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Minimally invasive treatment of diaphragmatic endometriosis: a 15-year single referral center's experience on 215 patients

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Abstract

Background Diaphragmatic endometriosis (DE) is a rare and often misdiagnosed condition. Most of the times it is asymptomatic and due to the low accuracy of diagnostic tests, it is almost always detected during surgery for pelvic endometriosis. Its management is challenging and, until now, there are not guidelines about its treatment.

Methods We describe a consecutive series of patients with DE managed by laparoscopy and videothoracoscopy (VATS) in our referral center in a period of 15 years. We developed a flow-chart classifying DE implants in foci, plaques and nodules and proposing an algorithm with the aim of standardizing the surgical approach.

Results 215 patients were treated for DE. Lesions were almost always localized on the right hemidiaphragm (91%), and the endometriotic implants were distributed as: foci in 133 (62%), plaques in 24 (11%) and nodules in 58 patients (27%), respectively. In all cases of isolated pleural involvement, concomitant diaphragmatic hernia or lesions of the thoracic side of the diaphragm VATS was performed, alone or combined with laparoscopy, resulting in a total of 26 procedures. Following the proposed algorithm, specific surgical techniques were identified as the better approaches for the different types of the lesion, such as Argon Beam Coagulation and diathermocoagulation for diaphragmatic foci, peritoneal stripping for plaques, and nodulectomy or full-thickness resection of diaphragm for nodules.

Conclusions It is crucial to standardize the surgical approach of DE, according to the type of lesion, thus reducing the rate of under- or over-treatments and intra or postoperative complications. This kind of surgery should be performed in a Referral Center by a gynecologic surgeon with oncogynecologic expertise and skills, with the eventual support of a laparoscopic general surgeon, a specialized thoracic surgeon and a trained anesthesiologist.

Keywords Endometriosis · Laparoscopy · Diaphragm · Minimally invasive surgery · Thoracoscopy

Endometriosis is a chronic inflammatory disease, usually located within the pelvis. However, up to 12% of patients can experience extrapelvic locations, firstly described and classified by Markman in 1989, including gastrointestinal and urinary tract, lungs, pleura, skin and nervous system. [1–3] Two of the most common sites of implantation of endometriosis outside of the lesser pelvis are the diaphragm and the thoracic cavity. [4, 5]

Although the pathogenesis of diaphragmatic endometriosis (DE) is not yet fully understood, the presence of diaphragmatic implants can be attributed to Sampson's theory of retrograde menstruation and to the physiological circulation of peritoneal fluid toward the subphrenic regions, allowing cells to infiltrate the diaphragm or to migrate to the pleural cavity via diaphragmatic fenestrations [6–8].

Clinical presentation of DE is silent in 70% of the cases while symptoms are usually not specific (shoulder, right upper quadrant, arm or chest pain). For these reasons, diagnosis is challenging and it occurs with concomitant

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diagnosis of pelvic endometriosis during laparoscopy. [9, 10]. Thoracic endometriosis, instead, may present with pneumothorax, hemothorax or hemoptysis and dyspnea, resulting in the well-known "Thoracic Endometriosis Syndrome" (TES) [4]. Imaging tests, such as CT scan, Magnetic Resonance Imaging (MRI), Chest X-ray or Trans Abdominal UltraSound (TAUS) have low specificity and sensitivity, especially in case of small implants, and the gold standard for a definitive diagnosis of DE is laparoscopy and video-assisted thoracoscopic surgery (VATS) for thoracic endometriosis [11, 12].

All we know about the treatment and management of DE is based on case reports and very small case series from Literature. In this study, we present, to the best of our knowledge, the largest single-center case series of DE treated by laparoscopy alone or by VATS. According to our surgical experience, and as Referral Center for endometriosis, we developed a flow-chart in order to stratify the different surgical approaches of the treatment of DE, according to the diameter of the lesions, their extension and depth of infiltration, proposing an algorithm with the aim of standardizing its treatment.

Materials and methods

Series description

This is a retrospective cohort analysis of 215 consecutive cases of patients with DE managed in a single Institution during a period of 15 years. This series includes patients already reported in a previous article and in this study we updated our experience.

All of the patients who underwent laparoscopy or VATS (concomitant or not with laparoscopy) between January 2004 and June 2019 in the Department of Obstetrics and Gynecology, Gynecologic Oncology and Minimally Invasive Pelvic Surgery (International School of Surgical Anatomy, ISSA) and the Division of Thoracic Surgery of the IRCCS Sacro Cuore-Don Calabria Hospital in Negrar di Valpolicella (Verona, Italy) for suspected DE and for pelvic pain were considered. Among these, the subgroup of patients with intraoperative diagnosis of DE was identified and analyzed in a retrospective chart review. Diagnosis of DE was based on the intraoperative visual finding and on histopathological examination of all specimens taken during surgery. IRB approval was not needed for this study; however, written informed consent for each patient was obtained.

Patients with high clinical suspicion of abdominopelvic or thoracic endometriosis, referring to our center, underwent anamnestical, clinical and instrumental evaluation. Clinical and anamnestical data were collected as routine practice and they included: age, BMI, history of previous endometriosis surgery, parity, presence of infertility and symptoms. Dysmenorrhea, dyschezia, dysuria, dyspareunia and chronic pelvic pain were evaluated using visual analogic scale (VAS) from 0 (no pain) to 10 (unbearable pain). Pain referred to the shoulders (mainly the right one), the hypochondrium, arm or chest were considered as "diaphragmatic symptoms" and their eventual correlation with menstrual period was included into the chart. Patients presenting with dyspnea, pneumothorax, hemothorax or hemoptysis were admitted first at Thoracic Surgery Division. Preoperative workout always included abdominal and transvaginal pelvic ultrasonography as routine. MRI and/or double-contrast barium enema were reserved in case of suspicious liver involvement or suspicious bowel infiltration. In cases of thoracic symptoms and in patients designated for VATS, CXR and CT scan were performed.

Diaphragmatic lesions were recorded and strictly described in the operative report and the severity of the disease was classified according to revised American Society for Reproductive Medicine (r-ASRM) staging [13]. Morphological characteristics, localization, diameter, depth and number of all lesions were considered. All data about surgical procedures and immediate postoperative period (surgical techniques, operative time, blood loss, intraoperative and early complications, days of recovery) were collected. Patients also underwent a follow-up with a post-recovery clinical evaluation 30 days after surgery, in order to assess their general status and late complications. Intraoperative, early (before 30 days from surgery) or late (after 30 days from surgery) complications were recorded and classified according to Clavien–Dindo standardized classification.

Laparoscopic surgical technique

Laparoscopy was performed under general endotracheal anesthesia, with the patient lying in a dorsal lithotomic position. A precise exploration of the diaphragm was always made as first step of our routine surgical practice. To obtain the best exposition of the diaphragm (especially the right one and its dorsal aspects) a steep-reverse Trendelenburg position was obtained and, furthermore, a 30-degree optic was used. Moreover, when the diaphragmatic lesions were not accessible from the suprapubic trocars, an additional 5-mm trocar was inserted at the level of the right or the left hypochondrium, according to the site of the implants. Generally, it was possible to detect and remove most of the endometriotic lesions, especially if the posterior diaphragm was not involved. In case of posterior or extended diaphragmatic involvement or in case of severe perihepatic adhesions, laparoscopic liver mobilization was performed (Fig. 2a), enabling the performance of wide diaphragmatic resections.

Three different types of DE lesions were observed and classified as:

(1) "Foci": bidimensional superficial lesions, generally ≤ 1 cm diameter (Fig. 1a);
(2) "Nodules": solid, tridimensional implants, associated with partial or full-thickness infiltration of underneath muscle layers and generally > 1 cm diameter;
(3) "Plaques": fibrotic bidimensional lesions, superficially infiltrating and thickening the diaphragmatic peritoneum, often resulting from confluence of different foci and responsible for dense adhesions between diaphragm and liver, > 1 cm diameter (Fig. 1c).

Argon Beam Coagulator (ABC) was used to vaporize small superficial lesions (i.e., without infiltration of muscle layers) taking advantage of its homogeneous and superficial (2 to 3 mm in depth) diathermy that, compared to electrocautery, destroys the lesions without burning the surrounding tissue [14] (Fig. 1b). When the laser was not available, superficial lesions were treated with diathermocoagulation (DTC). Superficial lesions with diameter > 1 cm were excised by "peritoneal stripping". The dissection always started in the peripheral disease-free peritoneum, which was incised, bluntly separated by the diaphragmatic muscular layers and finally removed, together with the disease, by bipolar scissors. The caudad diaphragmatic traction of the peritoneum created a pneumodissection that facilitated the division between the pathologic plaque and the muscular layers below, allowing its complete removal with free margins (Fig. 1d). Hemostasis was then achieved with the aid of the ABC or with DTC and any remaining superficial tiny lesion was vaporized in order to obtain a complete eradication of the disease (Fig. 3d).

When the disease infiltrated the muscle superficially, only a small amount of the involved fibers were removed, preserving the integrity of the diaphragm without opening the thoracic cavity: this type of procedure was defined as "nodulectomy"(Fig. 2b). In case of full-thickness infiltration of the diaphragm or dense adhesions to the central tendon of the muscle, entry into the pleural cavity resulted unavoidable. In these cases, after informing the anesthesiologist, the surgeon completed the removal of the lesion with a "full-thickness resection" of the diaphragm (Fig. 2c). The optic was placed inside the thoracic cavity through the diaphragmatic defect in order to detect any possible pleural o pulmonary lesions (Fig. 2d). The suture was performed laparoscopically with absorbable monofilament or poly filament, 2–0,

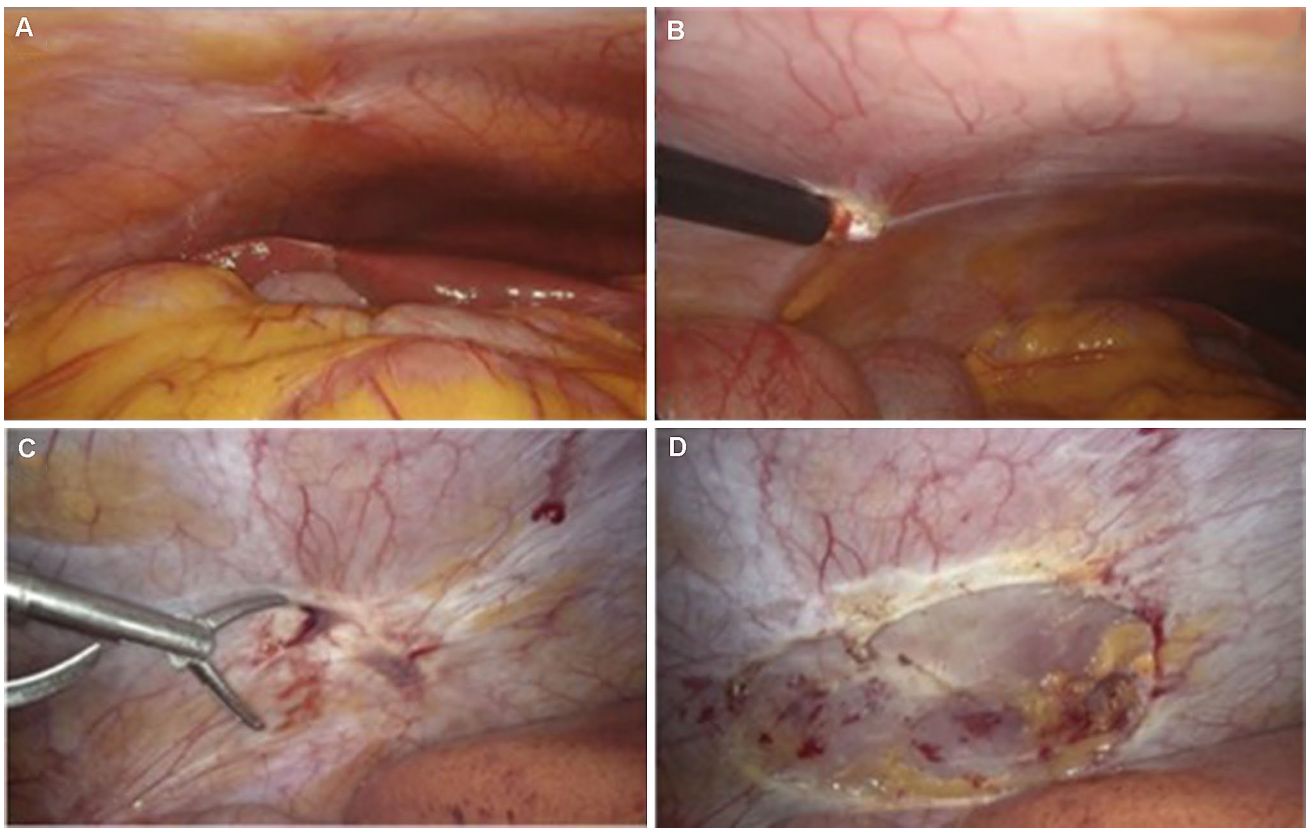

Fig. 1 **A** Laparoscopic view of right diaphragmatic foci. **B** Laparoscopic view of laser vaporization of right diaphragmatic foci by ABC. **C** Laparoscopic view of right diaphragmatic plaque. **D** Laparoscopic view of right diaphragmatic muscle skeletonized after peritoneal stripping of diaphragmatic plaque

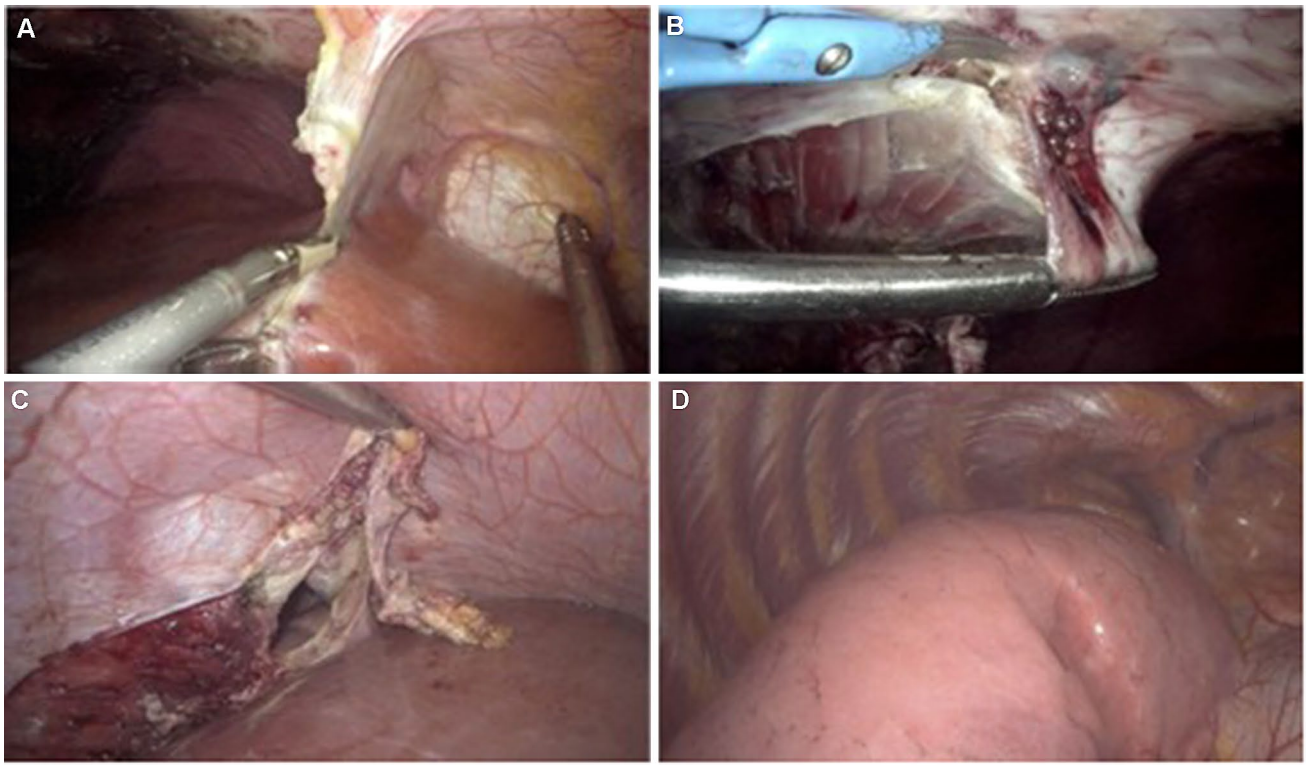

Fig. 2 **A** Laparoscopic view of laparoscopic section of hepatic falciform ligament in course of hepatic mobilization. **B** Laparoscopic view of diaphragmatic nodule in course of partial diaphragmatic resection. **C** Laparoscopic view of full-thickness diaphragmatic resection for right deep infiltrating nodule with opening of the thoracic cavity. **D** Laparoscopic view of the right thoracic cavity after introducing the optic through the diaphragmatic defect after diaphragmatic resection

1–0 on a 27-F needle with interrupted or running suture, depending on the localization and the diameter of the diaphragmatic defect (Fig. 3a). The pneumothorax was evacuated before closing the final stitch, after adequate expansion of the lung, obtained by positive pressure ventilation and putting the aspirator into the pleural cavity (Fig. 3b). Final closure stitches were placed using a pursestring technique, abutting the aspirator and held taught but not yet tied. After gentle suction, the aspirator was quickly removed as the remaining closure sutures were drawn taught and tight (Fig. 3c). The integrity of the diaphragm was checked by bubble test with the diaphragmatic dome filled with saline solution. Eventual residual pneumothorax was verified with intraoperative ultrasound thoracic scan.

Patients with severe thoracic symptoms and/or suspicious thoracic involvement at the preoperative workup underwent single or multi portal VATS to evaluate intrathoracic presence and extent of the endometriotic lesions. In case of endometriotic solid foci or perforations, based on their dimensions, either a stapling or an energy device was used to resect the affected area of the diaphragm, which was then sutured. In selected cases, suture line was reinforced with a polypropylene mesh. Talc pleurodesis was routinely performed in case of the patient had previous episodes of pneumothorax to minimize the risk of further recurrences [15].

Statistical analysis

Sample size was calculated according to the Survey Software algorithm provided by Creative Research Systems (Creative Research Systems 1709 Schaeffer Road Sebastopol, CA 95472). On a population sample of 300 women, for a confidence level o 95%, a sample size of 169 patients would be required. Statistical analysis was performed with SPSS Statistics 22.00 for Mac (IBM Corporation, Armonk, NY) GraphPad Prism version 3.00 for Windows (GraphPad Software, San Diego, CA). Data were reported as mean ± standard deviation for continuous variables and as median and range for non-continuous variables. Contingency 2 × 2 tables with Chi-square with Yates' correction value calculation were created in order to verify the higher risk of a single event in two groups. Continuous variables were analyzed with ANOVA tests to compare means among groups after descriptive statistics calculation. Post hoc values were calculated with LSD tests. The statistical significance was considered to be achieved when $p < 0.05$.

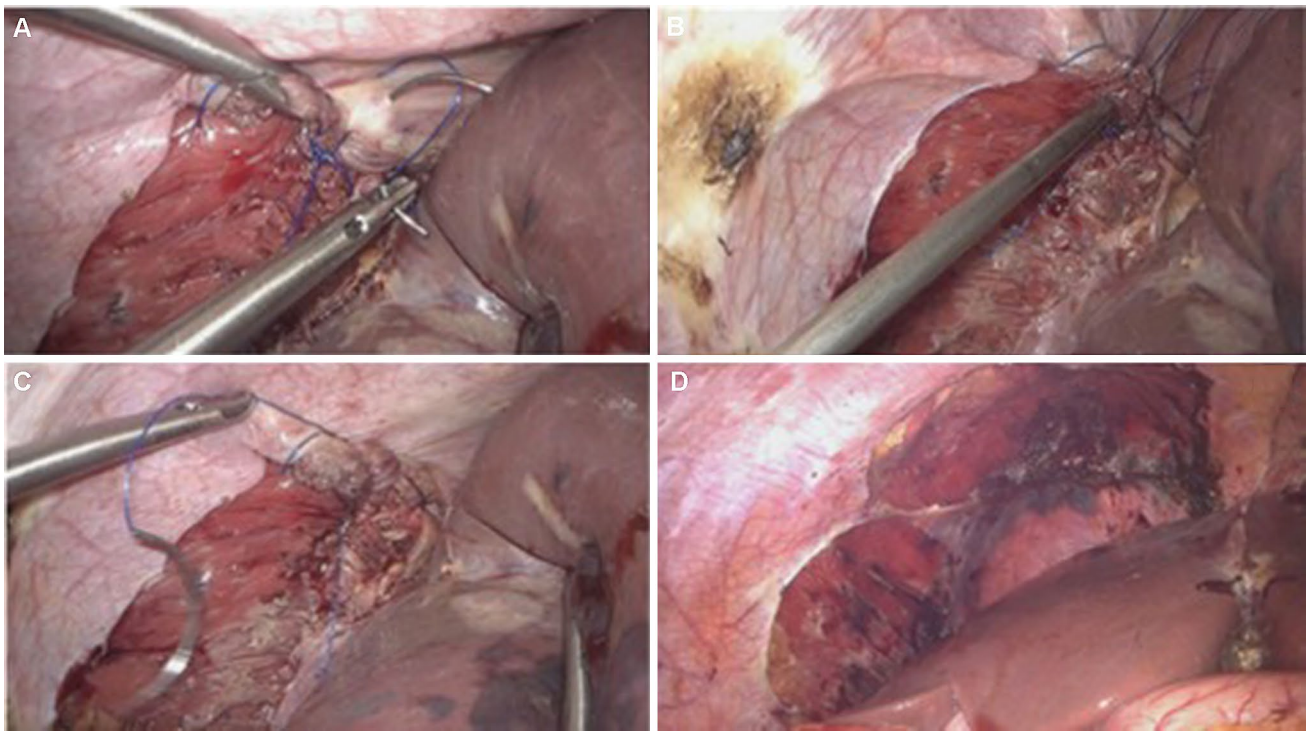

Fig. 3 **A** View of a phase of the laparoscopic suture of wide right diaphragmatic defect after resection of diaphragmatic nodule. **B**. Laparoscopic phase illustrating the introduction of the aspirator through the diaphragmatic defect, together with closure of the pursestring diaphragmatic suture. **C** Final laparoscopic view of right diaphragm after full-thickness resection and suture. **D** Final laparoscopic view of mobilized liver and right diaphragm after wide peritoneal stripping and laser vaporization with ABC

Results

From January 1, 2004, to June 30, 2019, 9178 patients underwent surgery for deep infiltrating endometriosis (DIE) in our Department. Among them, 215 patients (2.34%) were treated for DE and they were included in the dataset of this study. Table 1 resumes the clinical data and features of all patients. The median age at the time of surgical intervention was 35 years (IQR 30–38 years). Infertility was noticed in 39.5% of cases, while 20.5% of the patients had one or more previous pregnancies before surgery and 40% did not attempt to conceive.

The most frequent pelvic symptoms reported by patients were dysmenorrhea and dyspareunia with a median VAS score, respectively, of 7.4 (range 3–10) and 5 (range 2–10). Only 53 patients (24.6%) complained of diaphragmatic or thoracic symptoms at the time of hospital admission: among them, 34 (15.8%) experienced thoracic/retrosternal pain, 10 (4.6%) hypochondrium or side pain, 7 (3.2%) shoulder or arm pain, 1 epigastric pain (0.5%), and 19 (8.8%) presented with pneumothorax. These symptoms had a clear association with menstrual cycle in 11.3% of cases. DE was preoperatively suspected by imaging techniques in 34 cases (15.8%) by abdominal ultrasound, confirmed subsequently by MRI and CT scan. None of the remaining patients reported any symptom that could be directly related to DE and the disease was first detected during surgery.

More than half of the patients (58%), were submitted to previous surgery for the treatment of endometriosis that, in 22.4% of the cases, was described as "non-radical".

Pelvic DIE, especially in advanced stages, was detected in all the patients, and no isolated diaphragmatic lesions were found. 194 patients (90.23%) were at r-ASRM stage IV, whereas 8.37% and 1.39% were at stage III and II, respectively. 131 patients (60.9%) had intraoperative finding of endometriotic bowel or genitourinary tract infiltration, for which, 108 underwent rectal or rectosigmoid resection, 15 rectal shaving, 15 ileal or ileocecal resection, 6 bladder resection and 6 underwent ureteroneocystostomy.

The characteristics of diaphragmatic lesions are resumed in Table 2. DE lesions were almost always localized on the right leaf of the diaphragm (91% of cases), whereas left isolated or bilateral involvement was detected in 1% and 8% of cases, respectively. The lesions were multiple in 61.8% and single in 38.2% of cases with a median diameter of 13.4 mm (range 2–80 mm), considering as parameter the diameter of single lesions or, in case of multiple implants, the diameter of the major lesion. However, when considered the entire surface of the diaphragm involved by the disease (thus

Table 1 Characteristics of 215 patients with DE

Total number of patients	215
Prevalence of diaphragmatic lesions between patients treated for endometriosis	215/9178 (2.34%)
Clinical data	
Age (years), median (IQR)	35 (30–38)
Infertility	85/215 (39.5%)
BMI, mean (IQR)	20.9 (19.5–22.9)
Previous surgery for endometriosis	125/215 (58.1%)
Indications for surgery	
Abdominopelvic pain refractory to medical therapy	182/215 (85%)
Infertility	86% (40%)
Asymptomatic endometriomas (larger than 4 cm)	25 (12%)
Ureteral stenosis	6/215 (2.8%)
Diaphragmatic symptoms	53/215 (24.6%)
Thoracic/retrosternal pain	34/215 (15.8%)
Hypochondrium/side pain	10/215 (4.6%)
Shoulder or arm pain	7/215 (3.2%)
Epigastric pain	1/215 (0.5%)
Pneumothorax	19/215 (8.8%)
Imaging tests finding (Chest X-ray, TAUS, MRI, CT scan)	34 (15.8%)

including the not affected peritoneum), the median diameter of the specimen removed was 19.1 mm (range 2–120 mm).

The most frequent morphological type of diaphragmatic lesion, according to our definition, was represented by diaphragmatic foci in 133 patients (62%), while plaques were found in 24 patients (11%). The lesion was defined as deep ("nodule") in 58 cases (27%) causing a full-thickness infiltration of the muscle in 36 patients (16.7%). The remaining nodules (10.2%) were partially infiltrating the muscular layers, allowing the surgeon to perform a superficial shaving of the diaphragm without opening the thoracic cavity. In 21 cases, diaphragmatic lesions infiltrated the hepatic surface creating hepato-diaphragmatic adhesions or producing nodular implants on the Glisson's capsule. In these cases, perihepatic adhesiolysis with liver mobilization (15 cases) or eradication of liver implants by ABC or partial stripping of the Glisson's capsule (6 cases) were performed. Seven patients had pleural implants and four patients presented parietal endometriosis (abdominal scars, umbilicus, groin). One patient presented pericardial infiltration with concomitant bilateral diaphragmatic and pleural infiltration. In this case, the laparoscopic total liver mobilization enabled the surgeon to perform a bilateral wide diaphragmatic and pleural resection with a wide pericardial resection, combining a hand-assisted phase trough a xifo-supraumbilical midline mini-laparotomy (thus avoiding a xifo-pubic or a bilateral sub-costal marginal incision) after radical laparoscopic excision of pelvic DIE (including laparoscopic rectal disc resection) [16].

In all cases of isolated pleural involvement (5 cases) or concomitant diaphragmatic hernia (7 cases) or lesion of the thoracic side of the diaphragm (18 cases) VATS was performed, alone (25 cases) or combined with laparoscopy (1 case), resulting in a total of 26 procedures.

More than half (115 cases) of the diaphragmatic lesions were treated with ABC. Diaphragmatic stripping was performed in 15 patients with superficial lesions measuring more than 10 mm of diameter. DTC was used in 46 cases, alone or combined with other techniques. Deep nodules were treated in 22 cases by "nodulectomy", thus superficially resecting the muscular layers of the diaphragm, whereas in 7 patient a full-thickness resection was unavoidable because of the massive infiltration of the diaphragm or for the presence of a lesion located at the central tendon. The diaphragmatic defect was then sutured laparoscopically except for one patient in which the suture was unnecessary because of a 2 mm gap and no intraoperatory development of pneumothorax. A postoperative chest tube was applied in three cases approached by laparoscopy (1.6%) and routinely after thoracoscopy. All chest tubes were removed no longer than after 48 h.

During VATS procedures, diaphragmatic or pleural lesions were removed by direct excision or with endo-GIA staplers (4 patients), while the diaphragmatic defect was replaced by a biological mesh in 12 cases (46.1%).

Median operative time was 215 min (considering both pelvic and diaphragmatic phases of surgery) (IQR 130–300 min) and overall intraoperative median estimated blood loss was 100 ml (IQR 70–200 ml). Considering only the diaphragmatic phase of the surgery the median operative time was 8 min (IQR 4–21.7). However, deeper and larger lesions required longer operative time, leading to more

Table 2 Intraoperative finding and surgical procedures

Number and location of diaphragmatic lesions	
Single lesion	82/215 (38.2%)
Multiple lesions	133/215 (61.8%)
Right-side	196/215 (91%)
Left-side	2/215 (1%)
Bilateral	17/215 (8%)
Type of diaphragmatic lesions	
Foci	133/215 (61.8%)
Plaques	24/215 (11.2%)
Nodules	58/215 (27%)
Diaphragmatic hernia	7/215 (3.1%)
Perihepatic adhesions	15/215 (6.9%)
Glisson's capsule lesions	6/215 (2.8%)
Pleural lesions	6/215 (2.8%)
Pericardial lesions	1/215 (0.5%)
Surgical approach	
Laparoscopy	188
VATS	26
Laparoscopy + VATS	1
Laparoscopic procedures	
ABC (Argon Beam Coagulation)	115 (53.5%)
DTC (Diathermocoagulation)	46/215 (21.4%)
Peritoneal stripping	15/215 (6.9%)
Nodulectomy	22/215 (10.2%)
Full-thickness resection	7/215 (3.1%)
VATS procedures	
Traditional resection	21/26
Stapler resection	4/26
DTC	1/26
Stage (r-ASRM)	
IV	194/215 (90.2%)
III	20/215 (8.4%)
II	9/215 (1.4%)
Concomitant pelvic procedures	
Rectal or rectosigmoid resection	108/215 (50.2%)
Rectal shaving	15/215 (6.9%)
Ileal or ileocecal resection	15/215 (6.9%)
Bladder resection	6/215 (2.8%)
Ureteroneocystostomy	6/215 (2.8%)
Eradication of parietal DIE lesions (groin, umbilicus, scar)	34 (15.8%)

complex surgical maneuvers, respectively: foci 5 min (IQR 4–5 min); plaques 20 minutes (IQR 5–23.5 min); nodules 40 min (IQR 22.75–75 min).

No intraoperative complications occurred. Thirty-three patients (15.3%) developed postoperative complications, 11 of class II and 22 of class IIIb, respectively, sec. Clavien–Dindo. All these complications were related to the combined colo-rectal or ureteral surgeries (colo-rectal anastomosis dehiscence, ureteral fistula, recto-vaginal fistula). No one of these complications was strictly connected with diaphragmatic surgery: no pleural effusion, no subdiaphragmatic abscess, no hemidiaphragm paralysis occurred and no patient needed the positioning of a chest tube postoperatively for development of pneumothorax.

No specific diaphragmatic complication prolonged patients' hospital stay, which median was 6 days (IQR 4–9). Thirtieth-day postoperative follow-up showed a complete pain relief in all symptomatic patients; however, in the long-term follow-up no patients presented with recurrent DE or recurrent symptoms.

Discussion

The incidence of DE is not precisely known but the diaphragm together with the thoracic cavity is one of the most common localization of extrapelvic endometriosis. In our three previous works [15, 17, 18] we reported the prevalence of diaphragmatic lesions as 0.19% and 1.5%, respectively, among patients undergoing surgery for endometriosis. In this case series, based on 9178 treated patients, the percentage of diaphragmatic involvement is 2.34% and these data confirm our suspect that the prevalence if DE could be greater than estimated in Literature.

The diagnosis and management of DE still represent a challenge for the gynecologist, especially not in Referral Centers, due to the scanty of data reported in Literature, to the poor confidence of the gynecologist with upper-abdominal surgical procedures, to the difficulty of preoperative diagnosis, and the absence of guidelines.

The present study, once again, confirms the unpredictability of clinical presentation of DE and it shows, in most of the cases, the poor incidence and specificity of symptoms with only 53 patients (24.6%) complaining pain suggestive of diaphragmatic involvement. Except for recurrent catamenial pneumothorax, most of the times symptoms are not so peculiar and they can go unnoticed during routine evaluation.

Moreover, routinely diagnostic tests are unaccurate, especially with small lesions; nevertheless, we believe that upper abdomen TAUS should be part of the routinal practice in patients with suspected endometriosis. As Fischerova et al. demonstrated, TAUS is a valid, feasible and cost-effective instrument to evaluate the diaphragmatic surface and to detect both parietal and visceral peritoneal implants, for example in gynecological tumors [19, 20]. In cases of diaphragmatic specific symptoms, further investigations with other instrumental imaging tests (MRI, CT scan, Chest X-ray) are recommended. Despite of low specificity, the most sensitive tests for detection of pneumothorax and hemothorax are Chest X-ray and CT scan, whereas MRI is preferable for the detection of diaphragmatic endometriosis with a reported sensitivity of 78–83% [21, 22]. Positron

emission tomography-computed tomography (PET/CT) with an experimental estrogen receptor tracer (16α-[18F]fluoro-17β-estradiol; [18F]FES) can be useful for the detection of extragenital endometriosis but it is still experimental [23].

In our dataset, patients complaining of diaphragmatic/thoracic symptoms presented more serious organ involvement with an incidence of 65% of deep diaphragmatic lesions and requiring liver mobilization, diaphragmatic resection (partial nodulectomy or full-thickness resection) and VATS in 17%, 59% and 48% of the cases, respectively. Nevertheless, patients without diaphragmatic symptoms presented, in comparison, a significantly lower incidence of all these variables ($p < 0.01$): 15% of deep lesions, 6% of liver mobilizations, 12.4% of diaphragm resection and no VATS performed. Furthermore, symptomatic patients had larger diaphragmatic lesions (median 20 mm IQR 15–35) than found in asymptomatic patients (median 10 mm, IQR 5–20), $p < 0.01$ (Table 3). These data suggest the importance of performing a precise anamnesis and, in case of symptoms suggesting the presence of DE, to adequately inform the patient on one side but, on the other, to face this kind of procedure with the adequate surgical skills and surgical team in order to reduce intraoperative risks and morbidity.

The asymmetric distribution of the lesions observed in our patients (91% isolated lesions on right leaf of the diaphragm) gives support to Sampson's theory. As Drye and Foster asserted in 1948 and 1981 [6, 7], and confirmed subsequently by Vercellini et al. [24] in a 2007 review, endometrial cells, flowed into the peritoneal cavity backwards through the fallopian tubes, as they reach the right hypochondrium pushed by respiratory and bowel movements, are hindered by the falciform and phreno-colic ligaments that prevent their flow to the left subphrenic space across the midline, resulting in a higher frequency of endometriotic implants on the right leaf of the diaphragm compared with the left one [9, 10]. Moreover, as already stated by Ishimura and Masuzaki [25], DE is almost always associated with severe pelvic involvement. All our patients presented advanced pelvic disease (90.2% stage IV and 8.37% III stage r-ASRM), and 62.8% of them had intraoperative finding of endometriotic bowel or genitourinary tract infiltration; for this reason DE may be considered as an indirect "marker" for severe pelvic DIE.

Diaphragmatic surgery, in gynecology, is almost always performed by oncogynecological surgeons in course of cytoreductive surgery of advanced ovarian cancer. We believe that the technique of eradication of DE often mimics oncologic surgery, and for this reason it requires oncosurgical skills and a clear knowledge of anatomy of the upper abdomen. In case of diffuse infiltration of the diaphragm or perihepatic adherences, partial or complete hepatic mobilization is required and, in this case, the knowledge of the anatomy of both diaphragm and hepatic ligaments (falciform, coronary and triangular ligaments), innervation and variations in hepatic vascular anatomy are a necessary prerequisite for the avoidance of potential severe surgical and diaphragmatic complications. Different diaphragmatic surgical techniques were described in case of peritoneal carcinomatosis [26] ranging from ablation to peritonectomy and full-thickness resection. Furthermore, treatment of thoracic and abdominopelvic endometriosis was reported in small case series, describing from slightly invasive maneuvers like ablation or resection of the lesions [27] to extended procedures like Laparoscopic En-Bloc Right Diaphragmatic Peritonectomy in case of massive diaphragmatic involvement [28]. As the surgical management of patients with endometriosis should be "patient-tailored", the surgical excision of DE, once planned, should be "lesion-tailored"; in fact we believe that the right surgical technique should be decided intraoperatively according to size, deepness, number and extension of the lesions. This large amount of consecutive cases allowed us to propose an algorithm for the perioperative management and the surgical treatment of DE, according to the clinical presentation and to the characteristics of the endometriotic implants (Fig. 1).

Nowadays, no guidelines nor prospective trials do exist about indications to the treatment of DE. However, following the results of our previous series, reporting the higher benefits of radical surgery of DIE in patients with severe disease (III-IV stage of r-ASRM classification) [13], we believe that the treatment of DE should be included in the concept of complete eradication of the disease such as for pelvic endometriosis, even in asymptomatic patients. In fact, when DE is discovered during laparoscopic exploration, surgical treatment should be included, due to the possible progression of the lesions and to prevent patients from future symptoms

Table 3 Comparison between patients with or without diaphragmatic symptoms

	Symptomatic patients (n54)	Asymptomatic patients (n161)	*p* value
Deep lesions	35/54 (64.8%)	25/161 (15.5%)	< 0.00001
Partial or full-thickness diaphragmatic resection	32/54 (59.3%)	20/161 (12.4%)	< 0.00001
Hepatic mobilization	9/54 (16.7%)	6/161 (3.7%)	< 0.01238
Diameter of lesions (mean; IQR)	10 mm; (5–20)	20 mm; (15–35)	< 0.000023

and/or a more aggressive diaphragmatic surgery. However, it is mandatory not to increase the intraoperative risks (still present after pelvic radical excision including a high rate of bowel and genitourinary procedures) with additional morbidity due to diaphragmatic complications; thus, it is crucial to follow the appropriate surgical maneuvers.

At first, it is fundamental to maximize the visualization of the diaphragm and the involved structures, and then to eradicate every lesion without opening the thoracic cavity (except in cases requiring a full-thickness diaphragmatic resection). Thermal ablation is suggested for superficial lesions < 10 mm, preferring ABC to electrocautery, because its homogeneous and superficial (2 to 3 mm in depth) diathermy may avoid ischemia of surrounding tissue. DTC should be used to obtain hemostasis: in our case series cautious use of DTC has been shown to be safe resulting in no later fenestration due to ischemia and no pneumothorax or spontaneous rupture of the diaphragm. In case of lesion larger than 10 mm of maximum diameter, the incision of unaffected peritoneum followed by sharp dissection is recommended, in order to detect the level of the infiltration of the muscular layers of the diaphragm and, then, to make a "peritonectomy" in case of superficial lesions, or to perform a partial or full-thickness resection of the diaphragm in case of deep muscular infiltration. If the thoracic cavity is opened, the pleuras should be always explored, in order to detect thoracic involvement and to plan a concomitant or postponed pleural resection. The 0° or 30° laparoscope can be inserted into the pleural cavity through the diaphragmatic defect and an accurate inspection of the hemithoracic surfaces can be easily achieved. The diaphragmatic defect should be closed by laparoscopic suture that, according to our data, is feasible and safe, even if it requires high surgical skills. A gentle suction from the pleural cavity with a Foley catheter or by the suction probe could minimize residual pneumothorax, avoiding the positioning of a chest tube. The integrity of the diaphragm should be checked with the so-called "bubble test" and residual pneumothorax may be verified by intraoperative ultrasound thoracic scan.

It is always crucial to cooperate with other specialists: the anesthesiologist must be always informed about the risk of pneumothorax; the general surgeon could be required in for the hepatic mobilization and the thoracic surgeon is necessary intraoperatively only in case of wide diaphragmatic defects and preoperatively in order to better plan VATS as a first step or second look after laparoscopic surgery in cases of pleural involvement or acute thoracic symptoms. Patients should be accurately observed during the immediate postoperative days, in order to detect possible diaphragmatic complications such as pneumothorax, pleural effusion, subdiaphragmatic abscess or hemidiaphragmatic paralysis. A postoperative long-term hormonal therapy is fundamental to minimize recurrences of the disease. In Our Department, we indicate to start postoperative hormonal therapy and to assume it until looking for pregnancy. For infertile patients, a minimum of 3 months postoperative treatment is recommended, before starting with assisted reproductive techniques.

Conclusions

In conclusion, minimally invasive treatment of DE has shown to be safe, feasible and cost-effective, as it has a very low rate of complications. However, because of the rarity of the location, and in order to better tailor the surgical approach and to reduce the rate of under- or over-treatments and intra or postoperative complications, it should be routinary to classify diaphragmatic lesions and to follow a precise algorithm. Other Authors proposed different diagnostic criteria or algorithms in order to try to standardize the treatment of DE [29, 30]. As our series represents one of the largest single-Center experience, we believe that the proposed algorithm used in our Institution (Fig. 4) could represent a valid and reproducible tool to individualize the treatment of DE.

Finally, considering the peculiarity of the site of the disease and the expertise required for adequately select and treat these patients, we believe that this kind of surgery should be performed in a Referral Center by a gynecologic surgeon with oncogynecologic knowledge and skills, with the eventual support of a laparoscopic general surgeon, a specialized thoracic surgeon and a trained anesthesiologist.

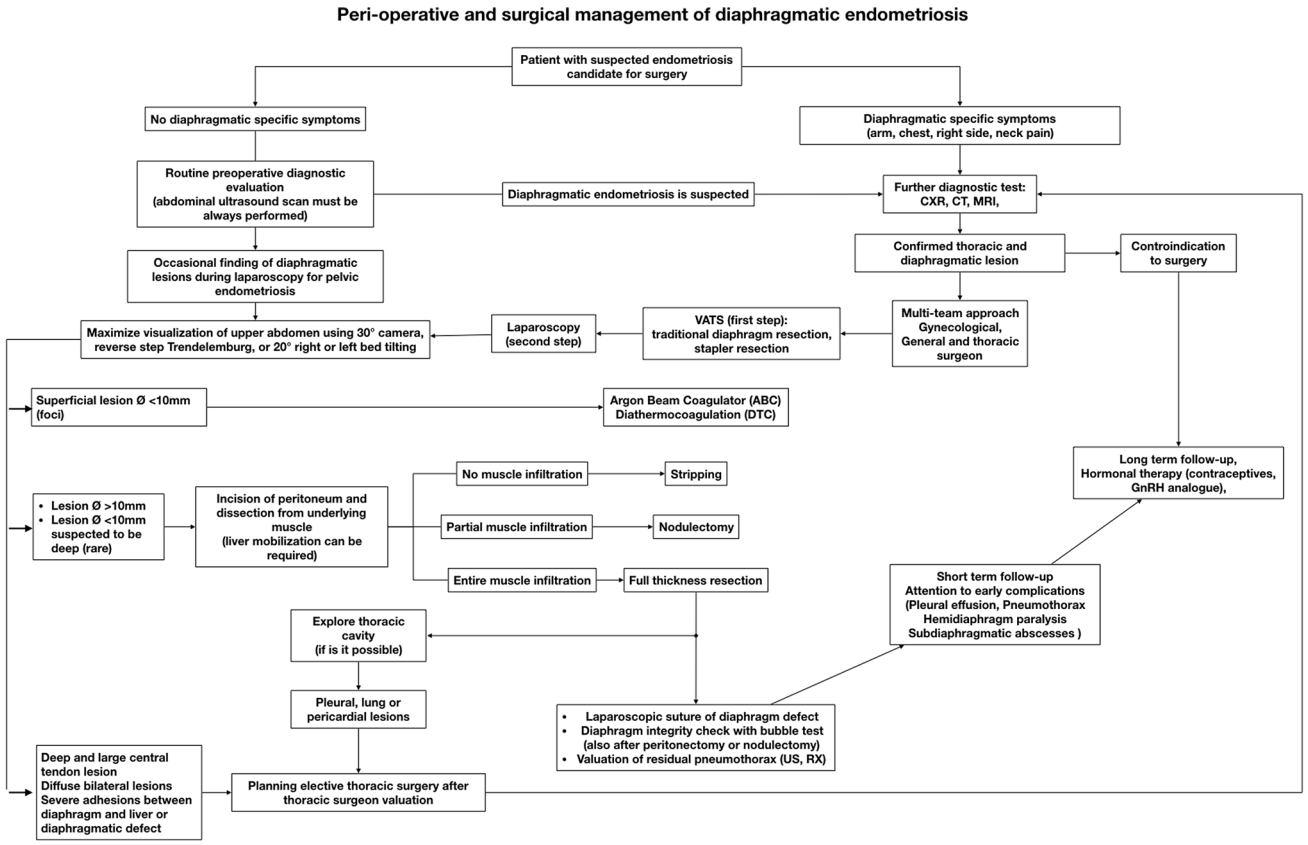

Fig. 4 Proposed algorithm used in our Institution for preoperative and surgical management of DE

Compliance with ethical standards

Disclosures Ceccaroni Marcello, Roviglione Giovanni, Farulla Antonino, Bertoglio Pietro, Clarizia Roberto, Viti Andrea, Mautone Daniele, Ceccarello Matteo, Stepniewska Anna, and Alberto Claudio Terzi declare that they have no conflict of interest.

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