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DOTTORATO IN FISIOPATOLOGIA E CLINICA DELL'APPARATO CARDIOVASCOLARE E RESPIRATORIO

Presidente: prof. Alfredo Mussi

Tesi di Dottorato

Valutazione clinica dello strumento robotico Da Vinci nella chirurgia polmonare.

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Revisori:

Thomas A. D'Amico MD, Gary Hock Endowed Professor and Vice-Chair of Surgery; Chief, Section of General Thoracic Surgery; Program Director, Thoracic Surgery; Duke University Medical Center. Durham, North Carolina, USA.

Alper Toker, MD, Professor of Thoracic Surgery, Hamidiye Mah. Barisyolu Cad Agaoglu MyCountry ; Sitesi G/5 Blok No:3 Cekmekoy Istanbul, Turkey.

Relatore: Prof. Alfredo Mussi **Candidato: Dott. Andrea Viti**

ABSTRACT

Purpose. The main end point of the study was to compare the surgical performance of robot-assisted pulmonary lobectomy with open (thoracotomy) lobectomy for clinical stage I (T1a N0 – T2a N0; T <5 cm) non-small cell lung cancer (NSCLC). Secondary end points were description of short and mid-term clinical outcomes of the robotic procedure, in particular in terms of pain perception and quality of life.

Methods. A retrospective analysis of prospectively collected data was performed, concerning totally endoscopic robotic lobectomies (RL) performed between January 2011 and December 2013 on 86 patients for Stage I NSCLC. The robotic procedures were conducted employing a four-arm robotic device (Da Vinci Robotic System) through a five port minimally invasive access (a fifth utility port was needed for insertion of suction devices and gauze placement). After lobectomy, a systematic lymphadenectomy was performed in all cases. The surgical outcomes were subsequently compared to a cohort of 160 patients who afforded standard "open" lobectomy (OL) in the same period, and the data were matched to the robotic group using propensity scores for a series of pre-determined preoperative variables.

Results. Clinical and pathologic characteristics were similar between the two groups. Conversion from robotic to open surgery was necessary in 4 cases. Median operating time was 168 min (110 – 308 min) for robotic procedures and 122 min (97 – 145 min) for open procedures. Median number of lymph nodes removed and rate of major complication were similar in the 2 groups. Pain perception in the first three post-operative days was significantly lower in the robotic cohort. Median postoperative drainage and hospitalization time were similar between two groups. Quality of life, determined by the Short Form Health Survey (SF 12), was evaluated after 4 weeks from

surgery. A better average mental and physical health perception was evidenced in the RL group as compared to OL (Mental: 56.2 vs 39, *p = 0.01*; Physical 43.8 vs 32.1, *p = 0.04*).

Conclusions. Robotic lobectomy with lymph node dissection for clinical stage I lung cancer proved to be equal to open lobectomy in terms of surgical performance. Furthermore, robotic approach allows a faster recovery with a long lasting limitation of pain perception, improvement of quality of life and faster return to the preoperative activity level.

INTRODUCTION

Lobectomy, achieved both trough a thoracotomic or minimally invasive approach is the treatment of choice for both early and locally advanced non-small lung cancer [1, 2]. A rapid shift from “classic” thoracotomic approach to minimally invasive techniques for lobectomy took place in the last decade, and Video-assisted thoracic surgery (VATS) Lobectomy became the gold standard in the treatment of stage I and even stage II NSCLC [3, 4]. It displays several advantages, first of all a minor degree of tissue trauma, with less post-surgical pain and faster recovery for the patients [5, 6]. Robotic surgical systems may facilitate major lung resections in a minimally invasive setting. In particular, the robotic device allows three dimensional vision and magnification of the surgical field and an incremented manoeuvrability of the instruments, given their 7-degrees of freedom [7]. The number of operative series progressively incremented over time, confirming the safety and feasibility of robotic lobectomy in the treatment of early stage NSCLC and its oncologic results [8]. We decided to compare robotic lobectomy (RL) to standard open lobectomy (OL) in order to directly identify the possible advantages of this technology over conventional open surgery. We therefore designed a nonrandomized, controlled trial with adequate number of cases in order to better define the surgical performance of the robotic device, in terms of surgical time, number of lymph nodes removed, perioperative complications, drainage and hospitalization time, long term complications and impact on quality of life, in comparison with a matched group of patients with similar clinicopathologic features who underwent standard lobectomy. Data collection and analysis was allowed by the Ethical Committee of the University Hospitals of Pisa.

MATERIAL AND METHODS

A retrospective analysis of prospectively collected data from January 2011 to December 2013 was performed on 144 patients subjected to robot-assisted lobectomy. Inclusion characteristics for this study were:

- Diagnosis of NSCLC
- Clinical Stage I
- Age <75 years,
- Eastern Cooperative Oncology Group (ECOG) Performance status 0-1,
- Adequate pulmonary function (Forced expiratory volume in 1 second >60%, Diffusion of Carbon Monoxide >80%; maximal oxygen consumption (VO_2 max) >18 ml/kg/min),
- American Society of Anaesthesiologists (ASA) score 1 to 3.

Only clinical stage I tumors (cT1a N0 – cT2a N0) were included; in particular we selected only tumors with a diameter <5 cm, without involvement of chest wall and/or mediastinum and/or diaphragm, main bronchus, and without overt lymph node metastases. We limited the study to clinical Stage I NSCLC because in the first year of the study period (2011), the use of the robot was limited to this setting of patients, although in the subsequent years the robotic approach was employed in more advanced stages. Patients of the robotic group were selected and operated by a single surgeon proficient in robotic surgery. All patients underwent complete preoperative staging and complete functional evaluation. In particular, PET-CT scan was performed on a routine basis and suspect lymph nodal involvement was ruled out with trans bronchial needle aspiration (TBNA)

and mediastinoscopy when needed. Functional evaluation included complete spirometric evaluation with diffusion of Carbon Monoxide (DLCO) and ergospirometry when required.

In the study period, 86 patients fulfilling the inclusion criteria were selected. A separate cohort of patients subjected to lobectomy through thoracotomy (open lobectomy, OL) with similar characteristics was defined employing propensity scores, a quasi-randomization method which allows group of patients to be well matched and to undergo proper performance and outcome comparison (see statistical analysis). During the study period a total of 467 open lobectomies have been performed. From these, 160 procedures fulfilled the predefined criteria for matching with the robotic procedures. Robotic approach was chosen on a non-randomized fashion, basing primarily on limited availability of the robot (1 or 2 times a week), given the rotation of other specialities on the same machine, and the presence of only one surgeon familiar with the robotic device.

Surgical performance parameters

The following were considered surgical performance parameters: number of lymph nodes removed, nodal upstaging, surgical margin positivity, operative time (minutes), need for blood transfusion, post-operative (30 days) complications. Complication magnitude was defined according to Clavien-Dindo Classification [9]. Minor complication requires no further (Grade I) or minimal treatment (Grade II). Major complication requires surgical, radiologic, endoscopic intervention (grade III) or intensive care unit management and life support (grade IV). Operative time was considered from skin incision to closure, and included frozen section examination when needed. Operative time included also the time needed for positioning the surgical cart and robot arms in the surgical field (docking time).

Outcome parameters

Post operative pain perception, duration of chest drainage, hospitalization time, time to return to preoperative level of activity or status were evaluated. Pain perception was assessed in the first three days and then once a week in the first three weeks, using the Verbal Numeric Rating Scale (VNRS). Pain was then evaluated as part of the quality of life assessment (see later). Chest tubes were removed in absence of air leak for at least 24 hours, or when daily drainage was inferior to 300 ml. Return to a "normal activity status" (working activity) was assessed by means of direct interview of the patient after about one month from intervention and was described as > or < of 28 days. Quality of life was defined by a Short Form Health Survey (SF 12) method, a widespread method for *quality of life* assessment in adult populations [10, 11]. The survey describes both the physical and mental health status basing on four scales for the physical component summary (PCS: Physical Functioning, Role-Physical, Bodily pain, General Health) and mental component summary (MCS: Vitality, Social Functioning, Role-Emotional, Mental Health). The survey was completed preoperatively, after four weeks and finally after five months from surgery. Data were acquired basing on telephonic interview or during outpatient clinical evaluation.

Robotic Lobectomy

All patients signed an informant consent to undergone lobectomy. The technique of robotic assisted lobectomy has been previously described in detail [6]. A four arm robotic device with high definition magnified 3D vision was employed in all cases. The patient, after general anaesthesia and double lumen tube intubation was placed in lateral decubitus, and the surgical cart of the robotic system was placed at the head of the patient. Four incisions allowed robotic arm positioning (Figure 1). The first port was placed in the seventh or eighth inter-costal space on

the middle axillary line for the camera (12 mm, 30° angled down scope). The other port incisions (8 mm) were performed in the fifth or sixth inter-costal space on the anterior axillary line, sixth or seventh inter-costal space on the posterior axillary line and in the auscultatory area (for the fourth arm). A utility, 8 mm port between the camera port and the anterior robotic port can be positioned to allow stapler or suction devices insertion by the assistant surgeon. In absence of preoperative diagnosis, the lesion was identified and resected with a robotically-assisted wedge resection, and frozen section analysis was performed. Dissection started at the level of pulmonary ligament and continued on the anterior hilum, employing Cadiere forceps and cautery hook. Vascular structures were isolated, and, as a general rule, arteries were ligated prior to veins, to avoid lung congestion. For vascular ligation, plastic clips (Hem-o-lok®,Teleflex Medical, Research Triangle Park, NC), or direct suturing with linen was preferred to stapler because it resulted a more time-saving approach than positioning a stapling device by the assistant surgeon. Veins and bronchi were sutured with endostaplers. Hilar and mediastinal dissection was performed after lobectomy with removal of lymph nodes at station 9, 7, 10, 4R and 2R on the right and at station 9, 7, 6 and 5 on the left (station 4L was not routinely dissected).

Statistical analysis

A greedy algorhytm was employed to create a cohort of propensity score matched patients with similar characteristics to the robotic lobectomy group for a given number of preoperative characteristics, as described in Table 1. Propensity scores were used to avoid the bias of the lack of randomization between the two groups [5]. Therefore, a group of 160 open lobectomies was selected. Logistic regression analysis was used to identify covariates among the baseline patient variables that were imbalanced between the two groups from which the model was derived. Resulting matched patients were analysed for differences in selected intraoperative and postoperative outcomes. Pearson's χ^2 test was used to calculate the probability value for the

comparison of dichotomous variables. Fisher's exact test was used when the number in any cell was less than five. Statistical and mathematical models were created and analysed using Wolfram Mathematica 8.0 (Wolfram Mathematica is a computational software program used in scientific, engineering and mathematical fields and other areas of technical computing. See http://www.wolfram.com/).

RESULTS

Clinicopathologic characteristics

At the end of the study period (January 2011-December 2013), 86 patients underwent robotic lobectomy for clinical Stage I NSCLC. Conversion thoracotomy was needed in 4 cases: in 3 for adhesions and in 1 to allow safer isolation of vascular structures in presence of calcified hilar lymph nodes. No major intraoperative bleeding requiring emergent conversion occurred. Patient characteristics are summarized in table 1. The robotic lobectomy group was matched with a cohort of patients with overlapping characteristics, who underwent thoracotomic lobectomy. The robotic group was composed by 26 right upper lobectomies, 7 middle lobe lobectomies, 15 right lower lobectomies, 24 left upper lobectomies, 14 left lower lobectomies. Distribution of lobectomies according to site was similar in the propensity score matched group, in particular upper lobectomies appeared in similar proportions in the two groups (see table 1). Pathologic diagnosis resulted Adenocarcinoma in 56 cases, Squamous Cell Carcinoma in 27 cases, large cell neuroendocrine cancer in 2 cases and adenosquamous carcinoma in one case. Pathologic stage was Ia in 24 patients, Ib in 37 patients, IIa (N1) in 17 patients, IIb due to multifocal neoplasia within the same lobe (T3) in 4 patients, and IIIa due to mediastinal lymph node involvement (N2) in 4 patients.

Surgical performance and short-term outcomes

Operative time resulted 168 minutes (range: 110 – 308) for robotic lobectomy and 112 (range: 108 – 188) for open lobectomy (*p <0.001*). Operative time encompassed docking time (mean 6 ± 3.2 minutes). Median number of lymph nodes removed was 21 (range 6 – 33) in the robotic group and 19 (range 5 – 38) in the thoracotomic group (*p = 0.752*). Number of N1 and N2 nodes were similar between RL and OL (9 vs 7 and 11 vs 13 respectively; *p = 0.571 and p = 0.653* respectively). Interlobar and Lobar lymph nodes (stations 11-12) were also harvested in similar number between the two groups (median number of 3 nodes in both groups). Nodal upstaging rate was higher in the robotic group, although this difference didn't reach statistical significance (21/90 patients in the RL group and 28/180 patients in the OL group; *p = 0.061*). Resection margins resulted negative in all patients.

Postoperative complications are showed in Table 2. The robotic group presented a lower incidence of delayed (not-intraoperative) emothorax and postoperative pneumonia (*p = 0.050* and *p = 0.049*). Furthermore, the patients in the robotic group presented lower rate of atelectasis needing bronchoscopy (*p = 0.026*). Minor complications rate was lower in the robotic group (*p = 0.02*). On the other hand, incidence of prolonged air leak resulted similar in the two groups (*p = 0.877*). Pain perception, assessed with VNRS scale, was significantly lower in the robotic group at three days and at three weeks (*p = 0.023* and *p = 0.015*). Chest tube removal time were similar between the two procedures (3 days, range 2 – 18 days in the robotic group; 5 days, range 3 – 16 days for the thoracotomy group; *p = 0.671*). Also post-operative hospitalization time was similar between the two groups (4 days, range 3 – 10 and 5 days, range 4 – 34; *p = 0.351*). Patients were discharged with chest tube connected to an Heimlich valve in 4 cases after RL and 7 cases after OL (*p = 0.451*).

Mid-term outcomes and quality of life evaluation

Late complications were evaluated after one month and then five months from the procedure (as part of SF 12 evaluation visit). Follow up information was complete in 94% of patients. The main complaint was persistent pain (18 cases in the thoracotomy group and 2 cases in the robotic group; *p = 0.020*) Patients from the RL group experienced faster return to normal activity than OL group (16 days, range 11 – 31 and 29 days, range 21 – 40; *p = 0.03*). In particular return to preoperative working activity level was >28 days in 4 cases in the RL group and 29 cases in the OL group (*p = 0.007*).

SF 12 survey evidenced a better average mental and physical health perception at 4 weeks postoperatively in patients who underwent the RL relative to patients who underwent an OL (Mental: 56.2 vs 39; *p = 0.047*; Physical 53.8 vs 32.1; *p = 0.020*). Both mental and physical health perception maintained a trend toward well-being in the RL group after five months; anyway, the difference in SF 12 scores did not reach statistical significance.

DISCUSSION

In 2008, Melfi et al. reported a retrospective evaluation on a large series of robot assisted lobectomies using a three arm robotic device [12]. With the development of a four-arm device, the technique has been slightly modified, allowing a totally endoscopic approach with encouraging results [13]. The new device brought a standardization of the technique (optimization of port mapping, identification of the more suitable instruments, and definition of the more rapid step sequence of the procedure). We decided to compare the robotic technique to the standard approach on clinical stage I NSCLC to better identify differences and avoid biases derived from more advanced stages, such as preoperative chemotherapy, larger lesions (>5 cm), or extensive lymphadenopathies that could modify standard surgical strategy. Propensity score matching allowed us to perform a comparison of the two methods, given the non-randomized nature of the technique. When evaluating our outcomes, operative time was longer in the RL group. However, from the beginning of the robotic program, a progressive shortening of the procedures was observed. In the study period (three years), median operative time resulted 168 minutes (110 – 308 minutes), while the procedures performed with the three arm robotic device lasted 237 ± 66.9 minutes, as previously reported [13]. The reduction of operative time resulted from dedicated training of personnel operating in the surgical theatre (surgeon, nurses, and anaesthesiologists) and improvement of instrumentation. Lymph nodal dissection harvested a similar number of lymph nodes in the two groups. Veronesi et al [7] reported a similar result in a series of 54 RL compared to 54 OLs. In their study population, lymphadenectomy retrieved a median of 17 lymph nodes (range 4-30) in the RL group and 18 (range 4-27) in the OL group. Cerfolio et al. [14] reported a median of 11 N2 and 5 N1 lymph nodes in course of 106 consecutive RLs with no differences when compared to a propensity score matched group of 318 OLs. The efficacy of

lymphadenectomy during RL is related to the powerful vision and manipulation capacity, in particular when removing N1 lymph nodes, which need careful dissection from hilar structures.

When analysing the complication rate, we found a similar incidence of major complications, according to the Clavien-Dindo classification. However, the incidence of post-operative hemothorax and pneumonia resulted lower in the RL group. This fact should be related to minor amount of blood loss in the robotic group, as suggested by the minor number of blood transfusion after RL, and minor pain leading to more appropriate coughing and faster respiratory rehabilitation. Both those factors probably lead to a limited incidence of Atrial Fibrillation in the RL group, a common complication of major lung surgery. Incidence of prolonged air leak was similar, this data may derive from a similar incidence of subclinical COPD in the two groups.

The main outcomes were related to pain perception and quality of life after surgery. Pain perception was significantly lower in the RL group, enhancing patient's recovery in-hospital and at home. RL group showed a trend toward shorter hospitalization, even if this difference did not reach statistical significance. This fact should be related to the lower incidence of minor complications (in particular supraventricular arrhythmia, atelectasis, surgical access hematoma/ infection and pain). Other authors observed a shorter hospitalization after RL: median of 2 vs 4 days ($p = 0.01$) [11], 4 vs 6 days ($p = 0.02$) [7]. In particular, Cerfolio et al. [14] reported a shorter drainage time after RL (1.5 days vs 3 days). We did not find a statistically significant difference in drainage time between the two groups, probably due to similar air leak duration. As far as quality of life is concerned, after RL patients experienced both physical and mental recovery in a shorter time. In particular, our analysis focused on the incidence of chronic pain, and its impairment of quality of life. When compared to thoracotomy, a robotic approach seems to limit the degree of intercostal neuropathy with a limited need for pharmacologic treatment and limited impact on quality of life and working activity. In this study, quality of life was assessed by SF 12 survey. The

main limit of this observation is based largely on its subjectivity. However, the results underlined the possibility of a faster recovery after RL, when compared to standard approach. This brought a gain in working days in the portion of population in the active age. The next step would be the evaluation of the robotic approach in comparison to VATS lobectomy (VL). Stephens et al. [15] evidenced that patients undergoing VATS had less perioperative morbidity compared with matched OL controls. Regional lymphadenectomy, nodal upstaging, overall and disease-free survival were similar between VL and OL groups. On the other hand, Faivar et al. [16] evaluated the results of 181 RL and compared the outcomes of OL and VL as reported in the STS database (respectively 5913 and 4612 procedures). They evidenced a minor morbidity and mortality in their RL cohort, with shorter hospitalization after robotic approach when compared to OL and VL. However, further studies are needed to compare minimally invasive approaches. In order to ensure adequate comparison, VATS lobectomy and Robot Assisted lobectomy should be performed in the same period of time with a state-of-the-art technology and skills in both cases, and possibly in a randomized fashion.

CONCLUSIONS

Robotic-assisted lobectomy with lymph node dissection for clinical stage I lung cancer proved to be equal to open lobectomy in terms of surgical performance. When directly compared to thoracotomy, the minimally invasive approach allows a faster recovery with a long lasting limitation of pain perception, improvement of quality of life and faster return to the preoperative activity level, when compared to the traditional approach.

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Preoperative characteristics	**Robotic Assisted Lobectomy Group (N = 86)**	**Open Lobectomy Group (N = 160)**	***P value***
Age (%)			
• ≤75	74	70	*0.739*
• >76	26	30	*0.593*
Sex (%)			
• Male	57	54	*0.776*
• Female	43	46	*0.751*
ASA Score (%)			
• 1	41	38	*0.736*
• 2	48	48	*N.A.*
• 3	11	14	*0.549*
ECOG Performance status (%)			
• 0	87	82	*0.700*
• 1	13	18	*0.369*
FEV1% (%)			
• 60 – 80%	40	45	*0.588*
• >80%	60	55	*0.651*
DLCO (%)			
• 60 – 80%	33	27	*0.439*
• >80%	67	73	*0.612*
Upper Lobes (%)	61	57	*0.712*

Table 1. Patients' characteristics.

	Robotic Assisted Lobectomy (N = 86)	Open Lobectomy (N = 160)	*P value*
Number of lymph nodes removed (median, range) [1]	21 (6 – 34)	19 (5 – 38)	*0.752*
Operative Time (min; median, range) [2]	168 (110-308)	112 (108 – 188)	*<0.001*
Major Complications [3]			
• Hemothorax	1	6	*0.050*
• Empyema	1	2	*N.A.*
• Pneumonia	1	6	*0.05*
• Broncho-pleural fistula	0	0	*N.A.*
• Major cardiovascular event	2	2	*0.523*
• ARDS	2	3	*0.723*
• Atelectasis needing bronchoscopy	1	13	*0.026*
Minor Complications [3]	10	43	*0.022*
• Atrial fibrillation	3	18	*0.048*
• Prolonged air leak	7	13	*0.877*
• Wound infection	1	12	*0.036*
Need for Blood transfusion	4	18	*0.005*
Drainage time (Days, median, range)	3 (2 – 18)	5 (3 – 19)	*0.671*
Days from intervention to discharge (Days, median, range)	4 (3 – 10)	6 (4 – 34)	*0.351*
Pain Perception (Verbal Numeric Rating Scale, median, range) [4]			
• First three days	3 (1 – 6)	7 (4 – 9)	*0.023*
• First three weeks	2 (1 – 4)	6 (4 – 8)	*0.015*
Late Complications (>1 month)			
• Persistent Pain (#)	3	18	*0.020*
• Thoracotomy revision	0	5	*N.A.*
• Development of keloids	0	3	*N.A.*
Return to working activity >28 days [5]	4	29	*0.007*
SF 12 [6] at 4 weeks			
• Mental	56.2	39	*0.047*
• Physical	53.8	32.1	*0.020*

Table 2. Surgical performance and outcomes.

Notes

1 *Lymphadenectomy included station 4R, 7, 10R, 8, 9 on the right and station 5, 6, 7, 9, 10L on the left.*

2 *From skin incision to skin closure. Included the docking time of the Da Vinci Surgical Chart.*

3 *Complication magnitude was defined according to Clavien – Dindo Classification [14]. Minor complication requires no further or minimal treatment. Major complication requires surgical, radiologic, endoscopic intervention (grade III) or intensive care unit management and life support (grade IV).*

4 *0 = No Pain, 1 – 3 = Mild Pain (nagging, annoying, interfering little with Activities of Daily Living ADLs), 4 – 6 = Moderate Pain (interferes significantly with ADLs), 7 – 10 = Severe Pain (disabling; unable to perform ADLs).*

5 *When applicable (only patient in working active age).*

6 *Short Form Health Survey (SF 12) method [15].*

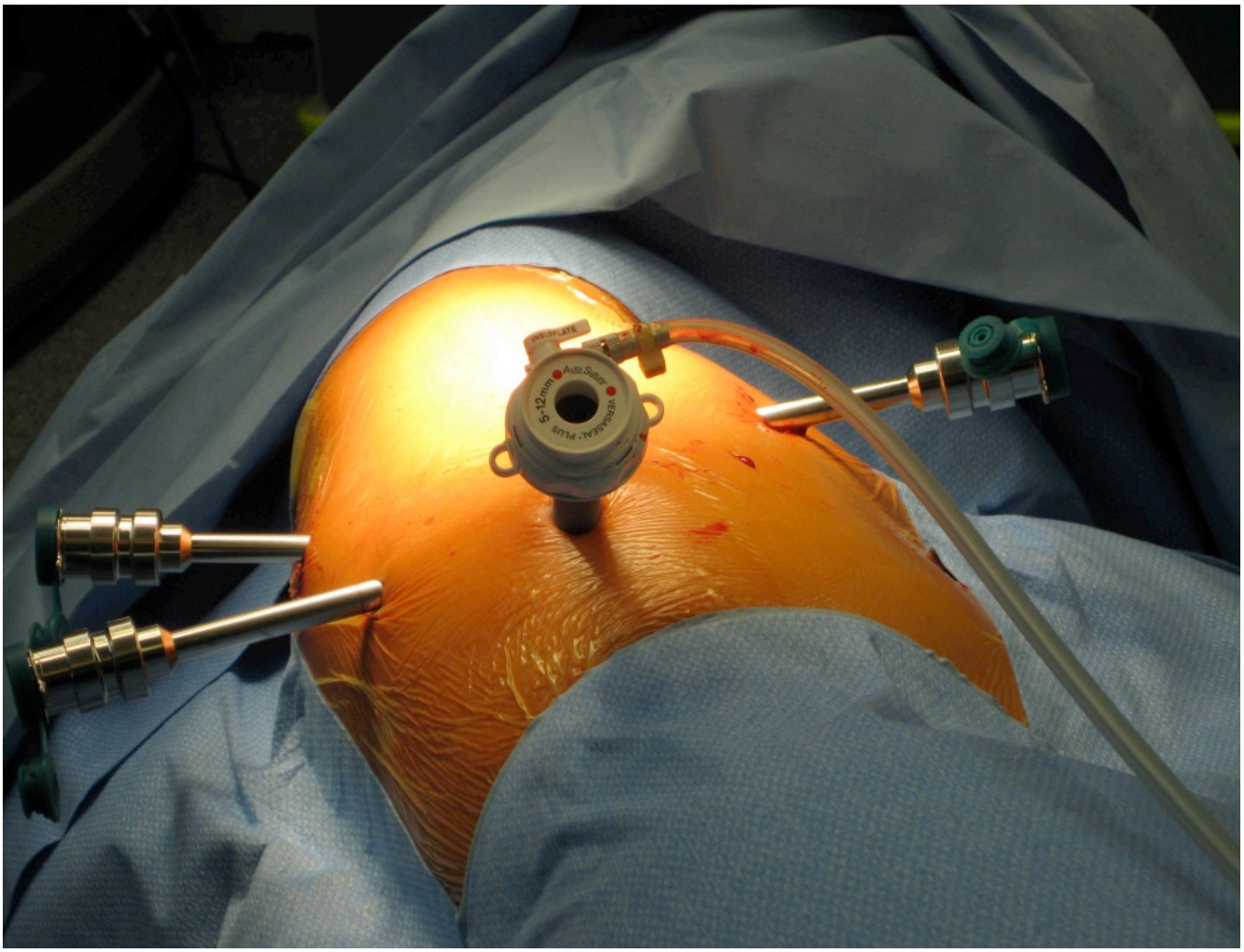

Figure 1. Port placement.

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