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REVIEW

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Diaphragmatic resection and liver mobilization during surgery for advanced ovarian cancer

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Abstract

Advanced ovarian cancer is a challenging disease that spreads principally to the peritoneal tissues. It is reported that diaphragmatic involvement occurred in 40% of patients with tumors localized in the pelvic cavity and 70% of cases with extrapelvic metastasis. Many gynecology oncology surgeons believe that invasive diaphragmatic disease is the most challenging disease localization to be wholly eradicated, second only to portal triad disease. The knowledge of diaphragm anatomy, the relevant hepatic attachments, and the central vasculature is substantial for the performance of radical surgery during debulking of upper abdominal quadrants in advanced ovarian cancer patients. Some surgical techniques are available to provide a proper cytoreductive effect for diaphragm involvement in ovarian cancer, including ablation using the Argon Beam Coagulator (ABC), aspiration using Cavitron Ultrasonic Surgical Aspirator (CUSA), peritonectomy (stripping), or full-thickness diaphragmatic resection. A multidisciplinary approach with the involvement of a thoracic surgeon could be beneficial for the correct assessment of the disease, the choice of the best treatment, and the success of the surgical procedure. To evaluate reconstructive surgery with meshes implantation during complex diaphragmatic procedures, care must be taken. No large study evaluated the perioperative outcomes related to diaphragmatic peritoneal stripping or diaphragmatic full-thickness resection; however, pleural effusion occurred in 43% of cases after peritoneal stripping and 51% after diaphragmatic full-thickness resections needing thoracentesis or chest tube placement in 4% and 9%, respectively. Moreover, the rate of postoperative pneumothorax (4% vs. 9%) and subdiaphragmatic abscess (3% vs. 3%) are similar after either of the two techniques. The current evidence from the literature suggests that the decision to drain postoperative effusion and the drainage method should be made in all cases at the discretion of the attending surgical team. Intraoperative pleural evacuation of fluid and air and closure of the diaphragm with eversion of the edges into the peritoneal cavity reduces postoperative effusions and pneumothorax. Typically, a chest tube is planned for patients with preoperative or postoperative large effusions, clinical signs of respiratory impairment, and radiological signs of pulmonary compromise. New minimally surgical approaches, technologies, energies, and postoperative care protocols are emerging to reduce the morbidity of this oncologic population.

Keywords

Diaphragmatic resection; Liver mobilization; Ovarian cancer; Radical surgery; Debulking

1. Introduction

1.1 Rationale of the Upper Quadrants' Abdominal Surgery in Advanced Ovarian Cancer

Ovarian cancer (OC) represents nearly 4% of gynecologic malignancies; however, most patients are diagnosed at an advanced stage, often involving the upper abdomen. The disease spreads principally to the peritoneal tissues. It is reported that diaphragmatic involvement occurred in 40% of patients with tumors in the pelvic cavity and in 70% of cases with extrapelvic metastasis [1]. To date, a recent relevant phase III clinical trial confirmed that cytoreduction and subsequent adjuvant chemotherapy with platinum are regarded as the most active therapy for high-stage EOC. Indeed, the report from the European Organization for Research and Treatment of Cancer (EORTC) protocol concluded that both the primary and interval debulking surgery with complete cytoreduction of all macroscopic cancer was the most relevant independent factor in the prediction of overall survival [2].

The same group reported that neoadjuvant chemotherapy and subsequent interval cytoreduction as a therapeutic strategy for patients with stage IIIC-IV ovarian cancer was not inferior to the primary cytoreduction procedure followed by chemotherapy. However, complete cytoreduction of all macroscopic cancer, both as primary and interval surgery, is the main goal whenever the debulking procedure is accomplished [2, 3]. Debulking surgery is a multi-visceral procedure including pelvic and abdominal organs aimed at attaining total resection of all macroscopic cancer implants to a microscopic cellular level [4, 5], hereafter also named cytoreductive surgery. The finding of extensive peritoneal involvement characterizes most advanced ovarian cancer patients. Therefore, the treatment of peritoneal carcinomatosis spreading to the upper abdominal quadrants and the pelvis is crucial for optimal cytoreductive surgery. Since the extraperitoneal dissection technique for peritonectomy and pelvic organs was described by Sugarbaker and coauthors [6], different operations, including pelvic or abdominal peritonectomy and diaphragmatic resection, have been used in advanced ovarian cancer with extensive peritoneal involvement, thus increasing the rate of complete cytoreduction up to 60%. This trend in achieving better debulking outcomes is parallel to the knowledge on new metastatic pathways theories affirming that ovarian cancer cells typically disseminate following a pathway from the pelvis to the diaphragms, particularly to the ride side. Thus, small bowel mesentery, the paracolic areas, the diaphragmatic domes, the omentum are common areas of dissemination. In addition, the anterior wall of the rectosigmoid colon and the peritoneum of the cul-de-sac are the most typical sites of pelvic spreading and infiltration [7]. Remarkably, the biology of EOC is different from gastrointestinal tract cancers. The spreading of EOC is essentially characterized by diffusion through the peritoneal surface and mechanisms of direct infiltration. This concept is recognized as a transfer pathway, and it clarifies the diffusion of cancer cells within the abdominal cavity. Fluid diffusion depends on the gravity and the negative pressure determined by diaphragmatic and lung movements at respiration combined with the peritoneum, omentum, and bowel across the falciform ligament in a clockwise direction. The lymphatics system is a significant route for spreading metastasis in ovarian cancer, while vascular spreading is less frequent. Consequently, dealing with the surgery of ovarian tumors requires knowledge of the possible metastatic pathways and comprehension of all relative assessments and operative tasks. Unlike colorectal cancer, malignant ovarian cells tend to invade superficial abdominal surfaces disseminating within the peritoneal cavity, thus involving the peritoneum layer and the omentum in most cases [8]. This different etiopathogenesis determines the possibility of resecting most superficial lesions by mesorectal or total peritoneal stripping, thus achieving optimal surgical outcomes. The upper invasive abdominal disease is frequently cited as an impediment to attaining complete primary surgical cytoreduction in ovarian cancer. A survey of the Society of Gynecologic Oncology (SGO) members showed that 84.7% of those surveyed reported that the upper abdominal disease was the main impediment in achieving optimal cytoreduction. Moreover, 76.3% of the respondents indicated that invasive diaphragmatic disease was the most challenging disease to be wholly eradicated, second only to portal triad disease [9].

1.2 Purpose

This review addresses the present technical aspects of diaphragmatic surgery for metastatic ovarian cancer. Included in the review are the anatomy of the diaphragm, the technique of liver mobilization for full diaphragm exposure and the technical aspects of diaphragm stripping, resection, and reconstruction including muscle flaps. The perioperative outcomes, management of complications, patient selection and the survival impact of resection of diaphragm metastases are discussed. Finally, diaphragm resection via minimally invasive surgery, a new classification of ovarian cancer surgery, and new technologies for resection of diaphragm metastases are addressed.

This document offers an additional tool in the portfolio of gynecologic surgeons approaching this challenging multiorgan surgery that could encompass multidisciplinary specialists in selected cases but is preferably performed by trained gynecologic oncologic surgeons.

2. Anatomical Landmarks

The knowledge of diaphragm anatomy, the relevant hepatic attachments, and the central vasculature is substantial for the performance of radical surgery during debulking of upper abdominal quadrants in advanced ovarian cancer patients. The diaphragm is a muscular and membranous dome-shaped structure at the basis of the chest and separates the abdomen from the chest cavity in mammals. It is bounded by the inferior aperture of the chest to the top, the vertebral column behind, the ribs, and sternum below; thus, it is divided into a lumbar, costal, and sternal part and it is in contact with the liver, kidney, spleen, and important vascular and nervous structures. These anatomical peculiarities make procedures on the diaphragm often technically challenging.

2.1 Foramina

In the diaphragm, there are three main foramina. The esophageal hiatus, through which the esophagus and the vagus nerve pass; the vena cava foramen through which the inferior vena cava (IVC) passes; and the aortic hiatus, through which the aorta, the aortic plexus, the thoracic duct, the azygos and hemiazygos vein pass. The diaphragmatic hiatus is contained in the lumbar part while the central tendon of the diaphragm borders the caval opening to the right of the midline. The caval hiatus is anchored to the central tendon by connective tissue, thus determining a solid connection between the pericardium and the cranial part of the central tendon. Indeed, the IVC is firmly fixed to the diaphragm through the opening of the vena cava.

2.2 Innervation

The phrenic nerve (C3–C5) provides the motor innervation to the diaphragm running from C3–C5 and laterally to the pericardium. The phrenic abdominal branch provides sensory innervation. The latter nerve is in the right side of the vena cava hiatus and provides the nervous supply to the upper abdomen and the peritoneal organs. The right phrenic nerve enters the central tendon lateral to the vena caval hiatus, and it is only visualized with dissection of the *bare area*. The left phrenic nerve usually enters the left diaphragm muscle above the central tendon and should be considered during surgery in the anterior part of the left diaphragm.

2.3 Ligaments

The liver is anchored to the diaphragm and the anterior abdominal wall through the round and the falciform ligaments, which contain the ligament teres. The peritoneal surface of the falciform ligament divides to form the anterior and posterior coronary ligaments. They reflect off the liver capsule and delineate the posterior extension of the diaphragm peritoneum. The anterior coronary ligaments continue laterally and inferiorly along the anterior liver edge joining the posterior right and left coronary ligaments to form the right and left triangular ligaments. The right triangular ligament reflects from the liver to the diaphragm, homolateral kidney, and adrenal gland. The left triangular ligament reflects principally to the diaphragm. The posterior left coronary ligament lies higher than the esophageal foramen; thus, the esophagus is usually not involved. The coronary ligaments on each side delineate the dorsocranial diaphragmatic surface of the liver called the *bare area*, which has close embryologic relation with the right diaphragmatic dome. Specifically, the right coronary ligament delineates the larger *bare area* on the right side and the left coronary ligament a smaller *bare area* on the left side, thus underlining the diaphragm's central tendon. The *bare area* of the liver is confined by fibrous tissue to the diaphragm and IVC. This area of the liver borders with the falciform ligament anteriorly, with the right triangular ligament in the right and with the left triangular ligament and the fibrous appendix of the liver on the left side. The fibrous appendix of the liver is involved in the fixation of the left hepatic lobe to the left diaphragmatic dome. Care must be taken during dissection in this area since the IVC lies to the right of the falciform ligament division. Notably, the right and left hepatic veins drain into the anterior surface of the IVC at this level and branches of the right and left inferior phrenic vessels may be encountered laterally in the anterior coronary ligaments. The posterior aspect of the right kidney rests on the lumbar part of the diaphragm and the lumbocostal triangle.

3. Liver Mobilization

Liver mobilization is the first surgical step before peritonectomy or full-thickness resection of the diaphragm to achieve optimal visualization of all diaphragm anatomy and metastatic sites. The surgery starts with the performance of a midline incision, then widening it on both sides using a retractor. Some operators place a Kent retractor on both sides of the diaphragm to attain a larger operating field and visibility. Our surgical team typically uses a Bookwalter retractor for radical multi-visceral surgery. The patient is usually placed in a modified dorsal lithotomy position, permitting the surgeon to stay both contralaterally to the hemidiaphragm involved side and between the patient's legs. Moreover, the so-called *airplaning* or rotation of the operating table on its long axis can maximize exposure of the diaphragm bilaterally. It is important to note that the extend of liver mobilization is strictly related to the diffusion of disease on the diaphragm and that large-volume tumor lesions are more likely to be in the right hemidiaphragm, which is challenging to reach because partially obscured by liver parenchyma. Exposure of the diaphragm for excision of implants can be challenging in many patients, particularly in short patients with a deep chest. The precise sequence of surgical steps will be modified and tailored according to the patient's anatomy and effort for exposition and the nodules distributions. The intrahepatic portion of the falciform ligaments that contains ligament teres is grasped between two Kelly camps, divided and ligated. After that, the membranous part of the falciform ligament is incised superiorly with the cautery, thus freeing the hepatic attachment to the anterior abdominal wall. The falciform ligament divides in the right and left sides, becoming continuous with the anterior homolateral coronary ligament. Care must be taken during the maneuvers for dividing the anterior right coronary ligament because the distal right hepatic vein and IVC lie beneath this plane of dissection. The peritoneal dissection continues laterally along the anterior right coronary ligament until the operating field allows the visualization of anatomical landmarks. While proceeding with this dissection, the lateral branches of the inferior phrenic artery and vein are cauterized or closed using clips as they are met. Gentle downward pressure on the liver with a laparotomy sponge can help continue the surgical step of peritoneal division and dissection. Additionally, if the operators retract the liver to the patient's left side during mobilization, the IVC may be compressed, thus possibly decreasing blood pressure. This inconvenience can be avoided by elevating the liver during retraction. In this view, the liver should be placed in a neutral position to avoid this hemodynamic modification or wait for perfusion to return. In fact, blood pressure can recover in less than one minute when the liver is repositioned in a neutral position, thus reducing hemodynamic risk for the patient. Once this part of the liver mobilization is achieved, the surgeon should focus laterally on the right triangular ligament, divided above the homolateral renal and adrenal reflection. The medial mobilization of the right hepatic lobe may be achieved by dividing the anterior and posterior right coronary ligaments, thus joining with the previous dissection along the right coronary ligament. According to the tumor distribution and patients' characteristics, the peritonectomy of the anterior diaphragm can be started laterally, and the triangular ligament detached after dissection of the lateral peritoneum from the right diaphragm. Tumor involvement on the left diaphragm is more easily resected without fully mobilizing the liver, although, in some instances, splenectomy may be necessary to clear the metastatic deposits [10, 11].

4. Overview and Rationale for Different Surgical Techniques and Thoracic Surgeon Involvement

Some surgical techniques are available to provide a proper cytoreductive effect for diaphragm involvement in ovarian cancer, including ablation using the Argon Beam Coagulator (ABC), aspiration using Cavitron Ultrasonic Surgical Aspirator (CUSA), peritonectomy (stripping), or full-thickness diaphragmatic resection. Stripping of the diaphragm can be performed safely from an intraperitoneal approach. Unlike the parietal pleura, which cannot be separated off the central tendon of the diaphragm, the peritoneum is less adherent and can be separated from all areas of the diaphragm, including the central tendon. Diaphragm stripping can be localized or may encompass a full hemidiaphragmatic peritonectomy. For localized regions, the peritoneum is incised around the site of the tumor and resected with the assistance of downward traction. A full hemidiaphragmatic peritonectomy is initiated by developing the peritoneal plane along the lateral thoracic wall and anterior costal margin and continuing the dissection posterior and medial. If extensive diaphragm stripping is performed, we recommend evaluation of the diaphragm for penetrations with an air leak test to detect pleural communication. Full-thickness diaphragm resections are necessary when tumor deposits invade into the diaphragm muscle, tendon, or into the ipsilateral pleural surface. If the pleural invasion is suspected on preoperative imaging, consultation with thoracic surgery for minimally invasive chest exploration prior to debulking can help demarcate the borders of disease. Diaphragm tissue can be divided with a harmonic knife, electrocautery, scissors, or a stapling device. If there are no pleural adhesions, the lung will retract from the resection site once a small pneumothorax is created. Downward traction on the diaphragm during resection also reduces the risk for intra-thoracic injury. If full thickness diaphragm resection is performed, closure is required to separate the pleural and peritoneal cavities. In many cases, the defects are repaired primarily due to the redundant nature of the diaphragm musculature. Primary closure is performed with a large-sized (0, #1, #2) nonabsorbable suture (Ethibond, Prolene) to reduce the risk of future diaphragmatic disruption inverting the edges into the peritoneal cavity. Multiple suture placement techniques are described. Options include primary running suture closure, horizontal mattress sutures to approximate the edges of the defect, or a two-layer closure combining the two techniques. The pneumothorax created by full-thickness diaphragm resection must be addressed at the time of surgery. For primary repairs, the pneumothorax can be evacuated by placing suction tubing or a red rubber catheter into the pleural space after the final stitch has been placed but not secured. The air can be evacuated with a combination of suction and a positive pressure ventilation Valsalva maneuver. The catheter is removed as the stitch is secured to prevent additional air entry, followed by an air leak test. In cases requiring prosthetic diaphragm repair, intraoperative chest tube placement should be performed.

Large felt pledges can be added to the suture, particularly in cases where the diaphragm tissue has thinned to bolster the repair [12–14]. Large defects in which primary repair would result in undue tension should be repaired using mesh. Size criteria for mesh reconstruction range from 5 to 8 cm, but there are often exceptions. Long narrow defects can be repaired primarily, while some small circular or oval-shaped defects may require mesh repair if they are in an area of limited diaphragm mobility.

4.1 Stripping of the Diaphragm

The extent of the peritoneal stripping of the diaphragm during ovarian cancer surgery depends on the diffusion of tumor nodules; thus, based on this detail, the surgical technique, the exposure of the operating field, and further operative steps can be tailored and modified. When a full right diaphragmatic peritonectomy is required, the first surgical step is the incision of the peritoneum on the anterior edge of the diaphragm, along the costal margin. The plane between the peritoneum layer and the muscular diaphragm is opened and developed along this line using either scissors or cautery. To facilitate the next surgical steps, the free peritoneal edge is grasped with a series of Allis clamps which are retracted downward to identify the line of attachment between the diaphragm and the peritoneum. The dissection of the peritoneum of the diaphragm muscle is carried out by combining both blunt and sharp dissection. Once the plane of dissection is well identified, the Allis clamps may be replaced with Péan or Kocher clamps. Typically, the cranial pole of the right kidney, the homolateral adrenal, and the right wall of the IVC are identified and exposed. With the help of the retractor, the surgical assistant executes a fixed upward retraction of the costal margin. This retraction counteracts the downward traction performed by the surgeon on the peritoneal layer. These counteractions are critical to maintain and modulate the adequate tension to continue a deeper dissection of the plan. During this maneuver, the liver can be rotated and dislocated medially, thus determining vagal stimulation and transient bradycardia and hypotension. In this view, the anesthesiologist team should be informed about this surgical step to prevent hemodynamic modifications thus, providing proper adjustments. The dissection is typically straightforward except over its central tendon, and the specimen can be removed en bloc, when feasible, at the end of peritoneal stripping. One of the most relevant technical hitches is related to the diaphragm penetration of tumor nodules that can require improvement of exposure and multiple peritoneal segmental resections. The dissection continues to the point where the anterior leaf of the coronary ligament and its posterolateral extension, the right triangular ligament, reflect onto the surface of the liver contiguous with Glisson's capsule. To avoid injury to the IVC, it is of relevance to point out that this dissection exposes the anterior edge of the *bare area* that the IVC crosses just to the right of the falciform ligament. Before entering the pericardial sac, the IVC passes immediately beneath the anterior leaf of the coronary ligament. Notably, the right phrenic nerve enters the diaphragm in the *bare area* just lateral to the IVC; thus, these anatomical structures are not encountered during this dissection. During diaphragmatic peritonectomy, the hemostasis of the surface of the resected area is easily attained with an argon beam coagulator which demonstrates minimal tissue penetration. Moreover, the small arterial and venous branches from the inferior phrenic vessels can be coagulated or clipped when identified. After completing the peritoneal stripping, checking the integrity of the diaphragm is mandatory. A ”bubble test” is usually performed to identify a diaphragmatic defect potentially responsible for a connection with pleural space. The patient is placed in a shallow Trendelenburg position, and the upper abdominal quadrant in which peritonectomy has been performed is filled with saline. A diaphragmatic defect is strongly probable if air bubbles are evident during inspiration and should be immediately identified and closed primarily to avoid complications related to pneumothorax. Small perforation can be closed by placing a pursestring suture around the hole. The preliminary surgical step is to insert a 14–16 french Robinson catheter into the pleural cavity through the hole. While the anesthesiologist maximally expands the lung, the suction is applied to the catheter, and the pursestring suture is tied down while the catheter is pulled out. In case of large perforations, the defects can be closed with a series of either interrupted, figure-of-eight permanent sutures. After closing the defect, the integrity of the closure and the remainder of the diaphragm should be checked [10, 11].

4.2 Diaphragmatic Resection

When the tumor nodules are fixed to the diaphragm’s muscle, full-thickness involvement of the diaphragm is suspected, and resection should be considered. This can be investigated and identified preoperatively by radiologic imaging, video thoracoscopy surgery, or intraoperatively. Generally, a full-thickness diaphragm resection is required if a diaphragmatic lesion infiltrates the peritoneal layer and muscle, including or not the pleural surface. After the liver mobilization, the anesthesiologist team must be informed that the pleural cavity will be entered, and a pneumothorax should be expected. The surgical technique will be selected based on the size of the defect. The EndoGIA stapler alone is used for the closure of small penetrating lesions without entering the pleural cavity. The tumor nodule is grasped by Allis clamp; thus, the diaphragmatic area with the lesion is retracted downward away from the lung parenchyma, and the stapler is used to resect and concomitantly to suture the tented tissue with the tumor trans-diaphragmatic implant. Larger tumor implants require entry into the pleural space. This procedure can be performed sharply using Metzenbaum scissors to avoid cautery burns to the lung. In the case the pleural cavity is entered, the involvement of the pleural space and the lung by cancer nodules can be examined with a thoracoscope. After visualizing and deflating the lung, the en-bloc resection of nodule, peritoneum, muscle, and pleural tissues can be performed using cautery or stapler. Frequently the defect can be closed primarily in case of limited tension of the edges using figure-of-eight permanent sutures. In case of large defects or abnormal tension on the closure, a permanent mesh secured to the diaphragm surface with interrupted nonabsorbable stitches can be required. In most cases, after diaphragm resection, the air can be evacuated using a red Robinson catheter during the closure of the pleural cavity as previously described. The patients who underwent large resections may require the intraoperative placement of a chest tube [11, 15] (Figs. 1,2).

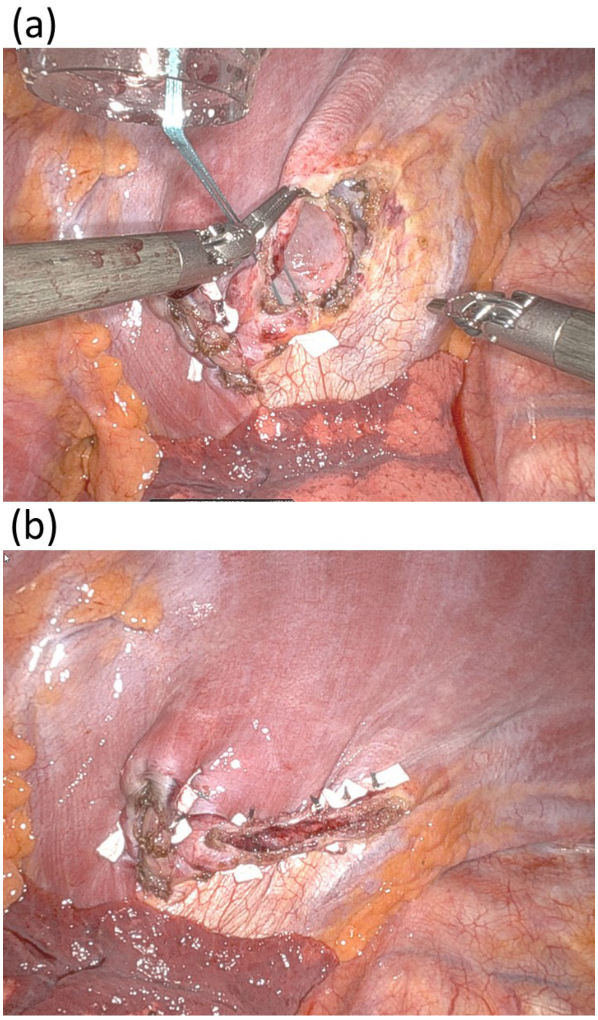

FIGURE 1. Diaphragmatic resection with robotic approach. (a) Closure of the defect in the diaphragm, primarily using non-adsorbable suture in an interrupted fashion. Horizontal matters statures provide optimal closure reducing the risk of sutures tearing through the diaphragmatic fibers. (b) Complete primary closure of the diaphragm.

4.3 Reconstructive Techniques

Most resection of the diaphragm can be repaired primarily in the cases there is adequate tissue on the edges that can be sutured without abnormal tension. To approximate the margins of the defects, a large nonabsorbable suture should be used in a horizontal matters fashion. However, some surgery team supports using a second running suture to a watertight seal to reduce fluid passing between the abdomen and the thoracic cavity so that defect up to 8 cm in diameter can be closed. In complete diaphragmatic resection or large defects, the diaphragm can be reconstructed with synthetic or autologous tissue. In this view, Polytetrafluoroethylene (PTFE), 2-mm thick, is one of the most used materials for reconstructive diaphragm surgery; and it seems to provide excellent outcomes, strength, and watertight. When a patch is placed, the defect of the diaphragm is accurately measured, and the patch is cut to be tailored to the defect. If the resection of the diaphragm is partial, the patch is sutured using a running nonabsorbable suture around the edges of the defect, taking

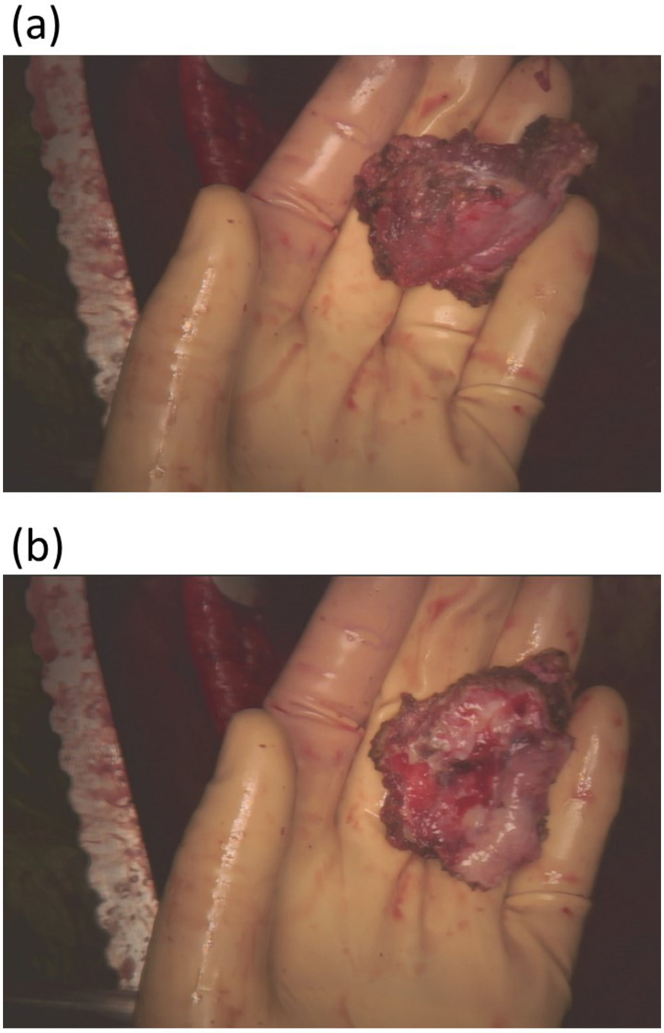

FIGURE 2. Detail of diaphragmatic specimen. (a) Pleural and (b) abdominal surfaces of a right diaphragmatic nodule after resection with open approach.

care of avoiding injuries to the anatomical structures below the diaphragm. For complete diaphragm resections, the PTFE patch is sutured starting from the most medial aspect, using a running nonabsorbable monofilament along the mediastinum, generally to the myocardial edge. To secure the patch in place, interrupted sutures are then placed around the ribs, from the level of the seventh rib anteriorly to the tenth rib posteriorly and the posterior crus. The surgeon must pay attention to place the sutures under the same tension, thus avoiding billowing of the patch. Non-permeable mesh in PTFE is used for reconstruction to prevent fluid shifts between the thorax and abdomen. Gore DUALMESH has two distinct surfaces, a small pore smooth surface and a larger pore rough surface. The smooth surface faces the pleural cavity to reduce lung adhesions, while the rough surface allows for desired adherence to the surrounding abdominal tissue. A 2-mm thick, appropriately sized mesh is selected. The mesh is secured circumferentially using interrupted pledged horizontal mattress nonabsorbable sutures [16, 17] (Fig. 3).

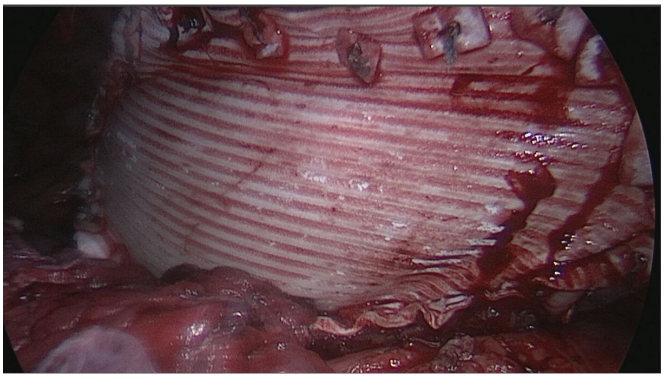

FIGURE 3. In complete diaphragmatic resection of large defects, the diaphragm can be reconstructed with synthetic or autologous tissue. Polytetrafluoroethylene (PTFE), 2-mm thick, is one of the most used materials for reconstructive diaphragm surgery; and it seems to provide excellent outcomes, strength, and watertight.

4.4 Muscle Flaps

Several reports describe the use of muscle flaps, including rectus, external oblique, latissimus dorsi, and transversus abdominis muscle flaps. The use of autologous tissue may be beneficial in selected patients. For example, autologous material may be valuable in sporadic pediatric patients in which autologous tissue allows for growth as the child ages while synthetic materials do not allow it, or in patients with post-obstructive pneumonia [16].

5. Perioperative Outcomes

In 1985 Deppe et colleagues [18] described the outcomes and surgical technique of debulking diaphragmatic metastases as part of cytoreductive surgery for advanced ovarian epithelial cancer in a series of fourteen patients. The authors reported no intraoperative complications, no significant increase in blood loss, no postoperative pulmonary adverse events, while deep vein thrombosis and bladder infection occurred in two patients. Three patients experienced prolonged ileus, which responded to conservative treatment with nasogastric suction. All patients started their course of combination chemotherapy within three weeks after their operations.

Similarly, in 1989 Montz [19] described the feasibility and the perioperative outcomes of 14 patients undergoing primary cytoreductive surgery for stage III ovarian malignancies with concomitant resection of diaphragmatic peritoneum, muscle, or both, to remove all metastatic disease. The authors accomplished an optimal cytoreduction in 93% of cases (13 of 14 patients), entering the mediastinum twice and resecting the diaphragm muscle four times. All the defects were closed primary, and a tracheostomy tube was placed in one case. The surgical team did not completely eradicate the diaphragmatic lesion in only one case due to major bleeding from the liver capsule. One patient developed a pneumothorax that resolved spontaneously, and no subdiaphragmatic hematomas or abscess occurred. Kapnick *et al.* [20] described the perioperative outcomes of 12 full-thickness resections of diaphragmatic lesions in eleven patients with involvement of diaphragm and upper abdominal quadrants by metastatic nodules of ovarian cancer. The investigators categorized patients into two groups according to primary (n:6) and recurrent (n:5) disease with penetrating diaphragmatic metastases. They compared these two groups to ten patients who underwent excision of non-penetrating diaphragmatic metastases. The author reported a significant ($p < 0.01$) difference between the volume of penetrating (5.0 cm) and non-penetrating (4.0 cm) lesions, and they pointed out that in patients with primary disease the invasiveness of diaphragmatic metastases was inversely related to their survival. This was not the case in patients with recurrent disease. the concept of attaining optimal cytoreduction continuously developed throughout the last two decades. In this scenario, diaphragmatic peritoneal stripping or full thickness resection are common procedures of cytoreductive surgery.

Feasibility, Efficacy, and Survival Impact of Diaphragm Resection

There is no consistent evidence concerning the real oncological value, feasibility, safety, and technical features of different surgical techniques specific for the diaphragmatic approach. An SGO survey in 2001 identified diaphragmatic resection as the main impediment to attain complete cytoreduction [9]. Cliby *et al*. [10] reported postoperative complications of diaphragm resection in a series of 41 patients with advanced ovarian cancer and described full-thickness diaphragmatic nodules in 85% of specimens, no gross residual disease in 80%, and residual disease <1 cm in 10% of cases. Eight patients experienced complications requiring treatment: two with pneumothorax, four with symptomatic pleural effusions, one patient with a subphrenic abscess, and another with a gastro-pleural fistula. Devolder *et al*. [21] described perioperative outcomes of 69 patients who underwent diaphragmatic surgery as a part of cytoreductive surgery for epithelial ovarian cancer with acceptable morbidity. The series involved 30 patients who underwent stripping and coagulation of tumor lesions, 22 patients who underwent coagulation of lesions, and 17 patients' coagulation alone. Sixty-three of 69 patients received red blood cell transfusion and 36 fresh frozen plasma intraoperatively, while in the first postoperative day, 12 and 13 patients underwent red blood cell and fresh frozen plasma transfusion, respectively. Pleural effusion occurred in 41 cases; 3 patients needed a chest drain, seven pleural punctures, and one both. In one case, bilateral pleural effusion occurred, and the patient developed pneumonia. Interestingly, the authors did not describe significant intraoperative complications related to diaphragmatic peritonectomy per se, and they reported a 30% rate of pleural effusion significantly ($p < 0.0001$) associated with the entry in the pleural space during diaphragmatic peritonectomy. Moreover, 12.5% of patients required thoracentesis [22]. Another investigation from Mayo Clinic reported the surgical technique and associated morbidity of 56 cases of diaphragmatic peritonectomy as a part of primary (n:37) and recurrent (n:19) ovarian cancer surgeries excluding patients who underwent diaphragmatic resection, excision of tumor implants with CUSA, cautery, curette, or finger fracture. Patients undergoing primary and secondary debulking showed a median survival of 59 and 23 months, and 5-years survival was 49% and 16%, respectively [22]. Fanfani and colleagues [23] reported the outcomes of eighty-seven patients who underwent the diaphragmatic procedure during primary (n:50), interval (n:16), and secondary (n:21) surgery for advanced and recurrent epithelial ovarian cancer. Interestingly, the most frequent complication reported in 37 (42.5%) patients was pleural effusion which significantly correlated with liver mobilization and the resection of large diaphragmatic lesions (>5 cm). More recently, a group from Oxford University compared the surgical and histological outcomes of 100 patients with stage IIIC–IV ovarian cancer who had diaphragmatic peritonectomy or full-thickness resection with pleurectomy at Visceral-Peritoneal Debulking (VPD). Sixty-four and 36 patients underwent diaphragmatic peritonectomy and full-thickness diaphragmatic resection with pleurectomy. Notably, the investigators did not find any significant differences in the rate of mortality (3% vs. 3%), overall intra- and postoperative morbidity (32.8% vs. 38.8%), pulmonary morbidity (9.3% vs. 19%). At pathologic assessment, histology showed tumor invasion in the diaphragmatic peritoneum (96%), muscle (28%), and pleura (19.4%). Microscopic free margins were described in 86% and 92% in the diaphragmatic peritonectomy and full-thickness resection with the pleurectomy group, respectively [1]. A Chinese research team evaluated the procedures and complications of diaphragm peritonectomy or full-thickness resection during primary cytoreduction in a population of 150 patients, most of them (96%) with advanced-stage epithelial ovarian cancer and prevalent (89.3%) serous histology. The Diaphragm peritonectomy was performed in 124 (82.7%) cases, while 26 (17.3%) patients underwent full-thickness resection. On the total 142 procedures involving the upper abdominal quadrants, no macroscopic residual disease was observed in 35.3% of the patients, while 84% of the total patient cohort had residual disease ≤1 cm. The most frequently described morbidities were pleural effusions (33.3%), pneumonia (15.3%), and pneumothorax (7.3%), whereas the total rate of postoperative pleural drainage was 14.6%. After full-thickness resection of the diaphragm, half of the patients received intraoperative (11.5%) and postoperative (38.5%) drainage. The authors highlighted that the incidence of pleural effusion at postoperative period was significantly associated to the full-thickness resection (HR, 4.9; 95% CI 0.2–19.9; $p = 0.028$) and long operative time (HR, 15.4; 95% CI 4.3–55.5; $p < 0.001$) as well as the tumor stage IV (HR, 17.2; 95% CI 4.5–66.7; $p < 0.001$) [24]. Finally, results from the DRAGON trial; a single-center, prospective, randomized trial enrolling 88 ovarian cancer patients who underwent monolateral diaphragmatic resection and receiving intraoperative thoracostomy tube placement (n:44) and no tube placement (n:44), sought the light on new evidence regarding the incidence of postoperative complications in this complex surgery. The authors described no difference in the rate of any grade of intra- and postoperative complications between the two groups. At the same time, they reported a significantly lower incidence of severe respiratory symptoms (6.8% tube vs. 22.7% no tube, $p = 0.035$) and moderate to large pleural effusions (18.2% tube vs. 65.9% no tube, $p < 0.0001$) in the group of patients underwent intraoperative thoracostomy tube placement. Interestingly, these data were also confirmed at multivariable analysis, demonstrating that patients who did not undergo intraoperative tube placement were likely (OR 14.5, 95% CI 3.7–57.4) to receive postoperative thoracostomy tube placement due to pleural effusion compared to the group of patients who underwent intraoperative tube placement [25]. The same group explored the overall survival (OS) outcomes of 244 patients with stage IIIC and IV epithelial ovarian cancer to identify the therapeutic value of diaphragmatic surgery in this oncological population. The investigators found that 5-years OS was improved in 181 patients who underwent stripping of the diaphragmatic peritoneum, full or partial thickness diaphragm resection, excision of nodules, or CUSA. Moreover, after multivariable analysis of the subpopulation with diaphragmatic involvement, residual disease <1 cm and performance of diaphragmatic procedure were identified as independent predictors of survival. Remarkably, in the subgroup of patients with RD <1 cm, a strong survival advantage for those patients who underwent diaphragm surgical procedures (5-year survival: 55% vs. 28%; p = 0.0005) were further described [26]. Devolder *et al*. [21] reported a median OS of 66 months in the stripping group compared with 49 months in the coagulation group. Remarkably, 56 patients (81%) experienced relapse, and the first site of relapse resulted in a diaphragm in 11 (20%) cases.

6. Complications and Postoperative Care

There is incomplete Data about the safety and effectiveness of diaphragmatic procedures as a part of cytoreductive surgery in advanced ovarian cancer. Indeed, no large study evaluated perioperative outcomes related to diaphragmatic peritoneal stripping or diaphragmatic full-thickness resection. However, it is well known that the onset of pulmonary adverse events and complications increases morbidity, mortality, hospitalization, and the complexity of the health care of this oncologic population. Hence, numerous reports on a limited number of patients aimed to assess the efficacy of postoperative approaches to decrease pulmonary complications after abdominal surgeries for ovarian cancer debulking. At present, there is no conclusive evidence to support breathing exercises, oxygen therapy, or intermittent positive pressure breathing during the postoperative period to decrease pulmonary adverse events. Growing evidence describes a strong correlation between delayed mobilization during the hospital stay and postoperative pulmonary complications in patients undergoing diaphragmatic procedures at cytoreductive surgery.

6.1 Pleural Effusion

Thus, a postoperative pleural effusion is a commonly observed postoperative event in these patients. A recent meta-analysis including 272 patients evaluated 75 (28%) diaphragmatic peritoneal stripping (DPS) and 197 (72%) diaphragmatic full-thickness resection procedures (DFTR). The authors estimated that the rate of pleural effusion occurred in 43% of patients with peritoneal stripping and 51% with diaphragmatic full-thickness resections and requiring thoracentesis in 4% or chest tube placement in 9% respectively. The rate of postoperative pneumothorax (4% vs. 9%; OR, 0.31; 95% CI 0.05–2.08) and subdiaphragmatic abscess (3% vs. 3%; OR, 0.45; 95% CI 0.09–2.31) were similar after the execution of DPS and DFTR [27]. The fluid that collects in the pleural space in patients presenting with ascites is a consequence of diffusion from the peritoneal cavity to the pleural space rather than from primary thoracic involvement. This concept was introduced by Meigs [28] in 1943, reporting the transfer of India ink via the lymphatic system into the thoracic cavity in patients presenting ascites and hydrothorax associated with ovarian fibroma. More recent data from the hepatic literature demonstrated that diaphragm defects might frequently be the cause of pleural effusions in patients with ascites due to primary hepatic disease. It has been assumed that ascitic fluid from the peritoneal cavity could be diffused up by negative intrathoracic pressure throughout diaphragm defects. These defects could be secondary to the formation and the subsequent rupture of pleural blebs [29]. The extensive dissection of the hepatic ligaments and the exposure of the *bare area* during liver mobilization seem to follow this hypothesis considering that these surgical maneuvers are significantly associated with an increased rate of pleural effusions [30]. Generally, all patients undergoing diaphragm procedures should have a chest radiograph in the operating room at the completion of surgery or in post-anesthesia care unit (PACU). The current evidence from the literature suggests that, according to the rate of pleural effusions or pulmonary complications occurring after diaphragmatic surgery for advanced ovarian cancer, the decision to drain postoperative effusion and the drainage method should be made in all cases at the discretion of the attending surgical team. Typically, a chest tube is planned for patients with preoperative or postoperative large effusions, clinical signs of respiratory impairment, and radiological signs of pulmonary compromise. These patients will require serial radiographs postoperatively. Some surgical teams routinely place chest tubes intraoperatively to avoid postoperative pleural effusions after liver mobilization with exposure of the central tendon [11]. This preventive intervention could reduce postoperative respiratory impairment due to pleural effusion, even if the rationale of the routine use of this practice is still a matter of debate. Pneumothorax rarely occurs and can be prevented by checking the integrity of the diaphragm after closure. It is critical to follow these patients with close attention to symptoms, planning serial postoperative imaging, and warranting rapid access to therapeutic interventions when required; thus, avoiding reintubation or consequent access to intensive care units for respiratory distress [31].

6.2 Hernia and Eventration

It is essential to point out the concepts of hernia and eventration. A hernia is leakage of an organ or adjacent tissues of the cavity where they are contained, while an eventration is a hernia that forms at the same time as the scars after abdominal surgery and, it is a complication of a laparotomy or abdomen surgery. It is important to note that the occurrence of a diaphragm eventration after diaphragm surgery in ovarian cancer patients is a rare but significant complication resulting from iatrogenic damage of the diaphragm, incomplete closure of a defect, or suture pull-through of a closed defect. Right-sided eventrations are unfrequent due to the interposition of the liver from the small bowel. They are more common and usually a surgical emergency in the left diaphragm consisting of the stomach or small bowel entry into the left thoracic cavity. They must be repaired immediately due to the risk of strangulation of the herniated stomach or bowel. While rare, diaphragm eventrations require prompt identification, intervention, and surgical correction to avoid serious complications [32] (Fig. 4).

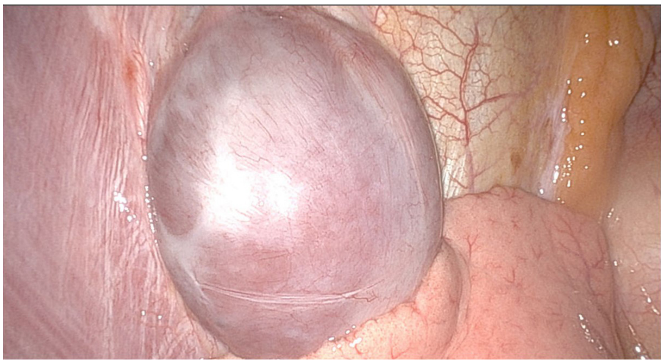

FIGURE 4. The occurrence of a diaphragm eventration after diaphragm surgery in ovarian cancer patients is a rare but significant complication resulting from iatrogenic damage of the diaphragm, incomplete closure of a defect, or suture pull-through of a closed defect.

Complications after diaphragmatic peritonectomy or resection in the leading case series are reported in Table 1 (Ref. [1, 10, 18–25, 31, 33–36]).

7. The Perspective of Diaphragmatic Surgery for Advanced Ovarian Cancer

7.1 New Classification Systems

Although almost 30 years have elapsed since the first study on diaphragmatic resection for advanced ovarian cancer. There is no systematic classification correlating the pattern of diaphragmatic tumor involvement and the appropriate surgical treatment. This makes it challenging to plan the appropriate intervention, the involvement of multiple surgical specialists, the perioperative health care required, and the comparison of data and reports. In addition, it is difficult to assess the level of surgical training required to undertake these interventions. Interestingly, Tozzi *et al.* [37] analyzed 170 FIGO stage IIIC-IV underwent Visceral Peritoneal Debulking (VPD) in three different institutions: 110 (64.7%) had a peritonectomy while 60 (35.3%) had a full-thickness resection with pleurectomy. The authors distinguished three surgical categories of diaphragmatic diseases, merging the disease findings with the proper surgical procedures. Type I treated 28 (16.5%) patients who had only anterior diaphragmatic implants, and they underwent peritonectomy without liver mobilization and no morbidity recorded. Type II was described in 105 (61.7%) patients who presented anterior and posterior disease requiring both peritonectomy or full-thickness resections and need partial or complete liver mobilization in some cases. This category of patients experienced 10% morbidity related to diaphragmatic surgery. Type III pertained to 37 (21.7%) patients who underwent full-thickness resection and total liver mobilization in all cases, suffering 30% related morbidity. The authors concluded that this novel classification model merging data about diaphragmatic disease and related surgery in a cohort of patients with advanced ovarian cancer could help standardize surgery, compare results, and define essential skills and training required.

7.2 Minimally Invasive Surgery

In the last few years, the value of minimally invasive surgery in the treatment of diaphragmatic metastasis in ovarian cancer patients has been investigated both at clinical and technical analysis. A novel report from Mayo Clinic described pulmonary complications and diaphragm recurrence after resection of diaphragm metastases by both traditional laparoscopic and robotic approaches for epithelial ovarian cancer in a series of 29 patients (robotics n:21; laparoscopy n:8) with advanced ovarian cancer. Twenty-three patients had a peritoneal resection, and six underwent full-thickness resection of the diaphragm. Complete resection was achieved in all patients with no conversions to laparotomy; two patients (6.9%) had pleural effusion as pulmonary complications. Six patients (20.7%) had diaphragm recurrence, and ten patients (34.5%) had recurrence at other abdominal sites. The authors demonstrated the feasibility and the safety of diaphragmatic procedures using minimally invasive surgery in this selective oncologic population [38]. In a subsequent report, they described the technical features of the robotic resection of diaphragmatic metastasis in ovarian cancer patients. The authors point out the need for careful selection of patients for MIS, the relevance of trocar placement that is dependent on the location of the disease for successful resection of tumor lesions. They advocated that the nodules involving the left diaphragm and the ventral aspect of the right diaphragm are accessed with trocars placed slightly cranial to the umbilicus; metastasis in the dorsal aspect of the right diaphragm can be resected with trocars in the upper quadrants, tumor lesions located in the lateral portion of the right diaphragm are excised using an intrahepatic approach, and those in the medial aspect are resected using a suprahepatic approach. The authors also suggested the setting of monopolar instrumentation, thus recommending that keeping monopolar tools at 10 Watts to 15 Watts can prevent contraction of the diaphragm and pleural perforation [39].

7.3 New Technologies and Energies

Recently reports in the literature have addressed new technical tools and energies to achieve optimal cytoreduction in advanced ovarian cancer. The PlasmaJet is characterized by a neutral plasma beam of ionized gas, transmitting kinetic and thermal energy, fading quickly. It is used to cut and coagulate tissue and vaporize tumors implants with minimal harm in the underlying healthy tissue. PlasmaJet has been identified as an innovative tool that can significantly minimize the volume of the residual disease thanks to the vaporizing abilities, concomitantly reducing the morbidity rates related

TABLE 1. Intra- and postoperative data of major studies on diaphragmatic surgery for ovarian cancer.

Study	Year	No.	Surgical procedure	Complication			Management
				Pleural effusion	Pneumothorax	Other complications	
Deppe *et al.* [18]	1986	14	DP	nr	nr	nr	nr
Montz *et al.* [19]	1989	13	10 DP	nr	1 (7.7%)	nr	Intraoperative chest tube
			3 DR				
Kapnick *et al.* [20]	1990	21	DR	nr	7 (33.3%)	nr	Intraoperative chest tube
Cliby *et al.* [10]	2004	41	11 RF	4 (9.7)	2 (4.9%)	1 subphrenic abscess	10 intraoperative chest tube
			7 DP			1 gastro-pleural fistula	3 pleural punctures
			1 DR				
			22 nodules resection				
Eisenhauer *et al.* [31]	2006	59	DP/DR	30 (50.8%)	1 (1.7%)	nr	7 intraoperative chest tube
							8 pleural punctures
Devolder *et al.* [21]	2008	69	17 DP	41 (59.4%)	4 (5.8%)	1 pneumonia	3 chest drains,
			22 ABC + DP			1 partial atelectasis	7 pleural punctures
			30 DP				1 both
			5 DR				
Dowdy *et al.* [22]	2008	56	DP	17 (30%)	7 (12.5%)	nr	2 intraoperative chest tube
							5 pleural punctures
Tsolakidis *et al.* [33]	2010	89	DP/ABC	60 (67.4%)	7 (7.9%)	5 pneumonia	10 intraoperative chest tube
Fanfani *et al.* [23]	2010	87	18 ABC	37 (42.5%)	4 (4.6%)	nr	12 intraoperative chest tube
			56 DP				7 pleural punctures
			13 DR				
Bashir *et al.* [34]	2010	45	DP/DR	23 (51.1%)	12 (26.7%)	nr	1 thoracentesis
							1 thoracotomy
Chereau *et al.* [35]	2011	148	DP/DR	55 (37.2%)	6 (94.1%)	3 pneumonia	21 chest drains
						7 pulmonary embolisms	
Pathiraja *et al.* [36]	2013	42	DP	2 (4.9%)	0	nr	nr

TABLE 1. Continued.

Study	Year	No.	Surgical procedure	Complication			Management
				Pleural effusion	Pneumothorax	Other complications	
Soleymani Majd *et al.* [1]	2016	100	64 DP	4 (6%)	1 (1.5%)	1 thromboembolism	nr
			36 DR	4 (11%)	2 (5.5%)	1 liver lobar collapse	
Ye *et al.* [24]	2017	150	124 DP	11 (8.9%)	0	nr	1 thoracentesis
			26 DR	10 (38.5%)	1 (3.8%)	1 hepatic vein rupture	1 thoracotomy
Cianci *et al.* [25]	2021	88	DR	37 (42.0%)	17 (19.3%)	nr	44 intraoperative chest tube
							11 postoperative drains

DP, Peritonectomy; DR, resection; RF, radiofrequency; ABC, argon beam coagulation; nr, not reported.

TABLE 2. Relevant surgical tools and technical issues, procedures performed concomitantly to diaphragmatic peritonectomy and major complications for diaphragmatic surgery in ovarian cancer.

Surgical techniques	Tissue dissection	Closure of defects	Concomitant procedures	Common complications
Argon Beam Coagulator (ABC)	Harmonic knife	Large-sized (0, #1, #2) nonabsorbable suture (Prolene)	Large bowel resection	Pleural effusion
Cavitron Ultrasonic Surgical Aspirator (CUSA)	Electrocautery	Primary running suture closure	Small bowel resection	Persistent ileus
Localized or hemidiaphragmatic peritonectomy (stripping)	Scissors	Horizontal mattress sutures	Splenectomy	Pancreatitis
Full-thickness resection	Stapling device	Two-layer closure combining the two techniques	Liver resection	Miocardial infarction
	Neutral plasma beam of ionized gas	Muscle flaps	Radical hysterectomy	Pelvic abscess
			Inguinal lymphadenectomy	Deep venous thrombosis
			Reconstructive techniques	Intraoperative atrial fibrillation
				Hernia and eventration

to surgical procedures associated with cytoreduction. Preliminary data concerning this novel energy source for the ablation of tumor implants in the advanced ovarian cancer population suggests it is safe and effective. A recent review and meta-analysis of 5 studies collected data of 77 patients (age 38 to 85 ys); 24 patients underwent primary debulking surgery, 42 patients underwent interval debulking surgery, six patients had optimal cytoreduction, while four patients underwent secondary debulking treatment. Notably, the total incidence of intraoperative complications was 32% (8/25), but none of them were due to the use of the new device. Seventeen out of 72 patients (23.6%) experienced postoperative complications such as systemic or wound-related complications and pneumothorax related to resection of diaphragmatic lesions. Complete cytoreduction was attained in 59 out of 70 (84.3%) patients, and no postoperative mortality was reported. Data about the use of this energy during diaphragmatic procedures in this specific oncologic population are inconclusive, and further investigations are needed [40, 41]. Technical issues and tools are summarized in Table 2.

8. Conclusions

The value of debulking surgery to achieve no gross residual for advanced ovarian cancer patients is well established. Diaphragmatic surgery consists of peritoneal stripping, electrocoagulation of nodules, or full-thickness resection, and they can be safely performed as part of debulking surgery to increase the cytoreductive effort, thus improving patients' survival. Performing diaphragm resection but leaving unresected disease elsewhere does not improve survival. It is necessary to acquire complete knowledge of upper abdominal anatomy and surgical techniques for diaphragmatic surgery and liver mobilization for any gynecologist operating on ovarian cancer patients.

AUTHOR CONTRIBUTIONS

AG and SB reviewed literature and wrote the manuscript. JM and KB edited the manuscript and participated to contents analysis and implementation. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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AG is serving as one of the Review Board members of this journal. We declare that AG had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Paul M. Magtibay. The other authors declare no conflict of interest.

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