The principles of safe and efficacious upper abdominal surgery

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Abstract: Upper abdominal debulking procedures represent an indispensable part of cytoreduction for advanced ovarian cancer. As a genuinely peritoneally disseminated malignancy, more than 70% of the patients will present in an advanced stage with tumor involvement of the upper abdominal organs, especially liver- and splenic capsule, lesser sac, Morrisons pouch and diaphragm. Studies have clearly shown the maximal survival benefit being derived from maximal effort surgery achieving total macroscopic tumor clearance. For that reason, gynecological oncology teams need to master the dissection techniques in the upper abdomen and also be able to handle the associated complications. We will review here the key issues around upper abdominal cytoreduction and focus on the spleen, liver, and stomach/lesser sac. Diaphragmatic surgery will be addressed in a separate, especially dedicated chapter. Safety and feasibility of complex oncologic upper abdominal dissections for advanced and relapsed ovarian cancer are based on the fundamental knowledge of anatomy, principles of peritonectomy techniques, as well as infrastructural support and collective knowledge and education of the entire team. Surgical and infrastructural expertise are of paramount importance to achieve best possible oncologic outcomes with an acceptable morbidity profile even for those patients with high burden disease.

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Basic principles

Attributed to the peritoneal metastastic spread of the disease, that usually respects the peritoneal borders, the basic peritonectomy principles of the "Sugarbaker" type dissection should be followed for safe cytoreduction (1,2). These principles are based on adequate tension, traction and countertraction of the affected visceral and parietal peritoneum. By following the natural tissue planes and through dissection into the avascular spaces, we can avoid unnecessary bleeding, despite extensive cytoreductive procedures, while facilitating *en bloc*, extraperitoneal complete resections, without cutting into or overmanipulating the actual tumor. Fundamental knowledge of the anatomy and adequate exposure and mobilization of the neighboring structures before actual tumor removal are the prerequisites for a safe oncologic resection technique. Adequate exposure ensures that even in case of injury of adjacent vital structures during tumorectomy, a safe "damage" control is possible, without having to blindly place sutures and/or clips and so causing additional field damage (1,2).

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Spleen, pancreas

Splenectomy will be required in approximately 20% of patients who undergo upfront ovarian debulking in order to achieve total macroscopic tumor clearance, across multiple prospective and retrospective series (3-5). This is mostly due to a splenic hilum involvement from a strongly adjacent omental cake and/or splenic capsule metastases, rather than true intrasplenic metastatic disease (4,5). While actual pancreatic parenchymal involvement is rather uncommon, in some cases of strongly adherent splenic tumor, a distal pancreatectomy may be required for complete tumor dissection (3,6). An *en bloc* dissection and resection technique is preferable in case of confluent tumor spread affecting multiple organs, in order to avoid cutting into tumorous structures that will cause only unnecessary bleeding and is potentially associated with higher risk of visceral injury of adjacent structures.

The principles of splenectomy are based on a pedunculated dissection technique to skeletonize the pedicles at the splenic hilum and so to safely ligate the vessels, ideally first the splenic artery and then the splenic vein to avoid blood loss and future arteriovenous fistula formation (5,7). There are two main types of dissection: the anterior and the posterior approach. In the former, the splenic vessels are dissected and ligated primarily at the splenic hilum followed by mobilization and dissection of the splenic body and the adjacent tumor. This is mostly recommended in larger tumors that affect the splenic hilum. In cases of predominantly splenic capsule and left diaphragmatic tumor infiltration and omental caking, we would mostly perform, the posterior approach with primarily mobilization and dissection of the splenic body together with the adjacent diaphragmatic peritoneum and the omental cake with subsequent dissection till the splenic hilum, dissection off the pancreatic tail and dissection of the splenic pedicle. The spleen is connected via ligaments with the adjacent organs such as omentum, stomach and left colic flexure (4,5,8). These particular ligaments supply safe avascular pathways to adequately mobilize the spleen. The splenic artery may give off several branches once it reaches the hilum and therefore careful dissection is crucial to avoid hemorrhage. The preferable way for us to perform the splenectomy starts with the dissection and ligation of the gastrosplenic ligament including the short gastric vessels. This is followed by division of the splenophrenic and splenocolic ligaments. The subsequent division of the splenorenal ligament results subsequently in complete organ mobilization so that the splenic vessels can be safely dissected and divided without pancreatic tail injury. Less frequently, it may be necessary to resect the pancreatic tail if involved by contiguous tumor infiltration (4,5,7-9). Potential complications of left upper quadrant resections with splenectomy include postoperative hemorrhage, pneumonia, pleural effusion/empyema, atelectasis, subphrenic abscess, pancreatic fistula, pancreatitis, pseudocyst formation, gastric perforation, gastric curve necrosis, thrombocytosis, leukocytosis, and increased risk of sepsis due to encapsulated microorganisms (3-5,7-9).

Retrospective data have shown that even post-splenectomy ovarian cancer patients develop a physiologic, usually transient, leukocytosis and thrombocytosis; platelet-to-white blood cell ratio does not appear to have a strong predictive value in differentiating between sepsis versus reactive changes similarly to trauma patients (5). A second leukocytosis peak on postoperative day 10, has however been shown to signalize a postoperative infection and not just represent a reactive leukocytosis in retrospective data (4).

Due to the lifelong high risk of overwhelming infections, postsplenectomy patients should be adequately educated. Also, postsplenectomy vaccinations approximately 2 weeks after the operation are part of the guidelines. A repeat vaccination after 5 years is necessary for the pneumococcal and meningococcal vaccine. Prophylactic long-term antibiotics are reserved for high risk and immunocompromised patients (4,5).

The most commonly associated major morbidity derived from dissection and resection in the area of the pancreatic tale is the pancreatic fistula formation (5,10). There is no specific technique of distal pancreatectomy that has been shown to be beneficial over another in terms of risk of clinically relevant pancreatic fistula formation. Most authors/teams tend to place a drain in the peripancreatic area after splenectomy and distal pancreatectomy to monitor the patient for any high amylase and lipase in case of fistula formation and to ensure adequate drainage. The International Study Group of Pancreatic Fistula classification has re-defined a clinically relevant postoperative pancreatic fistula as a drain output with an amylase level >3 times the upper limit of normal serum amylase combined with a relevant clinical picture with high inflammation parameters, pain, and equivalent imaging. A simple "biochemical leak", that was formerly classified as a "grade A" postoperative pancreatic fistula is no longer considered as a true pancreatic fistula since it has no clinical implications (10).

No significantly different rates of pancreatic fistula have been demonstrated after hand-sewn (20%) versus stapled pancreatic tail closure (24%) (11). However, small series have demonstrated a significantly lower rate (33% *vs.* 0) of clinically relevant postoperative pancreatic fistula with the triple combination of linear stapling closure, peri-firing compression plus continuous suture for stump closure of the pancreatic tail compared to linear stapling with peri-firing compression alone (12). Also, in a multicentre, retrospective evidence of 2,026 patients no better method of transection could be identified to protect from pancreatic leak. Suture ligation of the pancreatic duct, staple size, staple line reinforcement, tissue patches, biologic sealants, or prophylactic octreotide failed to show independent impact on the risk of postoperative pancreatic fistula formation (13). The same study identified following risk factors as independent risk factors for clinically relevant postoperative pancreatic fistula formation: age (<60 years: OR 1.42, 95% CI: 1.05–1.82), obesity (OR 1.54, 95% CI: 1.19–2.12), hypoalbuminemia (OR 1.63, 95% CI: 1.06–2.51), the absence of epidural anesthesia (OR 1.59, 95% CI: 1.17–2.16), neuroendocrine or nonmalignant pathology (OR 1.56, 95% CI: 1.18–2.06), concomitant splenectomy (OR 1.99, 95% CI: 1.25–3.17), and vascular resection (OR 2.29, 95% CI: 1.25–3.17). 3.17) (13).

Despite the data above, retrospective cohort studies in tertiary high-volume pancreatic centers showed that pancreas thickness and stapler cartridge may play a role in the risk of postoperative clinically relevant pancreatic fistula, with a seemingly fistula rate increase according to the thickness of the pancreatic stump (14). Group II staplers, i.e., closed height of 1.8 mm, resulted in a significant reduction of the pancreatic fistula rate compared to cartridges of closed height of ≤1.5 or ≥2.0 mm in pancreas with thickness <13 mm (53.5% *vs.* 21.7% *vs.* 36.0%, P=0.031). The type of cartridge didn't appear to have any significant effect on pancreas thicker than 13 mm (14).

The additional application of Fibrin sealant patches or Tachosil to the pancreatic stump have failed to provide any relevant benefit on the mortality, reoperation rate, blood loss or length of hospital stay after pancreatic tail resection (15-17). Even though some small case series have demonstrated a superiority of coverage with a flowable hemostatic matrix compared to thrombin-coated collagen patches, the evidence does not suffice to establish their routine use broadly (18).

There has been a belief that somatostatin and its analogues could prevent postoperative pancreatic fistula formation, through reduction of pancreatic, gastric, and enteric secretions. However, evidence around the potential benefit of perioperative prophylactic somatostatin use is conflicting with no significant overall impact on pancreas related morbidity and mortality (19-27). Due to the inhomogeneity of the studies any direct comparison is challenging and so no clear identification of any subgroup for which prophylactic treatment might be potentially more beneficial has been identified. For selected patients who develop high-output fistulas, somatostatin may be useful to control the volume of output (28).

A prospective randomised trial with pasireotide (900 micrograms pasireotide prophylactically on the morning of the pancreatic surgery continued for one week) *vs.* placebo, showed previously highly promising reduction of clinically significant pancreatic fistula, however the results have not been able to be replicated in subsequent studies in a similar way (29). Therefore, there is no value of the routine use of prophylactic somatostatin for patients undergoing splenectomy ± distal pancreatectomy in ovarian cancer debulking procedures. In selected cases of high-output fistulas, somatostatin analoga, especially its longer lasting derivates may be used.

Stomach

True gastric resections are rather rare in primary and relapsed ovarian cancer surgery (1-3). More common are resections along the major or lesser gastric curvature and stripping of the gastric serosa due to superficial lesions. Even in lesions that initially may appear to infiltrate the wall, careful dissection often reveals that the tumor can be safely and successfully addressed with resection of the gastric serosa without entering of the gastric lumen and necessity of full thickness gastric wall resection (1,2). Often a thick omental cake may appear to infiltrate the major curvature of the stomach, but after mobilization and resection of the gastroepiploic vessels, the mass can be removed without necessity of a partial gastrectomy. Major risk from such dissections and mobilization is the postoperative gastric perforation and the gastroparesis (30). For the preservation of the adequate vascular supply of the stomach, at least one out of the supplying arteries need to be preserved: left and right gastroepiploic arteries, right and left gastric arteries and short gastric arteries.

Postoperative gastric perforation

Gastric wall defects usually occur at infragastric omentectomy. For that reason, most perforations have been described to occur along the greater curvature of the stomach (1,2). Associated mechanisms of action are vascular compromise, overseen serosa defects and impaired wound healing through cytotoxic treatment. Seromuscular tears related to traction on the stomach wall and point pressure on the greater curvature from a long-term indwelling nasogastric tube have also been described (30,31). To minimize those risks, prophylactic oversawing of the greater curvature, after omentectomy with resection of the gastroepiploic arcade has been described as a potential protective course of action (30,31).

We would advise, any suspected serosa-defect at the gastric wall during dissection to be repaired as soon as recognized to avoid delayed perforation in the postoperative period. Even though postoperative gastric perforation at debulking represents a rare complication, conservative management is not recommended and reoperation is the mainstay of treatment (30). HIPEC in addition to cytoreduction has been described as a risk factor for gastric morbidity. If reoperation is necessary to manage postsurgical gastric perforation, successful management includes the suture plication of the gastric defect or just the resection of the affected part with a stapler and potentially additional oversawing of the suture line (31). Since some large-scale studies have demonstrated that surgical exploration of patients with postoperative gastric perforation often revealed protrusion of nasogastric tube through the gastric wall defects, commonly located at or near the greater curvature of stomach, nasogastric suction postoperatively should be avoided (30).

Postoperative gastroparesis

Postoperative gastroparesis in ovarian cancer i.e., delayed gastric emptying of solids in the absence of a mechanical obstruction, occurs usually after more extensive tumor resections at the major and lesser gastric curvature especially when in combination with splenectomy (32). Perioperative vagal injury may also be the cause, but that is very rare in ovarian cancer debulking. Most common symptoms include nausea and vomiting, early satiety, abdominal bloating, and pain (33). Postsurgical gastroparesis should be addressed as a first step with correction of electrolytes, appropriate dietary regimens, and as next steps pharmacological with metroclopramide, domperidone, and erythromycin. In general, liquid formulations are preferable to tablets since they are less likely to accumulate and cause gastric irritation.

Dietary modifications include avoiding of fatty, acidic, and roughage-based foods that intensify symptoms from delayed gastric emptying (33). Nondigestible fiber such as fresh fruits and vegetables require effective antral motility that is impaired in patients with gastroparesis postoperatively. Fat, additionally impairs this process. Digested fiber should be soluble or cooked to have reduced particle size so that it can be digested and emptied adequately (33). Carbonated drinks should also be avoided as they may aggravate gastric distention.

Pharmacologic therapy with prokinetics increases the rate of gastric emptying and should be ideally administered 10 to 15 minutes before meals with an additional dose before bedtime in patients with persistent symptoms. As compared with tablets, liquid formulations allow for easier dose titration and are less likely to accumulate in the stomach and cause erratic absorption (33-36).

In cases of refractory gastroparesis ultima radio is surgery including placement of an enterostomy tube (e.g., gastrostomy, jejunostomy), pyloromyotomy, transpyloric stent and pyloroplasty (34-36).

Liver porta hepatis/coeliac trunc/lesser omentum

Approximately 20% of patients with advanced disease who undergo primary debulking, will require resection at the porta hepatis/lesser omentum for complete tumor clearance to be obtained, with almost 9% necessitating some type of liver resection (3). In a prospective monocentric study of systematic exploration of key areas in the upper abdomen demonstrated that 67% of the patients who needed upper abdominal cytoreduction will have tumor involvement in the omental bursa, pancreatic surface, lesser omentum, caudate lobe, celiac nodes, portal nodes and triad nodes (37). The authors have stressed the paramount importance of the systematic inspection of the retrohepatic region including the anterior and posterior surface of caudate lobe after resection of left triangular ligament up to the gastro-esophageal junction. These are all maneuvers that have been shown to be associated with acceptable morbidity if left in the hands of expert surgeons and teams. Similar findings demonstrated the group by Heitz *et al.* on the example of 578 patients with primary debulking surgery (38,39). They showed that next to the small bowel mesentery and serosa, key upper abdominal structures like the porta hepatis, hepatoduodenal ligament, coeliac trunk, liver parenchyma, pancreas and gastric serosa were the most common sites of postoperative residual disease even within a highly specialized setting. As defined by the European Society of Gynecologic Oncology (ESGO), following criteria are considered to be associated with inoperability in advanced disease: diffuse deep infiltration of the small bowel mesenteric root and diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to a short bowel syndrome (remaining bowel <1.5 m), diffuse involvement/deep infiltration of stomach/duodenum, head or middle part of pancreas, tumor involvement of coeliac trunc, hepatic arteries, left gastric artery, central or multisegmental parenchymal liver metastases, multiple parenchymal lung metastases, nonresectable lymph node metastases, brain metastases (40). Tumor involvement of some key upper abdominal sites, such as the coeliac trunk, have been shown to be together with high preoperative tumor burden independently associated with decreased survival even after complete cytoreduction for advanced ovarian cancer. Many investigators identify tumor involvement for example of the coeliac trunk as a surrogate marker of diffuse disease and an independent risk factor for early recurrent disease (41,42).

Liver surgery is most commonly needed in ovarian cancer not due to true intraparenchymatous liver metastases but to liver capsule disease that usually is confluent to diaphragmatic carcinosis and Morrisons pouch carcinosis (43,44). Attributed to the flow of ascites within the abdominal cavity, involvement of the right, as opposed to the left, diaphragm and so liver capsule is more common. Adequate liver mobilization is crucial to evaluate the whole capsule and entire retrohepatic space. In addition to the Glisson capsule, each sulcus, round ligament, gallbladder, porta hepatis, retrohepatic region and the hepatic bridge should be visualized carefully. The hepatic bridge is located between the segments 3 and 4b covering some part of round ligament in the form of fibrous band or parenchyma (45). It is documented in 38% of women, and to achieve complete resection, it should be resected to facilitate exploration (45). No complication is reported for this procedure. During resection of the round ligament, extreme caution should be taken not to damage the portal vein which is very close to the root of the ligament. The umbilical vein is drained into the portal vein during fetal life. Therefore, we recommend that the root of round ligament should be sutured or secured by hemoclip.

Subcapsular metastases may infiltrate into the liver parenchyma, and they should be resected as wedge resection. It can be easily performed by increasing the level of cautery to the highest level without significant sequela or using the specially designed instruments like the Habib device. Bipolar forceps may also help to control bleeding in addition to argon beam cautery. The second type is the hematogenous parenchymal metastasis which necessitates precise pre- and intraoperative imaging for mapping and complete resection (46). Preoperative imaging and mapping are essential to identify and to resect all metastases from ovarian cancer. During intraoperative ultrasonography, the metastatic lesion within the liver is localized, and the vascular anatomy is identified to prevent massive bleeding and bile leakage. The parenchymal metastases could be resected by using different techniques where necessary: wedge resection, segmentectomy, lobectomy and/or hepatectomy (43,46). Although it is not needed for each case, Pringle manoeuvre may decrease the bleeding during liver resection.

Bristow *et al.* evaluated 84 stage IV EOC patients, of which 6 underwent optimal cytoreduction with 50.1 months median survival; 11 had residual hepatic disease with 27.0 months median survival, and 20 patients had hepatic and extrahepatic residuals with only 7.6 months median survival (47). No morbidity or mortality was reported specifically related to the liver resection. Similarly, Lim *et al.* did not report any biliary leak or liver abscess in their cohort of 14 patients after wedge resection (50%), segmentectomy (35.7%), and hemi-hepatectomy (14.3%) with negative margins (48). When they compared this group of patients with 97 stage IIIC patients, no survival difference was found between them. Residual disease and performance status were the most important prognosticators in these studies. In the recurrent setting, Niu *et al.* (49) analyzed the effect of liver resection at secondary cytoreduction in 60 patients with a median number of three lesions located unilaterally (48.3%) or bilaterally (51.7%). The type of liver resection was wedge resection in 28 (46.7%), radiofrequency ablation in 3 (5%), lobectomy in 7 (11.7%), trisegmentectomy in 7 (11.7%), bisegmentectomy in 12 (20%), and combined with radiofrequency ablation in 3 (5%). Median overall survival was 52 months for patients with negative margins (90%) *vs.* 22 months with positive resection margin (10%). None of the postoperative complications was directly related to the liver resection. In a selected group of patients, microwave ablation or radiofrequency ablation can be performed without a significant increase of the morbidity rates (43,44).

Gasparri *et al.* reviewed the published literature on the role of hepatic resection in ovarian cancer by analyzing primary and recurrent patients separately. They reported that complete tumor resection and long disease-free interval were the most important prognosticators for survival. Performance status, number of liver lesions and resection margins were also found to be significant. Complications that were directly attributed to liver resection such as bilioma, hepatic abscess or liver failure were seen in an only small percentage of patients (43). Panici *et al.* equally reported on their complications management after upper abdominal surgery in a cohort of 121 patients (50). They identified diaphragmatic resection, hepatic resection, pancreatectomy, and biliary surgery as independent predictors of surgical morbidity. Interestingly, no patient sustained a biliary leak or liver failure. Two patients with multiple hepatic resections had an intraoperative bleeding of more than 2 liters. One patient died of sepsis (50). The median time interval from surgery to initiation of chemotherapy was equal for those patients who sustained a surgical complication versus those who didn't (50). Therefore, precise pre- and intraoperative mapping would be crucial to increase success rates and to decrease complications.

Complications management of right upper quadrant cytoreduction

Transient derangement of the liver function tests (LFT) is one of the most common side effects of right upper abdominal dissection and liver mobilisation (51). In a large monocentric study, 74% of patients after extensive right upper-quadrant cytoreduction increased their LFTs postoperatively with a peak at 24- hours. Highest ALT median was 1.7-fold of upper normal limit (UNL), with the highest ALT value rising up to 28-fold UNL on the 1st postoperative day. Changes in the ALP levels were less prominent, with median value of highest ALP being within normal and the highest ALP value rising up to 4-fold UNL on the 5th postoperative day. Average bilirubin levels remained also within the normal range throughout the postoperative period. Mean LFT-normalization time was 7 days (range, 3–14 days). The authors described no relevant associated morbidity apart from one case (0.8%) of fatal fulminant hepatic-failure concluding that due to the existing risk of fulminant liver failure, albeit rare and difficult to predict, postoperatively elevated LFTs should be monitored until normalization. Liver toxic drugs should be avoided until a downwards trend of the LFT's is noted (51).

Further complications are biliary leaks, hepatic abscesses, bleeding, and liver failure. Postoperative biliary ductal injuries can result in significant morbidity, including biliary peritonitis, cholangitis, and sepsis (1-3). Postoperative bilomas can become colonized by bacteria and become infected if left undrained. Most evidence in literature is based on series published about post-cholecystectomy leaks. The International Study Group of Liver Surgery (ISGLS) established a uniform bile leak definition including a severity grading associated with postoperative morbidity and mortality (52).

The first-line treatment for biliary leaks, is endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy, stenting, or a combination of both techniques. The reported success rate of all these interventions is very high (>90%) without statistically significant differences between them. Complex injuries, such as transection, should generally be managed surgically. Naso-biliary drainage should be limited to patients with severe co-morbidities and/or coagulopathy to avoid a second endoscopic procedure (e.g., for stent removal) or sphincterotomy (53).

If sepsis and biliary peritonitis predominate, a percutaneous, endoscopic ultrasound assisted or surgical drainage are preferred as first line treatment. The percutaneous transhepatic biliary drainage is a challenging option in case of non-dilated biliary tree and should be considered mainly in cases of failure of ERCP or if it is not feasible for example due to the given anatomical conditions (53).

Conclusions

Safety and feasibility of complex oncologic upper abdominal dissections for advanced and relapsed ovarian cancer are based on the fundamental knowledge of anatomy, principles or peritonectomy and resection techniques, as well as infrastructural support and collective knowledge of the entire team. Surgical and infrastructural expertise are of paramount importance to achieve best possible oncologic outcomes with an acceptable morbidity profile even for those patients with high burden disease.

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Footnote

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