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Italian multicenter study on complications of laparoscopic myomectomy

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KEYWORDS:
Laparoscopic myomectomy;
Complications;
Adenomyosis;
Uterine rupture

Abstract

STUDY OBJECTIVE: To study intraoperative and postoperative complications of laparoscopic myomectomy and patients' characteristics influencing this risk.

DESIGN: Prospective study, with a review of the patient records by the first author (Canadian Task Force classification II-2).

SETTING: Four Italian referral centers.

PATIENTS: The incidence and type of complications occurring in 2050 laparoscopic myomectomies undertaken from January 1998 through December 2004 were recorded.

INTERVENTIONS: The surgical technique, as well as the expertise of the operators, was the same for the 4 centers. Injection of vasoconstrictive agents was used in 37%. The serosa was always incised in a vertical fashion; mechanical enucleation of the myoma was completed whenever possible; suture was performed in 1 or 2 layers with deep and large stitches swaged to 1 or 0 polyglactin sutures that were tied intracorporeally or extracorporeally.

MEASUREMENTS AND MAIN RESULTS: Single or multiple myomectomies ($n = 2050$) for symptomatic myomas measuring at least 4 cm in diameter were performed. Most patients (48%) had more than 1 myoma, with a maximum of 15 per patient (myomas removed for patients: 2.26 ± 1.8, mean $\pm$ SD). Myoma size ranged from 1 to 20 cm (mean 6.40 ± 2.6 SD). Myomas smaller than 4 cm were removed during myomectomy for larger ones. Total complication rate was 11.1% (225/2050 cases). Minor complications accounted for 9.1% (187/2050 cases) and major complications for 2.02% (38/2050 cases). The most serious events were hemorrhages (14 cases, 0.68%) requiring blood transfusions in 3 cases (0.14%); 10 postoperative hematomas (0.48%, one in the broad ligament and 9 in the myomectomy scar); 1 bowel injury (0.04%); 1 postoperative acute kidney failure (0.04%); and 2 unexpected sarcomas (0.09%). Failure to complete planned surgery occurred in 7 cases (0.34%). Two patients were readmitted for surgery (0.09%): 1 had a laparoscopic hysterectomy because of a severe blood loss, and the other had drainage of a hematoma in the broad ligament. After a follow-up period of 41.70 ± 23.03 months (mean $\pm$ SD), 386 (22.9%) patients conceived, with a pregnancy rate in patients wishing pregnancy of 69.8%; among them, 1 (0.26%) recorded spontaneous uterine rupture at 33 weeks gestation. Odds ratio computed to estimate the risk of complications in relation to the patient characteristics showed that the probability of complications significantly rises with an increase in the number (more than 3 myomas OR: 4.46, $p < .001$) and with the intramural (OR: 1.48, $p < .05$) or the

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intraligamentous location of myomas (OR: 2.36, p <.01) whereas the myoma size seems to influence particularly the risk of major complications (OR: 6.88, p <.001).

CONCLUSIONS: This is one of the largest series reported of laparoscopic myomectomy and the first focused on complications. The complication rate appears to be better than acceptable in comparison with complication rates reported after laparotomic myomectomies. Laparoscopic myomectomy, when performed by an experienced surgeon, can be considered a safe technique with an extremely low failure rate and good results in terms of pregnancy outcome.

Very few laparoscopic gynecologic procedures have been so much criticized and discussed as laparoscopic myomectomy (LM) has. Notwithstanding the fact that, more than 20 years after Semm[1] performed the first laparoscopic myomectomy, the definitive positive results in favor of this technique have been published. Recognized advantages of LM are in fact the ones peculiar to minimal access surgery, including shorter hospitalization and rapid recovery.[2–4] Well-designed randomized prospective studies have also demonstrated that laparoscopic myomectomy may offer patients the benefits of less postoperative pain, lower hemoglobin drop, and lower febrile morbidity in comparison to traditional laparotomy.[5] Moreover, clear evidence has shown that, although LM is regarded as a procedure of medium complexity that requires high mastery in endoscopic suturing[6] because it demands complete laparoscopic hemostasis and closure of the operative site to avoid uterine rupture in a potential future pregnancy, no significant differences were found concerning pregnancy rate and abortion rate[7] in comparison with "open" procedures.

However, as with any surgical procedure, the laparoscopic approach is associated with complications that must be offset against the expected clinical benefits. Anxiety has been expressed that the rate of complications associated with this technique may be greater than those associated with traditional abdominal myomectomy. Isolated sensational reports of adverse outcomes continue to raise doubts about the safety of the laparoscopic approach to myomectomy.[8,9] As a matter of fact, only a few reports with a small number of patients have been previously reported in literature,[10,11] and little is known about the concrete incidence of complications during and after this surgical procedure; also little is known about the patient characteristics that may influence this risk. With this large study we wanted to fill the gap of lack of prospective information on complications of laparoscopic myomectomy and on factors that may influence the rate of adverse events.

Subjects and methods

After agreement among the study participants and Ethics Board Committees of 4 referral centers in Italy, a common database for the collection of data was designed. From January 1998 through December 2004, 2050 single or multiple myomectomies were performed, and data were uniformly gathered. All the procedures were completed by 5 experienced surgeons who had already accomplished their learning curve and who used the same surgical technique. Diagnosis was performed by transvaginal and abdominal ultrasonography. Hysteroscopy was performed when ultrasound scans showed the probable involvement of the endometrium. Indications for surgery were infertility, recent and significant enlargement, and symptoms (pelvic pain or abnormal uterine bleeding). Inclusion criteria were age ≤42 years, the presence of at least 1 symptomatic myoma ≥4 cm, and the absence of submucous myomas that could be removed by hysteroscopy. No upper limit to myoma size was posed, as long as the myoma could be mobilized. Usually a number of myomas for patients ≤8 were the indication to myomectomy, but in some case the number of myomas was higher. Gonadotropin-releasing hormone (GnRH) agonists were prescribed for 3 months only in patients with very large myoma or severe anemia because of persistent menometrorrhagia to improve hemoglobin concentration before surgery (164 cases, 8%). At least 1 week before the procedure, blood for a possible autologous transfusion was collected in 1599 patients (78%). A standard bowel preparation and short-term antibiotic prophylaxis (cefoxitin 2 g) was given to the patients. Complications were classified as intraoperative events; a drop in hemoglobin levels >4 g/dL or intraoperative or postoperative bleeding necessitating transfusion; injury to the bladder, bowel or ureters; procedure failing; complications necessitating repeat surgery; readmission to the hospital; postoperative hematomas; uterine sarcomas undiagnosed before surgery; and uterine rupture in subsequent pregnancies were considered major complications and cystitis, febrile morbidity >38°C, and manipulator injuries that were considered minor complications. Conversion to laparotomy was defined as the need for a standard laparotomy at any time during the procedure, either because of complications or technical difficulties. The op-

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erative time was calculated from the anesthesia chart and included the induction of anesthesia and the positioning of the patient. The preoperative hemoglobin concentration was compared with that observed on postoperative day 1 and the perioperative hemoglobin concentration change thus calculated. Postoperative fever was considered to be body temperature >38°C in 2 consecutive measurements at least 6 hours apart, excluding the first 24 hours. The hospital stay was tracked in whole days. Urinary tract infection was recorded as isolation of more than 100 000 colony-forming units of a single species of bacteria per milliliter of urine sampled routinely 1 day after the urinary catheter had been removed or at any time when patients experienced symptoms. Transvaginal ultrasound examination was performed before, within 45 days after surgery (to verify the adequate healing of the myomectomy scar), and every 6 months, whenever possible. Data were prospectively collected at the time of surgery, discharge day, and completed at the time of recovery (30–45 days after surgery), and the patients were followed to note any morbidity or symptoms after myomectomy. Information about subsequent fertility and obstetric outcome was obtained from hospital records, physicians, and direct reports from the patients. Only patients with a follow-up period at least of 6 months were included in the study.

Operative technique

All the surgeons used standardized surgical techniques. Under general endotracheal anesthesia, the patient was positioned in a lithotomic position with arms at the sides. A Foley catheter was placed in the bladder. The cervix was grasped with a tenaculum, dilated with Hegar cones, and a uterine manipulator (Valtchev; Conkin Surgical Instruments, Toronto, Ontario, Canada; or MUR 18; Sofar, Trezzano Rosa, Italy) was inserted to allow correct exposure of the myomas and strong counter traction during enucleation and suturing. The abdomen was insufflated with CO_2 at a preset pressure of 18 mm Hg through a Veres needle inserted at the umbilicus. A surgeon used an open entry technique. Video laparoscopy was performed with a 10-mm laparoscope in standard umbilical position. Myomectomies were performed with standard technique[12,13] with 3 ancillary suprapubic ports. Two suprapubic access routes (5 mm and 10 mm) were inserted lateral to the deep inferior epigastric arteries and slightly higher than usual: in fact the accessory trocars should be inserted sufficiently high to provide an easy approach to the myomas for the laparoscopic instruments. A third trocar (5 mm) was inserted in the midline level, or higher than the other 2.

For pedunculated myomas, bipolar forceps and scissors were used for the smaller ones; otherwise, the pedicle was secured using a pre-tied or extra corporeally-tied loop and coagulated and transected with bipolar forceps and scissors. To reduce vascularization and blood loss, starting in 1997 we injected myomas with diluted ornithine vasopressin[12] and now, we are using diluted (20 IU: 500 mL) argipressin. The vasoconstrictive agent was injected laparoscopically between the myometrium and the myoma capsule, looking for the cleavage plane, until blanching occurred. For subserosal and intramural myomas, a vertical incision (hysterotomy), both for anterior and posterior myomas, was made on the serosa overlying the myoma down and through the myoma pseudocapsule with a unipolar hook and high cutting current.

After exposure of the myoma, a grasping forceps was positioned to apply traction on the myoma and expose the cleavage plane. Traction on the myoma applied with tenaculum with a counter traction on the uterus facilitated dissection. Mechanical enucleation was carried out. Division of some residual connective fibers surrounding the myoma was obtained with unipolar hook or with Ultrasonic Cutting and Coagulating System (SonoSurg; Olympus, Tokyo, Japan), the latter having the advantage of less tissue charring. The only exception to this technique was in case of unsuspected adenomyosis (3% of myomectomies performed). In this situation, the cleavage plane does not exist, and excision can be carried out with monopolar hook, sharp cutting or ultrasonic energy device, paying attention to use electrosurgery close to the myoma and not to the myometrium.

With regard to intraligamentous myomas, they usually are to be considered as pedunculated or subserosal myomas arising into the broad ligament. The peritoneum surrounding the myoma was incised. The myoma was gently enucleated by the surrounding areolar tissue. Hemostasis could be achieved with bipolar coagulation of the vessels reaching the myoma paying attention to dangerous structures such as the ureter or uterine vessels. When the base of the myoma has been reached, coagulation of the blood supply was obtained with bipolar forceps. For subserosal or intramural myomas, suturing was usually done along 1 or 2 layers, depending on the depth of the incision. It consisted of bringing the entire thickness of the edges of the myomectomy site together to prevent the formation of hematomas. We used large, curved needles (CT 1, 30 or 40 mm) swaged to polyglactin suture (1- or 0-Vicryl; Johnson and Johnson, Somerville, NJ). For 1-layer sutures, we used interrupted, simple, or more frequently cross-stitches, tied intracorporeally. In 78% of cases (3605 myomas removed), it was necessary to suture in 2 layers. In this case, suturing was usually done along different planes: one large stitch reaching the deep layers and 1 more-superficial suture to introflect the serosa. As for double-layer closures, a running suture was used in 10% of cases: it was applied first in the deeper plane starting from the apex of the myomectomy scar to the base, continuing along the more superficial plane from the base to the apex. The suture was in the end tied intracorporeally with the tail of the running suture.

Statistics

Data were analyzed with the R statistical package (R Foundation, from http://www.r-project.org). A description of the studied population was initially performed, and correlation between quantitative variables was calculated by a bivariate analysis according to Spearman. Subjects were then divided into 2 groups on the basis of the presence or absence of complications during or after laparoscopic myomectomy. A 2-way analysis of variance procedure, considering as factors the complications and the centers, was used to detect whether differences in the quantitative variables arose between the 2 groups, taking into account possible differences among centers. The interaction term (complication $\times$ center) was to be considered initially and then eliminated if not significant. For the qualitative variables, the Mantel Haenszel procedure was performed, with the center as confounding factor. For variable with k levels, with k >2, k-1 analyses were conducted, considering $2 \times 2 \times C$ tables where C is the number of levels of the confounding factor. For each analysis a value of $p \leq .05$ was considered to be significant.

To determine whether the studied variables (quantitative and qualitative) could be used to predict the development of complications, a logistic regression model was used, with development of complications as the dependent variable and number of myomas removed per patient (divided into 3 classes: 1 myoma, 2 or 3 myomas, more than 3 myomas), myoma size (divided into 2 classes: <5 cm, ≥ 5 cm), myoma type, age, operative time, length of hospitalization, hemoglobin plasma level before and after surgery, and use of a vasoconstrictor during surgery as independent variables. For the categorical variables with more than 2 levels, dummy variables separating the levels were created. Odds ratios were computed to estimate the risk for development of complications. For each categorical variable, the reference level was the level with the lower expected risk of complications. Subsequently, a forward stepwise procedure (Wald statistics)[14] was performed to obtain a final model, including only the subset of variables significant in predicting complications.

Finally, the group with complications was divided into 2 subgroups: patients with minor complications (fever, urologic complications, and manipulator injuries) and patients with major complications (postoperative kidney failure, bowel injury, hematomas, anemia, redo surgeries, uterine rupture, procedure failings, and sarcomas). The same statistical approach was then used to evaluate whether the quantitative and qualitative variables considered were predictive of the risk of major complications.

Results

Having obtained approval from the Institutional Ethics Board, we performed 2050 single or multiple myomectomies for symptomatic myomas measuring at least 4 cm in diameter. Table 1 illustrates the descriptive analysis of all the studied population. The mean age of the patients was 36.12 ± 5.35 SD years. A great percentage of women (48%)

Table 1 Main characteristics of the studied population (n = 2050)

Characteristics	No. (%)	Mean ± SD	(95% CI)
Age (year)	—	36.12 ± 5.35	(35.89–36.35)
Indication for laparoscopic myomectomy			
Infertility	553 (27)	—	—
Rapid uterine enlargement	570 (27.8)	—	—
Pelvic pain	451 (22)	—	—
Abnormal bleeding	476 (23.2)	—	—
Autologous donation	1599 (78)	—	—
GnRH agonist treatment	164 (8)	—	—
Number of myomas removed	4642	—	—
Myoma size (cm)	—	6.40 ± 2.61	(6.29–6.52)
No. of myomas/patient	—	2.26 ± 1.8	(2.18–2.33)
Depth of infiltration			
Pedunculated	267 (13)	—	—
Subserosal	658 (32.1)	—	—
Intramural	995 (48.5)	—	—
Intraligamentous	130 (6.3)	—	—
Operative time (min)	—	107.71 ± 43.42	(105.47–109.23)
Δ hemoglobin (g/dL)	—	−1.55 ± 0.54	(−1.53–1.58)
Length of hospitalization (day)	—	1.99 ± 0.87	(1.95–2.02)
Follow-up study			
Number of patients	1683 (82.1)	—	—
Months	—	41.70 ± 23.03	(40.59–42.80)
Number of pregnancies	386 (22.9)		
Delivery rate	309 (80)		
Vaginal delivery	68 (22)		
Caesarean section	241 (78)		
Miscarriage	77 (20)		
Premature labor	9 (2.3)		

Table 2 Complications (total procedures: N = 2050)

	No.	%
Major complications		
Hematomas*	10	0.48
Hemorrhages	14	0.68
Sarcomas	2	0.09
Repeat surgeries	2	0.09
Postoperative kidney failure	1	0.04
Bowel injury	1	0.04
Uterine rupture†	1	0.26‡
Procedure failings	7	0.34
Total	38	2.02
Minor complications		
Cystitis	70	3.41
Fever > 38°C	105	5.11
Manipulator injuries	12	0.58
Total	187	9.11
Total complications	225	11.1

*Two cases with double complication.
†Adenomyosis.
‡Data on uterine rupture are reported using the number of pregnancies (386 cases) as the denominator.

had more than 1 myoma, with a maximum of 15 per patient (number of myomas removed for patients: 2.26 ± 1.80 SD; 95% CI: 2.18–2.33). Myoma size ranged from 1 to 20 cm (mean 6.40 ± 2.61 SD; 95% CI: 6.29–6.52). Myoma smaller than 4 cm were removed during myomectomy for larger ones. Concerning myoma location, most of them were intramural (48.5%); subserosal accounted for 32.1% and pedunculated and intraligamentous for 13% and 6.3%, respectively. Autologous donation was performed in 1599 cases (78%), and 8% of women were treated with GnRH agonist before surgery. The mean operative time was 107.71 ± 43.42 SD minutes (95% CI: 105.47–109.23) and the duration of hospitalization 1.99 ± 0.87 SD days (95% CI: 1.95–2.02). The perioperative change in hemoglobin concentration was −1.55 ± 0.54 SD g/dL (95% CI: −1.53 to −1.58). A total of 1683 women were followed up for a mean of 41.70 ± 23.03 SD months after laparoscopic myomectomy. The clinical results in terms of pregnancy outcome after surgery are reported in the Table 1.

Table 2 shows a detailed description of the minor and major complications occurring during and after LM. Total complication rate was 11.1% (225 cases). Minor complications occurred in 187 cases (9.1%) and major complications in 38 cases (2.02%). Particularly, 70 patients (3.4%) contracted a urinary tract infection, 105 patients (5.1%) had unexplained transient pyrexia, which resolved quite promptly, and 12 reported manipulator injuries (0.6%) (uterine perforation was secondary to the manipulator). With regard to major complications, intraoperative bleeding occurred in 14 cases (0.7%), with 1 of these requiring transfusion. In 1 case of primary bleeding, the internal epigastric right artery was damaged with the unipolar hook during an adhesiolysis between the bowel and the abdominal wall. A laparoscopic suture immediately stopped the bleeding. Transvaginal ultrasound scanning in the postoperative period revealed the presence of 10 (0.5%) hematomas at the site of myomectomy scar. There were 2 cases of serious secondary hemorrhages, which were also responsible for the other 2 blood transfusions (for a total of 0.14%) and readmission to surgery (0.09%): 1 of these had a laparoscopic hysterectomy because of a severe hemorrhage from the left uterine artery, the other underwent drainage of a hematoma in the broad ligament under ultrasound vision. Failure to complete planned surgery occurred in 7 cases (0.34%): in 1 case, we converted to laparoscopic hysterectomy because of a large intraligamentous myoma occupying most of the lateral part of the uterus, after uterine vessels were skeletonized. We converted to laparotomy in 3 cases because of anesthesia problems, in 2 for lack of space and possibility of mobilization of very large myomas, and in 1 case because of a suspect sarcoma. A bowel injury occurred in 1 patient (0.04%) who had a previous laparoscopic myomectomy 10 years before and was presenting a leiomyomatosis peritonealis disseminata, with multiple myomas arising from the right round ligament, the right uterosacral ligament, and the peritoneum of the pouch of Douglas. All myomas were removed. The patient had a late bowel perforation on postoperative day 13, which was treated with thorough peritoneal washing, laparoscopic suturing, and drainage, without colostomy. During a long procedure for multiple myomas, a patient had a prolonged period of hypotension not recognized by the anesthesiologist. She had acute kidney failure (0.04%), which resolved after 3 days of dialysis. We had 2 cases (0.09%) of unexpected sarcoma. In one case, the malignancy was immediately recognized, and the procedure converted to laparotomy. In the second case the frozen section failed in making a correct diagnosis, the myomectomy was completed, and the myoma morcellated into the abdominal cavity. Seven days later, a laparotomy with hysterectomy and oncologic staging was carried out. During follow-up after surgery 386 (22.9%) patients conceived after laparoscopic myomectomy, with a pregnancy rate in patients wishing pregnancy of 69.8%; we had 1 (0.26%) spontaneous uterine rupture at 33 weeks gestation in a patient who had an 8-cm adenomyoma.

Each subsequent statistical analysis has been performed again, with each center considered as a confounding factor or as a between factor depending on the specific procedure applied. No significant differences were found.

Table 3 shows the main characteristics of the studied women after their division into 2 groups: the patients with no complications during or after LM (group 1: n = 1827) and the patients with complications (group 2: n = 223).

The analysis of variance procedure, performed on the quantitative variables, showed that there was a significant difference between the 2 groups with respect to hemoglobin level after surgery (11.33 ± 1.04 vs 11.12 ± 1.48, $p < .03$), the operative time (106.52 ± 43.59 vs 114.14 ± 42.85, $p < .01$) and the length of hospitalization (1.82 ± 0.63 vs 3.32 ± 1.30, $p < .001$). The Mantel Haenszel test on the

Table 3 Main characteristics of women without (group 1) and with complications (group 2) after laparoscopic myomectomy

Characteristics	Group 1 (n = 1827)	Group 2 (n = 223)
Age (year ± SD)	36.20 ± 5.35	35.50 ± 5.32
(95% CI)	(35.95–36.44)	(34.80–36.20)
Myoma size (n, %)		
1–5 cm (n = 402, 19.6%)	374 (20.4%)	28 (12.5%)
>5 cm (n = 1648, 80.4%)	1453 (79.6%)	195 (87.4%)*
No. of myomas removed per patient (%)		
1 (n = 932, 45.4%)	870 (47.6%)	62 (27.8%)†
2–3 (n = 727, 35.5%)	646 (35.3%)	81 (36.3%)
>3 (n = 391, 19.1%)	311 (17.1%)	80 (35.9%)†
Depth of infiltration (n, %)		
Pedunculated (n = 267, 13%)	247 (13.5%)	20 (9.0%)
Subserosal (n = 658, 32.1%)	595 (32.6%)	63 (28.3%)
Intramural (n = 995, 48.5%)	879 (48.1%)	116 (52.0%)*
Intraligamentous (n = 130, 6.3%)	106 (5.8%)	24 (10.8%)*
GnRH agonist treatment		
No (n = 1886, 92%)	1680 (91.9%)	206 (92.3%)
Yes (n = 164, 8%)	147 (8.1%)	17 (7.7%)
Autologous donation		
No (n = 451, 22%)	396 (21.7%)	55 (24.6%)
Yes (n = 1599, 78%)	1431 (78.3%)	168 (75.4%)
Vasoconstrictive agents during surgery (n, %)		
No (n = 1292, 63%)	1183 (64.7%)	109 (48.9%)
Yes (n = 758, 37%)	644 (35.3%)	114 (51.1%)
Hemoglobin before surgery (g/dL ± SD)	12.87 ± 1.07	12.89 ± 1.06
95% CI	12.82–12.91	12.75–13.03
Hemoglobin after surgery (g/dL ± SD)	11.33 ± 1.04‡	11.12 ± 1.48
95% CI	11.28–11.38	10.92–11.31
Δ Hemoglobin (g/dl ± SD)	−1.53 ± 0.47	−1.77 ± 0.94
95% CI	−1.51–−1.55	−1.64–−1.89
Operative time (min + SD)	106.52 ± 43.59§	114.14 ± 42.85
95% CI	104.52–108.52	108.58–119.67
Length of hospitalization (day ± SD)	1.82 ± 0.63†	3.32 ± 1.30
95% CI	1.79–1.85	3.15–3.49

*p <.005.
†p <.001.
‡p <.03.
§p <.01.

categorical variables was significant for the association of complications with the myoma size (p <.05) with the number of removed myomas (p <.001) and with the myoma type, recoded in 4 levels after having pooled the adenomyosis and intramural types (p <.005): group 2 had a smaller percentage of individuals with myomas of type pedunculated and subserosal than the group without complications, instead it showed a larger percentage of individuals with intramural and intraligamentous myomas.

To determine whether the probability for development of complications depended on the recorded variables, a logistic regression analysis was performed, and odds ratios were computed. At first, all variables were considered in the model. As reported in Table 4, results showed that, after applying the forward stepwise (Wald Criterion) procedure,[14] the probability of complications significantly rises with an increase in the number and with the intramural (OR: 1.48; 95% CI: 1.05–2.20, p <.05) and intraligamentous location of myomas (OR: 2.36; 95% CI: 1.22–4.59; p <.01). Specifically, with regard to the number of myomas removed, odds ratios were computed for the class 2 (2 or 3 myomas) and for the class 3 (more than 3 myomas) with respect to the baseline level (class 1: 1 myoma). Patients in classes 2 and 3 have significantly higher risk of complications (class 2: OR: 1.73; 95% CI: 1.07–2.82; p <.02; class 3: OR: 4.46; 95% CI: 2.59–7.66; p <.001) than those with only 1 myoma.

The group of patients with development of complications was then considered separately and divided into the 2 subgroups: patients with minor complications and patients with major complications. To determine whether the probability for development of major complications depends on the studied variables, a logistic regression analysis was again performed. As reported in Table 5, the risk for major complications was significantly higher for patients with myomas of dimension ≥5 cm (OR: 6.88; 95% CI: 3.40–13.79; p <.001), for patients who underwent a longer surgical operation (OR: 1.03; 95% CI: 1.01–1.04; p <.001) and for patients with intraligamentous myomas (OR: 6.44; 95% CI: 3.20–10.82; p <.03). Higher preoperative hemoglobin lev-

Table 4 Probability of developing complications computed on the basis of a logistic regression analysis after applying the Forward Stepwise procedure (underscored): Number of cases: No complications 1827; Complications 225

	Final model		
Variables	Odds ratio	95% CI	p
Myoma size			
1–5 cm	1		—
>5 cm	1.48	0.88–2.46	.13
No. of myomas removed per patient			
1	1		—
2–3	1.73	1.07–2.82	.02
>3	4.46	2.59–7.66	.001
Depth of infiltration			
Pedunculated	1		—
Subserosal	0.72	0.36–1.43	.29
Intramural	1.48	1.05–2.20	.05
Intraligamentous	2.36	1.22–4.59	.01
Vasoconstrictive agents during surgery			
No	1		—
Yes	0.94	0.56–1.59	.82
Age	0.98	0.94–1.01	.29
Hemoglobin before surgery	1.29	0.87–1.92	.38
Hemoglobin after surgery	1.63	1.06–2.51	.02
Operative time	0.99	0.99–1.00	.88

els (OR: 0.50; p <.001), as well as the use of vasoconstrictive agents during surgery (OR: 0.20; p <.05), are predictive of a lesser risk of major complications. Regarding the linear correlation between the myoma features and the other quantitative variables, the results can be summarized as follows: operative time was significantly positively correlated with the dominant myoma diameter (R = 0.43; p <.001) and the number of myomas removed per patient (R = 0.15; p <.01), but no correlation existed with the myoma location (Figure 1).

Discussion

Isolated reports of adverse outcomes, especially uterine ruptures in subsequent pregnancies,[15,16] continue to raise doubts about the safety of the laparoscopic approach to myomectomy. Therefore some national societies have or still advise against laparoscopic myomectomy in patients wishing pregnancy.[17,18] There was a need for large-scale prospective audits to provide detailed information on the outcome. This study has provided prospectively acquired data on the complications associated with 2050 laparoscopic myomectomy including also the long-term results.

Given that these results have been collected from data from among the most experienced surgeons in gynecologic laparoscopy in Italy, it can be stated that they may underestimate and not accurately reflect the problems encountered by less experienced laparoscopists. This study does at least provide a guide to optimally achievable levels of complications.

The most common complications were febrile morbidity (5.1%) and urinary tract infections (3.4%). Febrile morbidity is quite common among women undergoing laparotomic myomectomy (12%-33%)[19–21]; in fact, it is believed that abdominal myomectomy is associated with a high incidence of postoperative fever in the first 48 hours after surgery without an obvious infectious cause. Plausible explanations for these fevers vary from presence of intramyometrial hematoma formation to the release of unspecified factors from the myoma during its dissection.[20,21] Myomectomy was found to be an independent predictor for fever after operation (risk ratio 3.29).[22] Although common, the incidence of febrile morbidity after laparoscopy is much lower than those associated with the conventional approach. In a randomized study[5] the febrile morbidity was lower (12.1%) than after laparotomic approach (26.2%). Moreover, the quite low presence of postoperative hematomas (0.48%) could be an explanation for the lower morbidity fever of the laparoscopic approach.[5]

The use of the laparoscopic route has been proved to reduce the hemorrhagic risk associated with myomectomy.[5,23] This result is confirmed by our series: important blood loss was reported in only 0.68% of case, with requirement for transfusion in 0.14%.

Leiomyomatosis peritonealis disseminata (LPD) is a rare disease that occurs in women of reproductive age. Because

Table 5 Probability of developing major complications computed on the basis of a logistic regression analysis after applying the Forward Stepwise procedure (underscored). Number of cases: Total 2050; Major complications 38

	Final model		
Variables	Odds ratio	95% CI	p
Myoma size			
1–5 cm	1		—
>5 cm	6.88	3.40–13.79	.001
No. of myomas removed per patient			
1	1		—
2–3	1.01	0.70–2.12	.39
>3	1.31	1.09–2.66	.01
Depth of infiltration			
Pedunculated	1		—
Subserosal	0.78	0.56–1.62	.45
Intramural	1.20	0.66–21.09	.14
Intraligamentous	6.44	3.20–0.82	.03
Vasoconstrictive agents during surgery			
No	1		—
Yes	0.20	0.06–0.62	.005
Age	0.98	0.93–1.05	.93
Hemoglobin before surgery	0.50	0.35–0.71	.001
Hemoglobin after surgery	2.71	0.77–9.45	.12
Operative time	1.03	1.01–1.04	.001

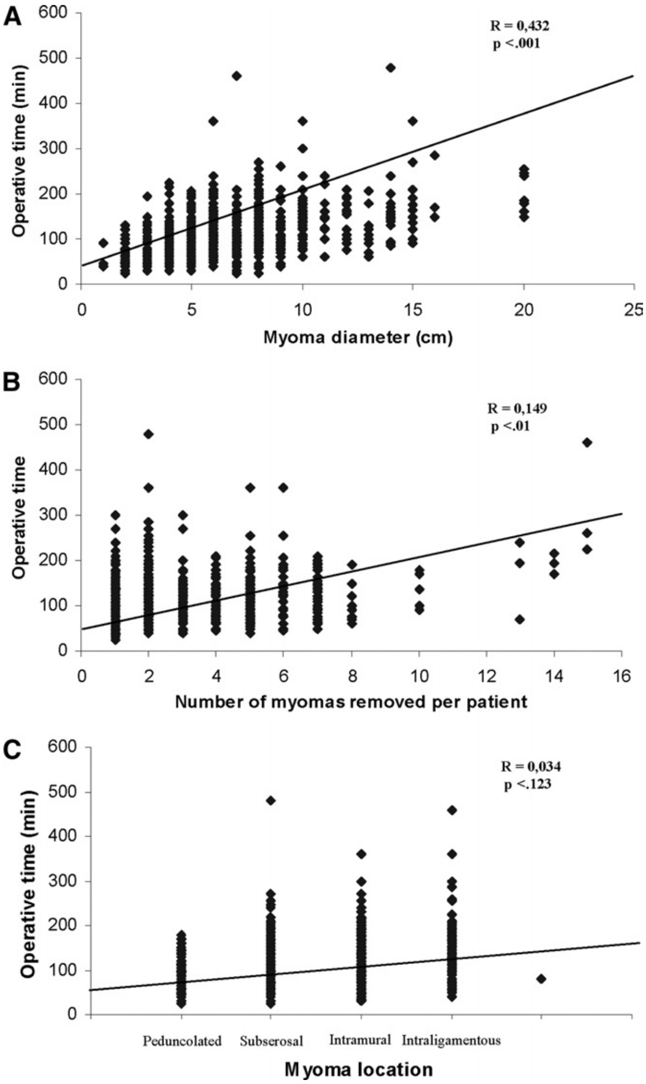

Figure 1 Linear correlation between operative time and myoma: (**A**) Relationship between operative time and myoma diameter in cm. (**B**) Correlation between the number of myomas removed per patient and the operative time is reported. (**C**) Relationship between the myoma location and the operative time is illustrated. Operative time is significantly positively correlated with the myoma dimension ($r = 0.42$; $p < .000$) and the number of myomas removed per patient ($r = 0.077$; $p < .01$).

of the macroscopic aspect (multiple small nodules <2 cm), a metastatic tumor is suspected during operation. These nodules consist of smooth muscle fibers and show benign histologic features. An increased level of cases with endometriosis (10%), uterine myomas, or functional ovarian tumors have been reported. Few cases of malignant transformation have also been described.[24] In the pathogenesis of LPD, a metaplastic change of submesothelial multipotential mesenchymal cells as an abnormal response on hormonal stimulation is proposed. We have found 3 cases of LPD in patients who had previous laparoscopic myomectomy in the early 1990s while the manual morcellation was still in use, making myoma removal a very tiring and frustrating part of the procedure. This frequency leads us to wonder whether the incomplete removal of pieces of myoma missed at morcellation can cause the intraperitoneal regrowth of these myoma particles.[25]

We have had 2 cases of unexpected sarcoma (0.09%), which is low considering that the incidence of leiomyosarcoma in uterine myomas is estimated to be between 0.13% and 0.29%[26,27] and that after hysterectomy in patients with presumed benign disease, histologic diagnosis of leiomyosarcoma was made in 0.49%.[27] Probably the incidence is low partly because of a thorough diagnostic workup before a laparoscopic myomectomy is scheduled and partly because of the younger age of the patients: in fact presence of sarcomas increases steadily from the fourth to the seventh decades of age.[27] In 1 case, we were able to recognize the malignancy, and an immediate conversion to laparotomy was performed. In the second case, we had doubts about the nature of the myometrial lesion, but the frozen section was negative, and the laparoscopic myomectomy was carried out. It is obvious that the morcellation of a sarcoma because of frozen section failure is a serious problem. Nevertheless, this event has been reported also during vaginal or laparoscopic hysterectomy with morcellation.[28] Considering patients inadvertently operated on for leiomyosarcoma, the rate of pelvic recurrence at 3 months was increased in patients who mistakenly underwent uterine morcellation for sarcoma, but this difference was not statistically significant. Overall and disease-free survival rates were similar in all the patients with sarcomas.[29]

A total of 386 (22.9%) patients conceived after laparoscopic myomectomy, with a pregnancy rate in patients wishing pregnancy of 69.8%. The miscarriage rate was 20%, more or less a normal rate.[30] Eighty-one percent of women delivered at term by elective caesarean section, in the other cases there was a normal vaginal delivery. These data are in accordance with many other favorable results of pregnancy outcome,[7,13,31] which demonstrate improved fertility rates reported after laparoscopic myomectomy.[32]

We recorded 1 (0.26%) spontaneous uterine rupture at 33 weeks gestation in a patient who had had an 8-cm adenomyoma, which accounted for the second case reported in the literature.[33] In this case a mechanical enucleation of the myoma was impossible because of the characteristics of the adenomyosis whose fibers merge with the surrounding myometrium, making impossible the delineation of a cleavage plane and subtracting substance to the uterus. In fact adenomyosis infiltrates normal myometrium so that excision of the diseased area subtracts myometrial mass from the total uterine volume. This can cause a reduction in myometrial capacity during pregnancy and production of scars with reduced tensile strength.[34] Fourteen reports of uterine rupture after laparoscopic myomectomy have been reported so far, although the precise frequency is difficult to evaluate. All are case reports never related to the real number of myomectomies performed and reflecting isolated cases in early experience with laparoscopic myomectomy. In only 1 study[35] of a series of more than 100 births after laparoscopic myomectomy, the uterine rupture rate was 1%. Authors cite application of excessive tissue coagulation[6,35] and use of unsuitable suture size (3-0, 4-0) with subsequent risk of intramural hematomas, indentations, and uterine fistulas as possible contributing factors.[36] In 1 case of a 4-cm subserosal myoma[37] suturing was not performed because hemostasis was already achieved with bipolar forceps. In another case in which the uterine wall suture was not used,[38] a uterine rupture occurred after a spontaneous vaginal delivery. Uterine rupture occurred in 2 cases of pedunculated myomas removed after transecting the stalk with bipolar forceps without suture.[16,39] Laparoscopic-assisted myomectomy has been recently advocated[40] to be less technically demanding and less time-consuming, thus being a more effective technique to prevent defective healing because with this method it is possible to perform better suturing, but a case of spontaneous uterine rupture after laparoscopic-assisted myomectomy has been reported,[41] as well as complications related to laparotomy.

It should be stressed that the risk, even if low, also exists when with laparotomy[42] and results in 1 of 40 to 60 uterine ruptures, an event that occurs in 1 of 1500 pregnancies.[43] In a retrospective review of pregnancy that included 14 years of activity in a university teaching hospital, the incidence of ruptured uterus was 0.24% in patients with previous myomectomy scars and 4.1% in those with previous primary caesarean sections.[44] Even uterine ruptures of the unscarred uterus[45,46] or after hysteroscopic resection[47] have been reported. Nevertheless, the attention that has been focused on the first laparoscopic myomectomies has resulted in increased reporting of complications, which has not always applied to standardized procedures such as laparotomic myomectomy. In our experience, we always performed the uterine suture as meticulously as possible, using 1 or 0 sutures and applying if needed "figure of eight" sutures in 2 different planes. The use of diluted POR8 or vasopressin (Pitressin; Monarch Pharmaceuticals Inc., Bristol, TN) has allowed reduced use of electrosurgery to achieve hemostasis and dissection in favor of sharp dissection. In this way, we tried to avoid defective scarring caused by tissue necrosis. The risk of 0.26% for uterine rupture is acceptable and even favorable in comparison with laparotomy. Moreover, the use of vasoconstrictive agents appears to favorably decrease the risk of hemorrhages during myomectomy, as previously reported.[12,48]

Even if it is important to stress that the indications for laparotomy and for laparoscopic surgery for myomectomy are completely different, the fertility results observed after these techniques are comparable.[7,13] Given that the advantages of laparoscopic surgery compared with laparotomy are now fully accepted,[5] myomectomy should be carried out by operative laparoscopy in most cases. Just the issue of the indications still remains debatable. In fact, although it is recommended by some authors[48,49] to schedule myomas measuring more than 8 to 10 cm or multiple myomas (over two-thirds) for laparotomy, we have disregarded this advice. We have considered most patients as candidates to the laparoscopic approach, with the only exception of multiple myomas, which could have been better treated with uterine artery embolization or a hysterectomy for myomas larger than 20 weeks. The extremely low conversion rate (0.34%) shows that laparoscopic myomectomy is feasible even with multiple large myomas, although it is in this case an extremely time-consuming procedure. The prolonged operating time is in fact probably responsible for the anesthetic problems encountered in 42.8% of laparoconversion. We noted that the rate of complications, even if very low, correlates positively with the number and larger diameter of the myoma, as previously reported.[50] Also the intraligamentous myomas have been confirmed to be at higher risk of complications, most of them hemorrhagic. Cumulatively, the rates of complications were, however, less than those expected in conventional surgery. In fact, the rate of complications for abdominal myomectomy ranges between 12%[16] and 21.48%.[51] A comparative study of women undergoing abdominal hysterectomy and myomectomy showed overall complication rates of 39% and 40%, respectively.[20] In a retrospective study comparing abdominal and laparoscopic myomectomy, laparoscopic myomectomy had lower morbidity, no identifiable trend of increasing hospital cost, minimal hospital stay, and fewer complications (5% versus 17%).[52] It would be invalid to claim that the rates of complication for LM are less than that for conventional surgery because the comparison is unmatched, but it would appear that laparoscopic surgery can at least compete with traditional surgery in terms of safety.

Conclusion

This study has provided prospectively acquired data on the complications associated with 2050 laparoscopic myomectomies. The clinical results and extremely low conversion rate suggest that laparoscopic myomectomy is a safe and reliable procedure, even in the presence of multiple or enlarged myomas.

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