Single Port Orifice Robotic Technology) Surgical System by Titan Medical Inc. (Toronto, Canada) that is expected to be commercially available by mid 2017. Robotic endoscope holders such as ViKY[48] could provide an alternative to complete telesurgery systems by offering a ‘third hand’ to the surgeon during a laparoscopic procedure. There have also been announcements of collaboration between Ethicon (Johnson & Johnson, Somerville, New Jersey, USA) and Google (Mountain View, California, USA) to develop surgical robotics. The introduction of these platforms could potentially lower the cost of robotic surgery by lowering initial overlay and instrument costs.

Ethical issues

Cost is a significant factor in the decision to offer services within the UK National Health Service. Until it can be proven that robotic surgery is superior to existing techniques, some may question the value of investing heavily in such novel technologies outside of clinical trials. Robotic and laparoscopic surgery have comparable outcomes; however the availability of advanced laparoscopic skills is limited by the steep learning curve. Robotic surgery has a shorter learning curve compared with laparoscopy and, therefore, potentially more surgeons would be able to acquire these skills. This would make minimally invasive surgery available to patients who would otherwise have been offered open surgery. Is it therefore ethical to deny patients the benefits of minimally invasive surgery solely based on cost? Moreover, the findings of Collins and Tulikangas[49] are interesting: randomised trials with new techniques are difficult to perform because patients would like to have the new technique, regardless of the evidence. In their study, the overwhelming majority opted to have the newer robotic technique. Should cost then take precedence over patient choice?

Conclusion

Robotic surgery has the potential to support gynaecological surgeons in offering the best care to their patients. The procedural benefits of greater precision and autonomous control by the surgeon appear to be reflected across benign and malignant disease procedures by a lower blood loss and a low conversion rate to laparotomy. The debate about robotic surgery has been ongoing[50] and reflects the dearth of good quality evidence. Further evidence is needed to understand the longer term outcomes for patients who undergo robotic surgery.

Disclosure of interests

RN and KK have no conflicts of interest.

TEJI received 2 days of practical training in robotic surgery in 2007, which included premium economy class travel to the USA and accommodation costs paid for, and organised by, Intuitive Surgical Inc. (CA, USA). Intuitive Surgical Inc also sponsored a day's preceptorship for TEJI at the Royal Marsden Hospital in 2013, and a day of training in Germany (including travel and accommodation) in May 2014. TEJI has not worked for Intuitive Surgical Inc as a proctor. TEJI is an officer of both the British and Irish association of Robotic Gynaecological Surgeons (BIARGS) and the British Society of Gynaecological Endoscopy (BSGE).

Author contributions

RN instigated the article, wrote the first draft and revised the manuscript. KK contributed to the first draft and revision of the manuscript. TEJI contributed to revision of the manuscript. All authors approved the final version.

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