

Ovarian Cancer Peri-Operative Management GUIDELINES

TABLE OF CONTENTS

1	Introduction.....	5
2	Acknowledgements.....	5
3	Responsibilities.....	5
4	Methods.....	6
5	Funding.....	7
6	Disclosure.....	7
7	General recommendations.....	8
8	Timing of surgery in relation to targeted and antihormonal agents.....	9
8.1	Bevacizumab.....	9
8.2	Poly(ADP-ribose) polymerase (PARP) inhibitors (Olaparib, Niraparib, Rucaparib, Veliparib).....	9
8.3	Antihormonal therapy.....	9
9	Preoperative bowel preparation.....	11
10	Skin antisepsis and hair removal.....	13
10.1	Body bath or shower.....	13
10.2	Surgical-site antisepsis.....	13
10.3	Vaginal antisepsis.....	13
10.4	Hair removal.....	13
10.5	Skin antisepsis for spinals and epidurals.....	14
11	Surgical safety checklists, patient positioning and retractors use.....	15
11.1	Surgical safety checklists.....	15
11.2	Patient positioning.....	15
11.3	Surgical retractors.....	16
11.4	Electrothermal devices.....	16
12	Anaesthesia, intra- and post-operative volume and replacement.....	18
12.1	Blood transfusion and oncologic outcome.....	18
12.2	Perioperative fluid replacement.....	20
12.3	Prevention of hypothermia.....	22
13	Major intra- and post-operative bleeding.....	24
13.1	Local haemostatic agents and surgical internal iliac artery ligation options.....	24
13.2	Surgical options.....	25
13.3	Medical options.....	26
13.4	Interventional radiology options.....	30
14	Prevention and management of upper abdominal complications.....	32
14.1	Liver resection and biliary leaks.....	32
14.2	Spleen, pancreas.....	33
14.3	Diaphragm.....	34
14.4	Stomach.....	34
14.5	Lesser sac, Porta hepatis, celiac region.....	35
14.6	Cardiophrenic lymph node resection.....	36
14.7	Postoperative pleura effusion.....	36
15	Prevention and management of infective and urological complications.....	39
15.1	Postoperative sepsis, collection, drainage.....	39

15.2	Urological complications: hydronephrosis, ureteric fistulas, nephrostomies	39
16	Management of bowel related morbidity, prophylactic stoma formation and stoma reversal	42
16.1	Anastomotic leak after colorectal resection	42
16.2	Stoma placement.....	43
16.3	Stoma reversal.....	44
16.4	Quality of life and low anterior resection syndrome.....	45
17	Antibiotic/microbiologic management and post-splenectomy management.....	46
17.1	Perioperative antibiotic prophylaxis	46
17.2	Post-splenectomy management	46
18	Postoperative pain management.....	49
18.1	Postoperative analgesia.....	49
18.2	Systemic analgesia	49
18.3	Non-neuraxial regional analgesia	49
18.4	Epidural/intrathecal analgesia	50
19	Perioperative thromboprophylaxis (pharmacological and mechanical) and management of postoperative thromboembolic events	52
19.1	Prophylactic anticoagulation in routine patients without thrombophilia or previous thrombosis.....	53
19.2	Mechanical thromboprophylaxis	53
19.3	Management of high risk patients with previous VTE already on anticoagulation (VKA, LMWH, DOACs).....	54
19.4	Management of high risk patients with previous VTE not anymore on anticoagulation and in high risk patients with a thrombophilia but without previous VTE	55
19.5	Bridging in patients on anticoagulation and/or antiplatelet drugs due to cardiovascular comorbidities: atrial fibrillation, biologic or mechanic valve replacement in mitral and aortic position, cardiac stents and stroke	56
19.6	Management of postoperative VTE events.....	59
19.7	Spinal/epidural anesthesia and anticoagulation.....	60
19.8	Indications and contraindications for insertion of an inferior vena cava filter.....	60
19.9	Types of inferior vena cava filter	61
19.10	Value of cava filter implantation in case of lower limb DVT related to tumor compression/infiltration	62
20	Wound considerations/complications	64
20.1	Prophylaxis of impaired wound healing.....	64
20.2	Wound care in high risk patients	64
20.3	Surgical necrotizing fasciitis.....	65
20.4	Hernia repairs, use of mesh	67
21	Nutritional management.....	69
21.1	Measures and principles of perioperative nutritional support.....	69
21.2	Refeeding syndrome.....	71
21.3	Dietary management of the patients with a bowel stoma	72
22	Prehabilitation, enhanced recovery, postoperative ileus prevention	74
22.1	Prehabilitation and ERAS concepts.....	74
22.2	Physical exercise	74
22.3	Nutritional interventions.....	75
22.4	Psychological, anxiety reducing support.....	75
22.5	Proactive measures for postoperative ileus prophylaxis.....	76
23	Postoperative physiotherapy and mobilisation	78

24	Frailty scores/Management of the fragile patient	80
25	Psycho-oncological and social support	82
26	References	85
27	Appendices.....	133
27.1	Appendix 1 - List of the international development group	133
27.2	Appendix 2 - Identification of scientific evidence.....	134
27.3	Appendix 3 - List of the 117 international reviewers	135

1 Introduction

Surgery for ovarian cancer has evolved significantly over the last decades with increasing implementation of a higher radicality with the aim to achieve maximal tumor clearance even in the most advanced stages of the disease¹. The European Society of Gynaecological Oncology (ESGO) has developed and established for the first time in 2016 and updated in 2020 quality indicators for advanced ovarian cancer surgery to audit and improve clinical practice in Europe and beyond^{2,3}. The aim of ESGO was to homogenise and standardize surgical care through well defined quality assurance programs and certification processes that will identify centres with the appropriate expertise and excellence to perform this type of radical debulkings without incremental increase of morbidity and mortality.

As a sequelae of the continuous effort to improve oncologic care in patients with ovarian cancer, ESGO has issued in 2018 a consensus guidance jointly with the European Society of Medical Oncology addressing in a multidisciplinary fashion twenty selected key questions in the management of ovarian cancer ranging from molecular pathology till palliation in primary and relapse disease^{4,5}.

In order to complement the above achievements and consolidate the promoted systemic advances and surgical expertise with the adequate perioperative management, the ESGO developed as next step, clinically relevant and evidence-based guidelines focusing on key aspects of peri-operative care and complications management as part of ESGO's mission to improve the quality of care for women with advanced ovarian cancer and reduce iatrogenic morbidity. These guidelines are intended for use by all health professionals that are involved in the surgical care of ovarian cancer patients, across all allied disciplines. Even though our aim was to present the highest standard of evidence in an optimal treatment setting of qualified ovarian cancer centres, the ESGO and the working group acknowledge the fact that there will be broad variability in practices between the various centres worldwide and also significant differences in terms of infrastructure, access to medical and surgical technology, but also training, medicolegal, financial, and cultural aspects that will affect the implementation of any treatment guidelines.

2 Acknowledgements

ESGO would like to thank the international development group for their energy, expertise and constant availability, to make the development of these guidelines possible, as well as the international reviewers and patients for their highly constructive comments to make our recommendations broadly implementable into clinical practice across the different countries and healthcare systems.

3 Responsibilities

These guidelines are a statement of evidence and consensus of the authors based on their views and perspectives of currently accepted approaches for the peri-operative management of patients with ovarian cancer. Any clinician applying or consulting these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. These guidelines make no warranties of any kind regarding their content, use, or application and the authors disclaim any responsibility for their application or use in any way.

4 Methods

The guidelines were developed using a five-step process as defined by the ESGO Guideline Committee Standard Operative Procedures manual (see Figure 1). Strengths of the process include a multidisciplinary international development approach as well as a robust external reviewal process consisting of both physicians and patients. This development process involved one pilot, introductory meeting and three two-days meetings of the international development group, chaired by Professor Christina Fotopoulou (Imperial College London, London, United Kingdom).

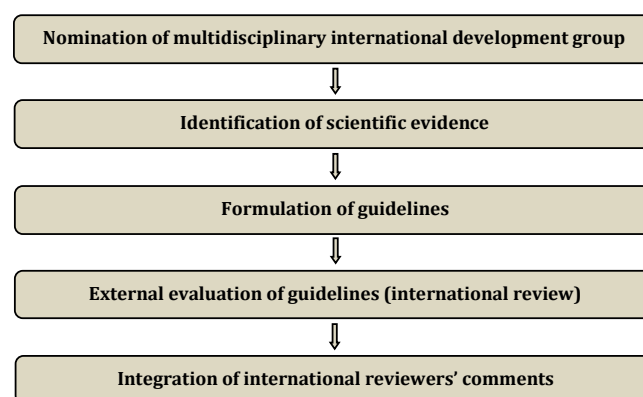


Figure 1. Development process

ESGO nominated practicing clinicians who are involved in the peri-operative management of ovarian cancer patients and have demonstrated leadership through their expertise in clinical care and research, their national and international engagement and profile as well as their dedication to the work and vision of the ESGO society. The objective was to assemble a multidisciplinary panel and it was therefore essential to include professionals from all relevant disciplines ie gynaecological oncology, anaesthetic and intensive care, interventional radiology, microbiology, haematology, nursing, psychooncology, and nutrition to contribute to the validity and acceptability of the guidelines. The list of the development group is available in Appendix 1.

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A systematic, unbiased literature review of relevant studies published between January 2015 and June 2020 was carried out using the MEDLINE database (see Appendix 2). The bibliography was also supplemented by additional older relevant references (if any). The literature search was limited to publications in English. Priority was given to high-quality systematic reviews, meta-analyses, and randomised controlled trials, but studies of lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, and *in vitro* studies. The reference list of each identified article was also reviewed for other potentially relevant articles. The development group was also allowed to consider older significant evidence (if any).

The development group developed guidelines for all the topics. The guidelines were retained if they were supported by sufficiently high level scientific evidence and/or when a large consensus among experts was obtained. An adapted version of the “Infectious Diseases Society of America-United States Public Health Service Grading System” was used to define the level of evidence and grade of recommendation for each of the recommendations⁶ (see Figure 2). In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group.

LEVELS OF EVIDENCE	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, experts opinions
GRADES OF RECOMMENDATIONS	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Figure 2. Levels of evidence and grades of recommendations

ESGO established a large multidisciplinary panel of practicing clinicians that provide care to ovarian cancer patients to act as independent expert reviewers for the guidelines developed. These reviewers have been selected according to their expertise and active involvement in clinical practice, while geographical balance ensured a global perspective. Ovarian cancer patients were also included. These independent reviewers were asked to evaluate each recommendation according to its relevance and feasibility in clinical practice (only physicians). Quantitative and qualitative evaluations were performed. Patients were asked to evaluate qualitatively each recommendation (according to their experience, personal perceptions, etc.). Evaluations of the external reviewers (N = 117) were pooled and discussed by the international development group before finalising the guidelines. The list of the 117 external reviewers is available in Appendix 3.

5 Funding

All costs relating to the development process were covered from ESGO funds. The development group members have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

6 Disclosure

CF: advisory boards for AstraZeneca, Clovis, Ethicon, Roche, MSD, GlaxoSmithKline, Tesaro, and grants for travelling from Sequana. AH: advisory boards for PharmaMar, Promedice GmbH, Pierre Fabre Pharma GmbH, Roche Pharma AG, Tesaro Bio, Germany GmbH, MSD Sharp & Dohme GmbH, and honoraria from AstraZeneca GmbH, Celgen, MedConcept GmbH, Med update GmbH, Mediculus, Pfizer, Promedice GmbH, Pierre Fabre, Roche Pharma AG, Tesaro Bio Germany GmbH, LEO Pharma. SSc: advisory boards for GlaxoSmithKline/Tesaro, Clovis, and grants for traveling from GlaxoSmithKline/Tesaro, Pharma Mar. JS: advisory boards for Roche, GlaxoSmithKline, AstraZeneca, Clovis, MSD, Merck, and grants for travelling from Roche, GlaxoSmithKline, AstraZeneca, Clovis. RUT: advisory boards for Atara Bio, research sponsored by Roche, grants for traveling from Roche, Atara Bio, Celgene, AbbVie, Glaxo Smith Kline and Janssen. TA, JC, LC, AC, OE, AF, DH, CH, PK, PM, FP, ES, SSu, and CT: no conflicts of interest.

7 General recommendations

Patients with ovarian cancer have clearly demonstrated and expressed in numerous studies their high need and willingness to be involved in the decision-making processes around their treatment management⁷⁻¹⁰. This need appears to be irrespective of their age and cultural background but also disease stage⁷. Patients appeal for more effective treatment strategies and even though multicentre data have shown that they would accept higher risks of iatrogenic and surgical morbidity and mortality in exchange for substantial gains in their survival, they still have the strong desire to be thoroughly and adequately informed about the adverse side effects of the proposed treatment pathways but also about the available alternatives^{7,8}.

This clear desire about adequate information flow has been shown to be apparent from the earliest stages of the patients' diagnosis and treatment journey, not to only be able to reach informed decisions but also to develop realistic expectations being aware of the risk and benefit profile of each proposed treatment strategy^{9,10}. In addition to that, patients have expressed their right of having access to second opinions and being able to participate and have access to clinical trials⁹. Establishing quality of life as an outcome parameter of those trials, is a natural sequelae of the increased patients' engagement and active involvement.

These well-defined patients' perspectives and wishes provide the clinicians with the necessary framework to not only discuss preferences with their patients but also to incorporate those preferences into any proposed treatment plans⁸.

General recommendations

- All patients should be adequately informed preoperatively about the risks and benefits of radical ovarian cancer surgery; about the most common complications and their management and also future steps of their journey [V, A].
- Early and continuous patient education, information and coaching within a multidisciplinary approach is advised to holistically support and empower patients [V, A].
- A risk stratification of ovarian cancer patients who are planned to undergo debulking surgery should be preoperatively undertaken to tailor management and proactively act against expected risks [V, A].

8 Timing of surgery in relation to targeted and antihormonal agents

8.1 Bevacizumab

Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody applied both in the primary and recurrent setting¹¹⁻¹⁵. In the GOG-218-trial bevacizumab was omitted at cycle 1 to avoid delayed wound healing if chemotherapy was initiated within 4 weeks of surgery¹¹. In this setting, 708 patients (95%) in the bevacizumab arm vs 737 (98%) patients in the standard arm showed no increased wound healing complications. However, bevacizumab treatment appeared to be associated with an increase in bleeding (mainly grade 1 mucocutaneous bleeding), hypertension of grade 2 or higher (18% with bevacizumab vs. 2% with standard therapy), thromboembolic events of grade 3 or higher (7% with bevacizumab vs. 3% with standard therapy), and gastrointestinal perforations (occurring in 10 patients in the bevacizumab group vs. 3 patients in the standard-therapy group) compared to the standard arm¹¹.

A further analysis of the GOG-218 trial revealed that especially patients with a history of inflammatory bowel disease and bowel resection at primary surgery are exposed to a higher risk of bevacizumab related gastrointestinal complications¹⁶. Similar results have been reported in the ICON7 trial with an increased rate of gastrointestinal adverse events in the bevacizumab group (1.3% vs 0.4% in the control group)¹⁷. In this trial, adjuvant treatment with bevacizumab was also initiated at cycle 2 of chemotherapy¹³. An association has also been suggested between emergency surgery after bevacizumab treatment due to bowel obstruction and/or fistulas and an impaired wound healing in advanced heavily pretreated platinum-resistant ovarian cancer patients¹⁸. Safety data also exist regarding the application of bevacizumab in the context of neoadjuvant settings with similar recommendations in terms of timing to the adjuvant setting^{17,19}. The European Medicines Agency therefore recommends that antiangiogenetic treatment should be started at the earliest 28 days after major surgery or after the surgical wound has completely healed and in the absence of any surgical fistulas. Patients who experience impaired wound healing under therapy should discontinue this until the wound has completely healed. Before an elective procedure, the therapy must be discontinued for at least 4 weeks as per recommendations of the licencing of bevacizumab in ovarian cancer²⁰. In routine clinical practice, often 6 weeks are preferred to minimize complications.

8.2 Poly(ADP-ribose) polymerase (PARP) inhibitors (Olaparib, Niraparib, Rucaparib, Veliparib)

Poly(ADP-ribose) polymerase (PARP) inhibitors are part of the initial and relapsed treatment strategies against epithelial ovarian cancer²¹⁻²⁴. They show activity in patients with pathogenic BRCA mutation (somatic and germ line mutations) as well as in patients with homologous recombination deficiency and patients with BRCA wild-type and no evidence of homologous recombination deficiency^{25,26}. They may be combined with bevacizumab or given as monotherapy^{27,28}. PARP inhibitors have not been associated with wound complications, so a distinctive negative effect on wound healing is not expected. Moreover, translational research data rather suggest even a favorable effect on wound healing processes^{29,30}. In general, recovery from bone marrow toxicity should be awaited before surgery.

8.3 Antihormonal therapy

Antihormonal treatment in the form for example of tamoxifen or letrozole, is commonly used in low grade histologies both in the adjuvant as well as maintenance setting³¹. Due to the well defined thrombogenic side effects, endocrine therapy should be stopped at decision to operate. A perioperative treatment free interval of 2-3 weeks seems reasonable. For patients who are on endocrine therapy due to other malignancies, for example under tamoxifen for breast cancer, the risks and benefits of discontinuing this to reduce thromboembolic morbidity perioperatively need to be counterbalanced with the oncologic

benefits, so risk stratification should be individualized. However, since endocrine therapy is usually discontinued during cytotoxic treatment due to increased thromboembolic toxicity and patients who undergo surgery for advanced ovarian cancer will almost certainly need postoperative systemic treatment; endocrine therapy tends to be stopped preoperatively to avoid unnecessary morbidity.

Timing of surgery in relation to targeted and antihormonal agents

Bevacizumab

- A treatment free interval of at least 28 days between bevacizumab administration and surgery is recommended [III, B].
- Patients who experience impaired wound healing under antiangiogenetic therapy should discontinue this until the wound has completely healed [III, B].

PARP inhibitors

- No specific time interval is defined between elective surgery and oral PARP therapy discontinuation. A general evaluation of the known side effects and their resolution before surgery is recommended [IV, B].

Antihormonal therapy

- In case of ovarian cancer progression on antihormonal therapy, this should be stopped at decision to operate to reduce risk of thromboembolic morbidity [III, B].

9 Preoperative bowel preparation

Most data regarding bowel preparation originate from colorectal surgery studies and no prospective randomised data exist specific for patients undergoing radical debulking surgery for advanced ovarian cancer. A major significant difference is that in the case of ovarian cancer debulkings, resections are commonly multivisceral, affecting the entire peritoneal and retroperitoneal cavity including multiple bowel segments, whereas surgery for colorectal cancer is usually more limited to single site organ resections. That, in addition to the fact that ovarian cancer patients often have large volume ascites at surgery, lead to a completely different morbidity profile between the two surgical settings, especially in terms of bowel related complications³². For that reason, any experience and data from colorectal studies should not be just readily translated one to one in the setting of ovarian cancer debulkings.

Although the first multicenter single-blinded randomized trial in 2010 demonstrated that rectal cancer surgery without mechanical bowel preparation was associated with higher risk of overall and infectious related morbidity, but without any significant increase of anastomotic leakage, further randomized control studies, systematic reviews and meta-analyses have shown no evidence of mechanical bowel preparation in reducing anastomotic leak, overall surgical site infections, extra-abdominal septic complications, reoperations or second intervention rates and death³³⁻⁴⁰.

The guidelines of the American Society of Colon and Rectal Surgeons (ASCRS) state that preoperative mechanical bowel preparation alone, without oral antibiotics, is generally not recommended for patients undergoing elective colorectal surgery⁴¹. Preoperative enemas alone, without mechanical bowel preparation and oral antibiotics, are generally not recommended for patients undergoing elective colorectal surgery⁴¹. The use of enema did not show any superior benefit in terms of enhancing surgical field visualization and the efficacy of bowel packing when compared to the no-enema group⁴². In a clinical practice guideline endorsed by the Canadian Society of colon and rectal surgeons, mechanical bowel preparation before surgery should also be omitted⁴³. In addition, the Enhanced Recovery After Surgery (ERAS) Society does not recommend preoperative bowel preparation before vulvar and vaginal surgeries but consider that enemas may be considered to reduce the stool burden at the time of vaginal surgery⁴⁴.

The combination of oral antibiotics (oral neomycin and tetracycline or erythromycin) + mechanical bowel preparation is recommended to decrease postoperative complications such as superficial surgical site infection, and intra-abdominal infections in colorectal surgery^{41,45-50}. Reduction in anastomotic leakage rate was observed in few studies^{41,45,51}. Clostridium Difficile infection's rate are not affected^{41,46}. The role of oral antibiotic bowel preparation alone is not clear due to the low number of studies with low number of patients enrolled where indirect comparison is suboptimal^{37,46}. The largest retrospective study including more than 20,000 patients showed worse results of oral antibiotic alone vs oral antibiotics + mechanical bowel preparation⁵².

As per the American College of Surgeons and Surgical Infection Society and the American Society of Colorectal Surgeons, mechanical bowel preparation is usually performed with polyethylene glycol solution with oral antibiotics following mechanical bowel preparation in the afternoon or evening before surgery^{41,53}. Usually three repeated doses of one of the following combinations of antibiotics are given orally over a period of approximately 10 hours: 1g neomycin sulfate and 1g erythromycin or 1g neomycin sulfate and 1g metronidazole⁵⁴.

Other regimens include drinking one bottle of MiraLax powder beginning 24h before surgery with clear liquid diet followed by a combination of antibiotics and laxatives⁵⁵. In Gynecological oncology surgery, if bowel preparation is desired for patients at high risk of needing a colorectal resection as part of the gynecologic procedure, trend is to consider use of oral antibiotics along with mechanical bowel preparation⁵⁶. Nevertheless, as more than half of the patients who undergo a maximal effort debulking surgery for advanced ovarian cancer will require some type of bowel resection it is difficult to accurately

preoperatively predict which patients indeed will need a bowel resection³². Therefore, decisions around any bowel preparation should depend on the overall patients profile and tumour dissemination patterns.

Preoperative bowel preparation

- **Mechanical bowel preparation alone is not routinely recommended [I, A].**
- **If mechanical bowel preparation is performed, this should be done in combination with oral antibiotics to decrease postoperative complications [II, A].**

10 Skin antisepsis and hair removal

10.1 Body bath or shower

Despite the encouraging results of some smaller studies in regards to a risk reduction of surgical site infections through bathing or showering with 4% chlorhexidine gluconate, overall compliance appears low, while larger meta-analyses have failed to demonstrate any clear benefit on surgical site infections from bathing or showering with any antiseptic versus non-antiseptic preparation such as common soap⁵⁷⁻⁶⁰. These data affect both intensive care unit and non-intensive care unit inpatients⁵⁷. Patients are advised to shower or have a bath using common soap, either the day before, or on the day of, surgery for the prevention of surgical site infections and the overall hygiene⁶¹.

10.2 Surgical-site antisepsis

The impact on skin colonization using a combination of chlorhexidine gluconate and povidone-iodine for surgical site preparation has shown that “decolonization” rates (ie, no growth of skin cultures) were higher for the combination of chlorhexidine gluconate followed by povidone-iodine (90%), when compared to chlorhexidine gluconate alone (65%) or povidone-iodine alone (47%)⁶². A recent meta-analysis of 30 studies including 29,006 participants revealed that chlorhexidine was superior to povidone-iodine in the prevention of postoperative surgical site infection in both clean surgery and especially the clean-contaminated surgery⁶³. However, there was no statistically significant difference in the incidence of skin adverse events between the two groups. Contraindications that need to be considered for the use of iodine antiseptic solutions are iodine allergy and thyroid comorbidities.

10.3 Vaginal antisepsis

Vaginal and perineal cleansing should be performed before surgery. To avoid mucosal irritation, solutions that contain low alcohol concentrations, such as the commonly used 4% (or 2%) chlorhexidine gluconate soap containing 4% alcohol, are usually preferred and may be used as an alternative to iodine-based preparations in cases of allergy or when preferred by the surgeon⁶⁴⁻⁶⁶. 4% chlorhexidine vaginal preparation is considered one of the five-point surgical-site infection prevention bundle in women undergoing surgery for ovarian cancer⁵⁵.

10.4 Hair removal

Perioperative hair removal is not recommended but results from few studies cannot be generalized to all surgical procedures because certain surgical subspecialties (eg, neurosurgery, gynecology) may involve body parts that are covered with more hair and are located in areas more prone to colonization by *Staphylococcus*, such as the groin, perineum, and axilla^{67,68}. A nationwide survey among 638 primary, secondary and tertiary health care gynecological departments in Germany showed that preoperative hair removal was performed very heterogeneously and the awareness of preoperative hair removal and surgical site infection among junior doctors was very low⁶⁹. Systematic reviews were performed to investigate whether the method (eg, using clippers, depilatory cream, or shaving with razors) and timing of hair removal versus no hair removal affect the incidence of surgical site infections. Fifteen randomized controlled trials or quasi-randomized controlled trials were identified, as well as several meta-analyses⁷⁰⁻⁸⁴. The three hair removal methods did not affect the incidence of surgical site infections compared with no hair removal. However, when hair is removed, clipping significantly reduces surgical site infections compared with shaving. Because they have similar potential to cause microscopic skin trauma, no hair removal and clipping were combined in an additional meta-analysis, which showed that they are associated with significantly reduced prevalence of surgical site infections compared with shaving. There is no recommendation regarding the timing of hair removal, because the only one study assessing this question had no relevant results, but removal by clipping shortly before surgery seems the safest approach. Hence, the Association of Perioperative Registered Nurses Guidelines suggest clipping of hair is favored instead of shaving, when removal is deemed to be absolutely necessary, with the aim of reducing

minor skin injury and the risk of bacterial colonization and subsequent surgical site infection^{67,85}. More research is necessary to determine if clipping or no hair removal is the best option for various patient populations.

10.5 Skin antisepsis for spinals and epidurals

Chlorhexidine gluconate is a potent, broad-spectrum antiseptic that is effective against nearly all bacteria and yeasts. It has been shown in several studies to result in a more rapid and superior bactericidal effect than povidone iodine, and its effects last for several hours beyond its initial application^{86,87}. In one of these studies, Kinirons *et al.* compared colonisation of epidural catheters following skin preparation with 0.5% chlorhexidine in alcohol with skin preparation using 10% povidone iodine⁸⁷. Catheters inserted following the use of chlorhexidine were six times less likely to be colonised than when povidone iodine was used.

Caution should be used when using chlorhexidine gluconate for antisepsis prior to spinal or epidural insertion because it is known to be neurotoxic, and there have been cases of permanent neurological injury in which chlorhexidine gluconate was thought to be responsible. In one case, a whole syringe of chlorhexidine gluconate was mistakenly injected into the epidural space; in another case it was suggested that a syringe of bupivacaine injected spinally had been contaminated with chlorhexidine gluconate. All patients developed a chronic adhesive arachnoiditis causing progressive neurological deterioration leading to paraplegia.

Skin antisepsis and hair removal

- **Preoperative patients bathing or showering with antiseptic solutions such as chlorhexidine gluconate has no benefit in reducing surgical site infections and is therefore not recommended over shower or bath with common soap [II, B].**
- **Preoperative hair shaving is not recommended [III, A].**
- **Surgical site antisepsis should be performed using 4% chlorhexidine gluconate with alcohol [II, B].**

11 Surgical safety checklists, patient positioning and retractors use

11.1 Surgical safety checklists

Surgical safety checklists were implemented less than 2 decades ago by the World Health Organization in an effort to improve the safety of patients undergoing surgical procedures by bringing together the whole operating team (surgeons, anaesthesia providers and nurses) to perform key safety checks during vital phases of the perioperative care: team briefing before starting the operating list, prior to the induction of anaesthesia, prior to skin incision, after completion of each operation and after completion of the entire surgical list. The Checklist helps to ensure that important safety steps are reliably followed for each and every operation⁸⁸⁻⁹¹. Every centre that performs ovarian cancer surgery should adhere to safety checklist protocols to ensure maximum patient safety in theatre.

11.2 Patient positioning

The aim when positioning a patient for surgery is to provide the best surgical access while minimising the risk of nerve and tissue injury. This risk is the highest in patients undergoing general anaesthesia as they are unable to make others aware of painful or compromised positions⁹²⁻⁹⁴. Apart from the actual positioning, shearing forces from moving/transporting the patient can damage skin and nerve tissues, especially in patients who are elderly, debilitated or obese. Careful moving techniques should be used to prevent this. Basic principles of positioning the ovarian cancer patient on the surgical table to be able to sustain long hours of a cytoreductive debulking include keeping the eyes closed using eye tape to reduce the risk of ocular injury, while the occiput should be well padded due to the risk of developing pressure sores in this area. Any limitation of joint movement or previous orthopaedic surgery must be assessed and considered before induction of anaesthesia to indicate important constraints on positioning.

Patients undergoing surgery for ovarian cancer are usually in the lithotomy or Lloyd Davies positions, and this is modified with the addition of head-down (Trendelenburg) tilt. The key difference between the lithotomy and Lloyd Davies positions is the degree of hip and knee flexion. However, the resulting physiological changes and complications of these two positions are similar and therefore they will be considered together⁹⁵⁻⁹⁷. Peripheral nerve injury may occur when a nerve is subjected to compression, stretch, hypoperfusion or direct trauma. During the peri-operative period, these may result from suboptimal patient positioning and surgical retraction, can be severely debilitating, and are an avoidable complication of surgery for ovarian cancer. Staff members' training and education should be implemented to prevent and reduce positioning-related complications⁹⁸. Risk factors for intra-operative peripheral nerve injury are prolonged operative time, high ASA score and high body mass index⁹⁵⁻⁹⁷. Both legs should be flexed at the hips and knees simultaneously. Extreme flexion, abduction and external rotation of the hip joints can cause neuronal damage by stretch (sciatic and obturator nerves) or by direct pressure (compression of the femoral nerve as it passes under the inguinal ligament). Hip and knee movement should be therefore limited to the amount needed for adequate surgical exposure. The common peroneal nerve appears most susceptible to compression injury as it winds around the neck of the fibula. This is a particular risk if the patient's knee and leg are resting laterally against stirrups. There should be adequate padding of this area to minimise compression. Calf support using a boot-like device is preferred to other supporting leg holders to reduce the risk of peripheral nerve injury.

During the pelvic part of the debulking when patients are put into the Trendelenburg position to facilitate surgical access; injury to the brachial plexus may occur from the use of shoulder supports. If the support is placed too medially, the brachial plexus may be compressed against the first rib. If the support is placed too laterally, the brachial plexus may be stretched because of upward force on the shoulder while the head and neck move downwards under gravity. The ideal position for the position of a shoulder support is over the acromioclavicular joint.

If the arms are placed by the side, the fingers should be protected to prevent crushing injury when the leg section of the operating table is replaced. If the arms are placed on an arm board, they should not be abducted by more than 90° to reduce the risk of brachial plexus injury. Ideally, the arms should be in the supinated position to minimize stretching of the ulnar nerve. The ulnar nerve is vulnerable to compression in the ulnar groove behind the medial epicondyle of the humerus. This area should be padded adequately.

11.3 Surgical retractors

Care must be taken during the placement of the retractor to avoid bowel entrapment and compression of the femoral nerves through deep lateral blades. The femoral nerve may be injured by compression from the use of self-retaining retractors, and has a reported incidence of 7-12% during abdominal hysterectomy⁹⁹. Therefore, when using self-retaining retractors, the shortest lateral blades possible that effectively retract the abdominal wall should be used to avoid compression of the psoas muscle. Rolled laparotomy sponges may be placed between the retractor and abdominal wall to additionally reduce the risk of nerve compression especially in thin patients.

11.4 Electrothermal devices

Diathermy is widely used for coagulation and cutting during surgery for ovarian cancer, but harbours potential risks of electrothermal injury if adherence to rules of use are not followed. Although advances in the safety of electrosurgical devices have contributed to the reduction of such accidental injuries, knowledge of electrosurgical safety by the surgeon and anaesthetist is essential¹⁰⁰. The diathermy plate for the use of unipolar diathermy must be in close and even contact with a large area of skin, ideally over an area of well-vascularised muscle mass (usually the patient's leg). Incorrect attachment of diathermy plates may cause burns, e.g. if contact is only made over a small surface area. If the diathermy plate is detached or malpositioned, diathermy current may flow through any earthed metal the patient touches (e.g. drip stands, ECG leads), causing burns at the site of contact. It is therefore essential that the patient does not have contact to any earthed metal during surgery. Failure of insulation surrounding surgical instruments can lead to electrothermal injuries as a result of unwanted current leak. It is important to check all electrosurgical instruments for breaks in insulation before use. Moreover, burns may occur if the surgeon accidentally activates the diathermy especially after long debulking procedures. Therefore, when not used, the forceps or diathermy knife should be kept in a protective non-conducting holder. Since diathermy may act as an ignition source of flammable substances, e.g. alcoholic skin preparation solutions, these must have dried before diathermy is used.

Surgical safety checklists, patient positioning and retractors use

Safety checklists

- Safety checklists are mandatory in ovarian cancer surgery [III, A].

Patient positioning - General recommendations

- Safe positioning requires planning and good communication between members of the operating room team and should be checked periodically [V, B].
- All members of the team should have adequate training in patient positioning [V, B].
- Intravascular lines, the endotracheal tube, urinary catheter, epidural catheter, and any other devices/equipment should be secured before any movement, and their position and function reassessed after repositioning [V, B].

Arm positioning

- The arms may be positioned either by the side of the patient, or abducted and placed on an arm board. Abduction of more than 90 degrees should be avoided [V, C].

Surgical retraction

- When using self-retaining retractors, the shortest blades possible should be used for adequate retraction without nerve- or muscle compression. Rolled laparotomy sponges may be placed between the retractor and abdominal wall to reduce nerve compression especially in thin patients [V, B].

Electrothermal devices

- Electrosurgical instruments should be checked to ensure that they are safe to use [V, B].

12 Anaesthesia, intra- and post-operative volume and replacement

12.1 Blood tranfusion and oncologic outcome

There are numerous conflicting data regarding the impact of blood transfusion on oncologic outcome. Possible mechanisms of action that have been described include transfusion-related immunosuppression, cytokine release, or proangiogenesis with vascular epithelial growth factor^{101,102}. Although many retrospective studies showed better recurrence free survival and overall survival in ovarian cancer patients without blood transfusion, this might be a selection bias effect, since those patients with lower tumor burden and less complex surgery are those that will less likely require a transfusion and also have a more favorable oncologic outcome and fewer surgical complications¹⁰³⁻¹⁰⁷. Hence, these studies had many limits including the absence of appropriate control for between-group differences of prognostic determinants. Hunsicker *et al.* conducted a retrospective study with a matched cohort to limit the risks of biases¹⁰⁸. This study showed that transfusion does not worsen oncological long-term outcome after surgery. The meta-analysis recently published by Pergialiotis *et al.* suggested transfusion of blood products during the perioperative period is not an independent risk factor for inferior survival in ovarian cancer patients¹⁰⁹. Further studies are required, however, to determine whether transfusion-related immunomodulation may be related to ovarian cancer recurrence.

Evaluation of the anemia and iron deficiency

According to the World Health Organization, a hemoglobin level ≥ 12 g/dl is considered normal in non-pregnant women. Severe anemia is defined as a hemoglobin level < 8 g/dl. Although numerical cutoffs do not reflect patients' comorbidities, they are the main parameters to guide transfusion practice. Studies show that 48% of gynecologic cancer patients are anemic. The most common factors associated with anemia are blood loss (during surgery or directly from the tumor), renal dysfunction, and marrow dysfunction (chemotherapy)¹¹⁰. Preoperative anemia was independently associated with an increase of the 30-day surgical mortality and composite morbidity rates in a retrospective study including 12,836 gynecologic surgery patients¹¹¹. Preoperative anemia was also associated with significantly increased perioperative transfusion rates. Blood administration during ovarian cancer surgery is common with incidence rates ranging from 25% to 77%^{110,112}. Ackroyd *et al.* found the following variables were associated with blood transfusion in ovarian cancer surgery: advanced age (>65 years), preoperative anemia, low platelets, presence of ascites and/or disseminated tumor disseminated patterns as well as radical surgical resection techniques¹¹². A diagnosis of anemia should be made with a screening complete blood count, ideally 3-4 weeks prior to the surgical procedure whenever possible.

Iron deficiency is one of the causes of preoperative anemia. In patients with functional iron deficiency, oral iron is poorly absorbed in the duodenum. Oral iron also requires a long treatment period and commonly causes gastrointestinal side effects, potentially limiting dosages and compliance. Kim *et al.* demonstrated a decrease in blood transfusion in patients with cervical carcinoma undergoing chemotherapy who received iron supplementation¹¹³. A large review assessing intravenous iron administration showed no increased risk and rare short-term adverse drug events such as hypersensitivity reactions or anaphylaxis with low-molecular weight iron preparations. Gastrointestinal adverse events were decreased compared to oral iron and the risk of discontinuation of therapy was lower¹¹⁴. Treatment with iron might favor neoplastic cell growth due to the high metabolic rate of tumor cells and the associated iron overturn¹⁰¹. However, cancer-related functional deficiency is unclear and the theoretical fears of stimulating tumor growth with a single iron supplementation are probably outweighed by the benefits of a higher hemoglobin level.

Threshold for blood transfusion

Literature does not provide consensus about the optimum hemoglobin level at which to initiate transfusion. A single hemoglobin value cannot serve as a transfusion trigger without accounting for patient and clinical variables, while literature is conflicting regarding a liberal versus restrictive approach. However, since most ovarian cancer patients will need chemotherapy, more liberal transfusion thresholds may be used. The European Society of Anesthesiology recommends a target haemoglobin concentration of 7 to 9 g/dl during active bleeding¹¹⁵. A large randomized controlled trial looked at a restrictive (hemoglobin level < 7 g/dl) versus a liberal (hemoglobin level < 10 g/dl) transfusion strategy¹¹⁶. Mortality was lower in the restrictive strategy group. In ovarian cancer, Altman *et al.* showed in a retrospective study better survival by maintaining average hemoglobin level > 8g/dl¹⁰³. The usual restrictive strategies ranged from use of a hemoglobin trigger of 7 g/dl to 8 g/dl^{104,117-119}. De Almeida *et al.* conducted a prospective trial to assess transfusion requirements in surgical oncology patients who had undergone abdominal major surgery with a restrictive (< 7 g/dl) or liberal (< 9 g/dl) transfusion strategy¹²⁰. Unlike the previous study, they showed that a liberal transfusion strategy was superior in terms of 30-day mortality and severe clinical complications. Bergamin *et al.* conducted the other randomized study comparing two blood administration strategies in patient with solid cancers¹²¹. The mortality rate was also lower in the liberal group. These two studies presented debatable results essentially because the transfusion trigger was not maintained at the same level for the whole stay. A meta-analysis published in 2016 showed that restrictive transfusion strategies appear to decrease blood utilization without increasing morbidity or mortality in oncologic patients¹¹⁸. Educational based transfusion awareness programs have been shown to be successful in improving awareness around the correct indication for blood transfusion¹²².

Cell salvage

Cell salvage aims to reduce or eliminate the need for allogeneic blood transfusion by recovering blood from surgical field, and then cleaning, filtering and reinfusing it into the patient. Cell salvage is routinely used successfully in other surgical specialties (cardiothoracic, vascular, orthopaedic and hepatobiliary). Theoretically, circulating tumor cells can be found in cell saver reinfusions and can potentially lead to metastases, and consequently cell salvage was initially contraindicated in cancer. However, patients with metastatic cancer are known to have circulating tumor cells in the blood, and operative manipulation of tumor leads to peripheral blood concentrations of malignant cells. In addition, leucocyte depletion filters which are used to reinfuse the salvaged blood are highly efficient at removing malignant cells. In patients undergoing oncologic surgery, leucocyte depletion filters have been shown to eliminate viable nucleated malignant cells from salvaged blood¹²³. There are currently no data to contraindicate blood salvage in ovarian cancer surgery. However, the TIC TOC study (intraoperative cell salvage versus transfusion in ovarian cancer) may provide further evidence especially in terms of long term oncologic safety for those patients¹²⁴. Nevertheless, the presence of large volume ascites and cystic tumors in ovarian cancer surgery makes the use of cell salvage techniques particularly challenging and it therefore cannot be recommended.

Tranexamic Acid

Tranexamic acid is routinely used in the perioperative setting in several surgical specialties. In a Cochrane review from 2011, tranexamic use has been shown to decrease blood loss and reduce the relative risk of allogenic blood transfusion by 39%¹²⁵. Lundin *et al.* published the results of a multicentre randomized double blind placebo-controlled trial which demonstrated that a single dose of 15 mg/kg intravenous tranexamic acid significantly reduced blood loss in women undergoing ovarian cancer surgery¹²⁶. The use of transfusion was more frequent in the placebo group, but only postoperative transfusion showed a significantly lower rate in favor of tranexamic acid in the univariate analyses. They included only 50 patients in each group, among them 56 participated in ultrasound assessment five weeks after the surgery. Thromboembolic events occurred in seven patients (7%), 2 in the tranexamic group and 5 in the

placebo group. A retrospective study showed a decreased rate of perioperative blood transfusion after the implementation of a tranexamic-acid based protocol in gynecologic oncology surgery¹²⁷. Patients were predominantly operated on for ovarian cancer. Patients received 15 mg/kg intravenous tranexamic acid within 30 minutes of surgical incision. In this study, only 60.7% of patients in the intervention cohort received the drug. There was also a statistically significant reduction in median estimated blood loss and mean operative time in the historical and intervention cohort respectively. Among the 54 patients receiving tranexamic acid, only one patient developed a venous thromboembolism. The authors analyzed the subgroup of patients with ovarian cancer and showed a 60.3% risk reduction in blood transfusion compared to the historical cohort. Zakhari *et al.* conducted a review in 2020 supporting the use and safety of tranexamic acid in gynecologic surgery for procedures in which excessive bleeding is predictable such as ovarian cancer surgery¹²⁸.

Theoretically, tranexamic acid may be associated with an increased risk of venous thromboembolism. However, the literature confirms the benefits from tranexamic administration and the rare incidence of thrombosis after surgery. Clinical trials from trauma, orthopedic or general surgery confirm this¹²⁹⁻¹³¹. In addition, transfusion itself may increase the risk of a thromboembolic event^{107,132}. Transfusion related complications are not rare and this justifies transfusion-sparing practices.

Various dosing regimens have been reported in the literature. In ovarian cancer surgery, tranexamic acid is administered as a single dose of 15 mg/kg just before the beginning of the surgery^{126,127}. In a prospective double blind control trial of mostly gynaecological cancer patients, authors compared two different dosing regimens of tranexamic acid for patients undergoing laparotomy for abdominal cancer: 10 mg/kg IV preoperatively or a bolus dose of 10 mg/kg IV followed by an infusion (1 mg/kg/h) until 4h postoperatively of tranexamic acid or saline. Patients receiving tranexamic acid as a bolus followed by an infusion had higher postoperative hemoglobin values and lower blood loss from the surgical drains than when tranexamic acid was given as a bolus alone¹³³.

12.2 Perioperative fluid replacement

Serum albumin concentration is an important laboratory measurement to evaluate the nutritional status of patients. Hypoalbuminemia in cancer patients may result from malnutrition, low appetite, weight loss, and cachexia due to the host responses to the tumor and antitumor therapies. Low intake of amino acids and a negative nitrogen balance and a reduction in albumin synthesis are determinants of serum albumin levels. It was reported that 24% of patients with gynecological cancers are malnourished, and those with advanced ovarian cancer have the highest rate of malnutrition at 67%¹³⁴.

Albumin level was independently and significantly associated with overall survival. Subgroup analysis showed that patients with an albumin level < 32.5 and ≥ 32.5 g/l had mean estimated overall survival of 40.6 and 96.0 months, respectively¹³⁵. The preoperative albumin levels appeared to be an independent prognostic factor for overall survival in optimally debulked epithelial ovarian cancer patients. Hypoalbuminemia is also a predictive factor for severe post-operative complications. Furthermore, median overall survival time of patients with hypoalbuminemia was 24 months compared to 83 months in patients with normal albumin. Hypoalbuminemia was independently associated with shortened overall survival even after adjusting for established prognostic factors such as age, tumor stage, performance status, and post-operative residual disease¹³⁶.

Serum albumin levels provide a non-invasive method to assess the risk associated with surgical intervention. A preoperative albumin level of less than 3.5 g/dl has been associated with poor survival outcomes in multiple studies. A meta-analysis by Ge *et al.* found that 0.1 g/dl increases in serum albumin levels were significantly associated with improved survival outcomes¹³⁷. Patient with severe hypoalbuminemia should therefore be considered for preoperative nutritional support for one to two weeks to optimize surgical outcomes.

The use of albumin as a source of protein for nutritional support is of no value. After administration, albumin is metabolized by the body and the majority is consumed as a source of calories. Albumin has low bioavailability and only a small fraction of the dose is metabolized into amino acids as materials for protein regeneration in the liver. Since only small amounts of the essential amino acids tryptophan, isoleucine, and methionine are formed, albumin is of little value as nutritional support.

Use of albumin replacement during paracentesis

Large volume paracentesis decreases the circulating plasma volume, and may result in renal impairment and hyponatremia. Paracentesis-induced circulatory dysfunction is a major complication with a high morbidity. Albumin has been shown to help prevent these adverse effects. In a study comparing large volume paracentesis with and without albumin replacement, patients receiving albumin replacement were less likely to develop renal impairment or electrolyte abnormalities. Albumin has also been compared with other colloid solutions because of its cost: paracentesis-induced circulatory dysfunction occurred significantly less frequently in patients treated with albumin compared to those receiving dextran 70 solutions or polygeline¹³⁸.

Perioperative fluid management and goal-directed fluid therapy

The management of perioperative fluid balance in women undergoing cytoreductive surgery for advanced ovarian cancer poses unique challenges. A combination of pre-operative hypoalbuminaemia and mechanical bowel preparation, intra-operative drainage of ascites and pleural effusions, blood loss, fluid loss from extensive peritoneal resection and vasodilatation from the effects of epidural analgesia creates a complex fluid management problem throughout the peri-operative period^{136,139}.

The aim of intravenous fluid therapy during the perioperative period is to maintain an adequate circulating volume to ensure end-organ perfusion and oxygen delivery to the tissues. Insufficient fluid replacement may cause hypovolaemia and decreased tissue perfusion leading to acute kidney injury¹⁴⁰. However, excess fluid administration may lead to tissue and pulmonary oedema, and in patients undergoing surgery for advanced ovarian cancer has been shown to increase the risk of surgical site infections, anastomotic leak and length of hospital stay¹⁴¹. In order for the anaesthetist to make decisions regarding perioperative fluid management, clinical parameters such as heart rate and arterial pressure and measures of organ perfusion such as urine output and serum lactate have traditionally been used. However, a healthy patient may lose up to 25% of their blood volume before there is a decrease in arterial pressure or an increase in heart rate. As a consequence, relying on these conventional methods is not sensitive enough to guide fluid therapy and results in wide variations in fluid volume administration across surgical specialties and procedures¹⁴². Goal-directed fluid therapy is a more individualised method of fluid administration based on objective feedback of the patient's fluid responsiveness. Fluid boluses (usually a colloid) are administered to increase the stroke volume by more than 10% (measured using a minimally invasive cardiac output monitor) to optimise patients on their individual Frank-Starling curve. Once fluid boluses no longer improve the stroke volume, ongoing arterial hypotension may be treated with vasopressors. Inotropes may also be considered in patients with reduced contractility (cardiac index < 2.5 L/min) to achieve adequate oxygen delivery to the tissues¹⁴³. Although early studies on goal-directed fluid therapy showed a significant reduction in postoperative complication rates and length of stay when compared with conventional fluid therapy, more recent studies performed within the context of enhanced recovery programmes have shown no difference in outcome¹⁴⁴⁻¹⁴⁸. A meta-analysis of 23 studies involving 2,099 patients has shown that goal-directed fluid therapy in patients undergoing elective major abdominal surgery was associated with a significant reduction in morbidity, hospital length of stay, intensive care length of stay and time to passage of faeces. However, no difference was seen in mortality, return of flatus or risk of paralytic ileus¹⁴⁹.

The presence of malignant ascites has been shown to be a major determinant of haemodynamic stability during surgery for ovarian cancer¹³⁶. Hunsicker *et al.* showed that in patients with ascites >500ml

undergoing surgery for ovarian cancer, in which fluids were administered as part of a goal-directed algorithm, administration of fresh frozen plasma (FFP) was associated with greater increases in stroke volume, prolongation of the time to fluid bolus requirement and decreased noradrenaline requirement compared to artificial colloid or crystalloid solutions¹⁵⁰. Fresh frozen plasma should not be used for routine volume replacement, but may be beneficial during multivisceral resections to avoid coagulopathy and provide haemodynamic stability.

12.3 Prevention of hypothermia

Peri-operative hypothermia is defined as a core body temperature $< 36^{\circ}\text{C}$ and is a common consequence of anaesthesia for patients undergoing major surgery including ovarian cancer surgery. Both general and neuraxial anaesthesia contribute to peri-operative hypothermia due to vasodilatation and impairment of shivering, causing heat to redistribute from the core to the peripheral compartments of the body, leading to heat loss¹⁵¹. It is well established that peri-operative hypothermia may be associated with increased morbidity, mortality and length of hospital stay, and patients describe being cold in the post-anaesthesia care unit as one of the most distressing aspects of their surgery¹⁵². Hypothermia increases bleeding and transfusion requirements, increases the rate of adverse cardiac events and decreases anaesthetic drug metabolism¹⁵³⁻¹⁵⁵. Patients at higher risk of peri-operative hypothermia and its sequelae include ASA grade 2-5, pre-operative hypothermia, those undergoing a combination of general and regional anaesthesia, major surgery, low body mass index and those at risk of cardiovascular complications¹⁵⁵. It is essential to measure core temperature accurately and continuously during surgery for ovarian cancer. This may be done using as a nasopharyngeal temperature probe or a zero-heat-flux cutaneous thermometer on the forehead. Body temperature may be maintained peri-operatively using several methods. These include maintaining an ambient operating theatre temperature of at least 21°C , warming and humidifying inspired anaesthetic gases, warming intravenous and irrigation fluids and using a forced air warming device. A small randomized controlled trial including 47 ovarian cancer patients scheduled for cytoreductive surgery showed that prewarming at 43°C reduces the drop in body-core-temperature and maintains normothermia without impeding the perioperative routine patient flow¹⁵⁶.

Anaesthesia, intra- and post-operative volume and replacement

Blood transfusion and oncologic outcome

- Iron supplementation for correction of anemia should be considered (IV or oral depending on timing, availability, and patient's profile) [III, B].
- There is no well-defined threshold for blood transfusion in advanced ovarian cancer surgery. Since many patients need chemotherapy, more liberal transfusion thresholds may be used [II, B].
- Tranexamic acid should be considered perioperatively to reduce blood loss [I, B].

Perioperative fluid replacement

- The use of intravenous albumin should not be considered as a substitute for nutritional support [III, B].
- Hypoalbuminemia should not be used as a single marker for patient selection for surgery but as guidance for preoperative optimization of patients [III, B].
- Balanced crystalloids should be used for routine fluid replacement [III, B].

Prevention of hypothermia

- Continuous temperature monitoring is recommended. Methods to actively warm patients should be applied [III, B].

13 Major intra- and post-operative bleeding

Major intraoperative haemorrhage during ovarian cancer cytoreductive surgery is not very common, especially under the increasing specialization and centralization of care in expert centres. Early preoperative identification of risk factors and adaptation of treatment protocols, including preoperative optimization of patients, additionally minimize the risk. Still in the occasions it occurs, the gynecological oncology team needs to be aware of all available surgical and non-surgical treatment options. Major haemorrhage protocols and fail safe algorithms developed within a multidisciplinary setting are mandatory in centres where advanced ovarian cancer surgery is performed, to minimize associated morbidity and mortality¹⁵⁷.

13.1 Local haemostatic agents and surgical internal iliac artery ligation options

Local haemostatic agents can be used as a supplementary to traditional surgical coagulation and ligation technics in order to obtain bleeding control. There is nowadays a wide range of agents which include collagen, fibrin and synthetic glues or adhesives, gelatin or cellulose based products that can be used especially when access to the site of bleeding is more difficult¹⁵⁸⁻¹⁷⁵. For the appropriate use of the right agent for the right indication, it is essential to understand the mechanisms of action and the possible adverse effects related to each agent¹⁷⁶.

Absorbable agents

Oxidized cellulose-based haemostatic agents (Surgicel Original®, Surgicel Nu-Knit®, Surgicel Fibrillar®, Interceed®, Gelitacel®, Veriset®) have demonstrated their effectiveness in numerous case reports and prospective observational human studies since years¹⁷⁷. Oxidized regenerated cellulose-based agents support a physical matrix for initiation of the clot and the low pH promotes antimicrobial effect¹⁷⁸. The oxidised cellulose-based product can be impregnated with polyethylene glycol and other salts and achieves comparable and more rapid haemostasis compared to fibrin sealant patch (TachoSil®)¹⁷⁹. Gelatin-based products are useful as a physical matrix for clot initiation (Surgifoam®, Gelfoam®, Gelfilm®, Gelita-spon®, Geli putty®), or can be combined with Thrombin (FloSeal®, Surgiflo®)¹⁷⁴. Swelling of the gelatin in contact with blood reduces the blood flow and, in combination with a thrombin-based component, enhances haemostasis¹⁸⁰⁻¹⁸². Although this property provides good hemostatic mechanical action, it also harbors the risk of complications of compressive origin when used in confined spaces or near nerve structures. Unlike the other topical hemostats with gelatin, FloSeal® is a gelatin matrix based on bovine collagen containing microgranules, crosslinked with glutaraldehyde (biological glue) and human thrombin that are mixed at the time of use. The gelatin particles when contact with blood, swell and induce a buffering effect¹⁸³⁻¹⁸⁵.

Collagen-based agents (Instat®, Helitene®, Helistat®, Avitene®, Avitene flour®, Avitene Ultrafoam®, Endo Avitene®, Avitene Ultra Wrap®) provides a generous surface area that, when in contact with blood, allows adhesion and platelet activation, promoting thrombus formation¹⁸⁶. They are often combined with a procoagulant substance such as thrombin to enhance the haemostatic effect. Considering that its mechanism of action depends on platelet activation, they are less effective in patients with severe thrombocytopenia or coagulopathies. However, they also successfully reach hemostasis even in heparinized patients¹⁸⁷⁻¹⁹⁰.

Biological Agents

Fibrin sealants (Evicel®, Tisseal®, Crosseal®, Quixil®) were some of the first clinically available hemostatic agents, having both haemostatic and sealant properties. The classic fibrin sealant consists of clustered human lyophilized fibrinogen and bovine or human thrombin, sometimes also containing concentrated coagulation factor XIII and aprotinin¹⁸⁷⁻¹⁹⁰. Thrombin and Fibrinogen are combined at the time of application. Thrombin degrades Fibrinogen into fibrin, forming clot. Factor XIII is a proenzyme activated by thrombin in the presence of calcium ions (fibrin stabilizing factor). Once activated, factor XIII forms

cross-link between fibrin chains, stabilizing the clot formation. Aprotinin is a protease inhibitor (bovine lung tissue) that inhibits trypsin, plasmin and kallikreins, delaying plasmin-mediated clot lysis¹⁹¹. A compression period is required for polymerization of the sealant components. Fibrin sealants are especially suitable for controlling low pressure venous bleeding and from raw surfaces such as kidneys, liver and spleen^{192,193}. Several controlled randomized studies have shown their significant effect on haemostasis in vascular, bone, skin and visceral surgeries¹⁹⁴⁻¹⁹⁶. A multicenter prospective randomized study reported, Fibrin sealants (Crosseal®/Quixil®) as the most effective hemostatic, with less time for effective hemostasis, less intraoperative bleeding and less induction of complications when compared with the control group (Avitene®, Surgicel®, Surgicel Nu-Knit®, Gelfoam®, Gelfoam + thrombin®)¹⁹⁷. Finally, a further form of fibrin sealant (TachoSil®) which resembles a spongy plaque has demonstrated its utility not only as a hemostatic, but also in intestinal anastomoses due to its high adhesive capacity¹⁹⁸⁻²⁰¹.

Synthetic agents

Polyethylene glycol (CoSeal®) is a fully synthetic polymer used to cover vascular anastomoses. It uses two synthetic polyethylene glycols that, once mixed, can be applied directly to the surfaces of the tissues or used to seal synthetic suture lines or grafts. Polyethylene glycol is an effective agent for vascular and cardiac hemostasis or in surgical applications where volume expansion of the product is not a concern. Its performance in the anastomotic seal is equivalent to Gelfoam with thrombin, but the main advantage of CoSeal® lies in the rapidity with which it reaches hemostasis^{202,203}. Although the evidence is mainly observational, these agents have become widely used.

Surgical ligation of the internal iliac artery for control of pelvic bleeding

Ligation of the internal iliac artery has been described for obstetrical indications (massive bleeding from invasive placenta previa) but also for bleeding during gynecologic oncology (mainly exenterations). Bilateral ligation of the internal iliac arteries leads to a reduction of pelvic arterial blood flow by 49% and pulse pressure by 85%. Usually, ligation of the anterior division of the iliac artery is enough to control massive bleeding in the pelvis. Collateral circulation is developed following the ligation of the internal iliac artery and will maintain its re-functioning in the long-term²⁰⁴.

13.2 Surgical options

A surgical vascular tray for emergency situations should be part of the armamentarium of surgical equipment in gynaecological cancer theatres. "Packing" has been successfully applied in trauma surgery and obstetrics with significant reduction of mortality associated with major vessel injury, parenchymal liver or splenic trauma as well as pelvic trauma and pelvic venous plexous bleeding²⁰⁵⁻²⁰⁷. In ovarian surgery, evidence is limited. One small case control study where 3-6 povidone-iodine soaked roller gauges were used for packing during intraoperative bleeding, showed that operative mortality could be avoided in 14 out of 16 packed patients (87.5%)²⁰⁸. Packing removal was done through exit sites on abdomen, 48h after packing at bedside.

Several methods and variations of the technique of abdominal and pelvic packing have been described, such as the "umbrella pack"²⁰⁹⁻²¹². Despite the fact that no standardized method has been described, the technique must be meticulous, as evidence suggests that inadequate packing (packs placed in wrong locations or fewer than required) and insertion of an intra-abdominal drainage may reduce its efficacy in controlling blood loss²¹³. Various materials may be used, including gauze sheets, plastic bags (eg, drawstring bag used to cover radiographic film) or cloth containers with wet gauzes for more weight that for example in the case of pelvic bleeding can be placed it against the pelvic bleeding area with subsequent traction of the attached drawstrings through the vagina to exert pressure against the pelvic floor with equivalent efficacy in controlling bleeding²¹⁴. Hemostatic agents, such as tranexamic acid, can be additionally applied directly to the bleeding tissue or included in the packing material to increase efficacy, even though control randomized studies are lacking. Kaolin impregnated hemostatic agents such as

Combat Gauze™ and Trauma Pads™ have also been described; however, according to preliminary reports these do not seem to provide additional benefit²¹⁵.

Even though no consensus exists on the indication, type and duration of prophylactic antibiotics while the pack is in place, given the general high incidence of postoperative febrile morbidity, prophylactic broad-spectrum antibiotic therapy is widely used and reported as an additional effort to reduce morbidity and mortality. The duration of packing has not been standardized. Evidence from damage control surgery in the field of abdominal trauma suggests that in patients with coagulopathic hemorrhage due to extensive blood loss, abdominal packing should not be removed before the completion of the first day following surgery, whereas it seems ideal to keep the packing in place for 48-72 hours²¹⁶. Longer intervals are associated with increased risk of infectious complications. The team should be familiar with the various techniques of temporary and permanent abdominal closure, including early and delayed fascial closure, mesh insertion, vacuum-assisted closure components separation, planned ventral hernia, either alone or in combined use²¹⁷.

13.3 Medical options

Transfusion management and general considerations

Multiple factors contribute to the complex causes of haemorrhagic diathesis in surgical patients. These include acquired platelet dysfunction, anticoagulation, blood loss, haemodilution, coagulation factor consumption, hypothermia, acidosis and the activation of fibrinolytic pathways.

Platelet inhibitors and anticoagulants are the most frequent cause of acquired haemostatic defects. Although aspirin can increase the blood loss after major surgery, this usually does not result in an increased need for red blood cell transfusion. Moreover, improved surgical outcomes and prevention of adverse cardiovascular events postoperatively have been demonstrated with the continued use of aspirin²¹⁸. Aspirin and thienopyrimidins have a short serum half-life, but their effect on thrombocyte function can last considerably longer. The effect can effectively be reverted by transfusion of platelet concentrates after these substances have been stopped for at least 12 hours²¹⁹. In the management of haemorrhagic shock, a restrictive volume strategy with crystalloid solutions during the initial phase is widely accepted. The main reason for this is that all colloid solutions can alter haemostasis²²⁰. For critically ill patients, a balanced electrolyte solution should be favoured over 0.9% sodium chloride, and if a 0.9% sodium chloride solution is used, it should be limited to a maximum of 1-1.5 l²⁰⁵. Randomized clinical trials that have evaluated hemoglobin concentration thresholds for transfusion in critically ill patients have consistently found that restrictive transfusion strategies (Hb thresholds between 7 and 9 g/dl) are as safe as, or safer than, liberal strategies (thresholds ≥ 9 g/dl), but these studies excluded patients with massive bleeding^{116,221}. In a randomized clinical trial of 921 patients with acute upper gastrointestinal bleeding the probability of survival was slightly higher in patients with a restrictive transfusion strategy (Hb threshold 7 g/dl) than with a liberal strategy (Hb threshold 9 g/dl) in patients who had bleeding associated with a peptic ulcer, and it was significantly higher in patients with cirrhosis and Child-Pugh class A or B disease. The restrictive transfusion strategy was associated with further bleeding in 10% of the patients as compared with 16% of the patients in the liberal transfusion strategy group²²². In the management of major bleeding and coagulopathy following trauma, a target hemoglobin concentration of 7-9 g/dl has been recommended²⁰⁵. There are no specific data for ovarian cancer surgery. However, if more than 4 units of packed red blood cells (PRBCs) are necessary to maintain a hemoglobin concentration of 7-9 g/dl, balanced resuscitation of PRBCs and FFPs is recommended and additional platelet infusions and fibrinogen substitution in following rounds of transfusion in clinical guidelines for perioperative bleeding are recommended. The optimal ratio of PRBCs to FFPs in balanced resuscitation of patients who require massive transfusion still is in question, albeit retrospective data favour a ratio of 0.75-2.3 to 1. FFP generally should be considered when bleeding is accompanied by prothrombin time/activated partial thromboplastin time (PT/aPTT) > 1.5 times normal and platelet transfusions are

recommended in case of thrombocytopenia < 50-100/nl. The recommended threshold for fibrinogen substitution is 2g/l. If refractory bleeding is noted, further factor concentrates should be considered²²³.

Data from a meta-analysis of case reports and case-series using recombinant factor VIIa (rFVIIa, NovoSeven) in the treatment of bleeding after abdominal, vascular or urogenital surgery showed a reduction or cessation of bleeding in 39/50 patients after administration of rFVIIa²²⁴. The risk of thromboembolism was not increased compared with data from a meta-analysis of eight placebo-controlled clinical trials. However, a randomized controlled trial evaluating rFVIIa in the management of refractory traumatic haemorrhage in 573 patients who bled 4 to 8 RBC units within 12 hours of injury found no difference in 30-day-mortality in patients assigned to rFVIIa (200 µg/kg initially; 100 µg/kg at 1 hour and 3 hours) or placebo. Mortality was 11.0% with rFVIIa versus 10.7% with placebo in patients with blunt trauma and 18.2% with rFVIIa versus 13.2% with placebo in patients with penetrating trauma. Thrombotic events were similar across the two study cohorts²²⁵.

A retrospective observational study comparing tranexamic acid with no tranexamic acid in 896 patients with wartime injury and haemorrhage identified a lower mortality in the tranexamic acid than the no-tranexamic acid group despite a higher injury severity score in the tranexamic acid group²²⁶. The benefit was greatest in the group of patients who received massive transfusion and was associated with a lower incidence of coagulopathy. A retrospective study of 201 patients with peritoneal malignancies, that had cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy and were treated with tranexamic acid or cryoprecipitate upfront in addition to FFP or with FFP alone, not only found a reduction in PRBC, FFP and platelet transfusions associated with the use of tranexamic acid but also no increase in the postoperative venous thromboembolism (VTE) rate²²⁷. Moreover, 2 x 15mg/kg tranexamic acid in an interval of three hours did not show an increased risk of thromboembolic events in patients with high-energy fractures of the pelvis, acetabulum, and femur after major traumatic injury and up to 2g tranexamic acid in addition to standard care significantly reduced death due to bleeding in women with post-partum haemorrhage with no adverse effects in a randomised, double-blind, placebo-controlled trial of 20,060 women^{228,229}. Given its good safety profile, the use of tranexamic acid is recommended in many massive transfusion protocols²³⁰.

In massive transfusion, measurement and substitution of ionized calcium in case of hypocalcaemia are recommended. Hypothermia is associated with an increased risk of bleeding and is a significant contributing factor to the morbidity and mortality of patients with major haemorrhage. Both prothrombin time (PT) and partial thromboplastin time (PTT) are only minimally different at temperatures between 37 and 41°C, but strongly altered by hypothermia. In a situation where factor levels were all known to be normal, PT increased from 11.8s to 12.9s to 16.6s and PTT increased from 36s to 39.4s to 46s when the temperature was lowered from 37 to 34 to 31°C, respectively²³¹. Platelet aggregation and adhesion were already significantly reduced at a temperature of 33°C, and a pH decrease from 7.4 to 7.0 reduced the activity of FVIIa by over 90% and FVIIa/TF by over 60%^{158,159}. Normothermia and the prevention of acidosis are therefore critical to control haemorrhage effectively. Target values in the setting of massive transfusion (traditionally defined as transfusion of 10 units of PRBCs within a 24 hour period) are a pH of 7.35-7.45 and a body core temperature of > 34°C²³⁰. In massive transfusion prewarmed infusions and a blood warmer can help to prevent a critical drop in the patient's body temperature. An experimental study about haemolysis and hypothermia found that the use of a blood warmer set at 41.5°C in conjunction with a compression sleeve at 150 or 300 mmHg does not generate haemolysis, but at 300 mmHg a blood warmer set at 41.5°C also did not totally avoid the risk of hypothermia associated with transfusion¹⁶⁰.

Calcium is a critically relevant part of the membrane bound procoagulant complexes of coagulation factors VIIIa/IXa, VIIa/TF and Xa/Va, but hypocalcaemia commonly occurs during massive transfusion due to citrate and serum calcium chelation. In a retrospective study of trauma patients who received massive transfusion, 152/156 patients included experienced hypocalcaemia (ionized calcium < 1.12 mmol/l), and 111/156 had severe hypocalcaemia (ionized calcium < 0.90 mmol/l). Mortality was significantly higher in the severe hypocalcaemia group (49% versus 24%) and patients with severe hypocalcaemia received

significantly more blood products (34 versus 22 PRBC)¹⁶¹. Another retrospective, single-center study of 7,431 trauma patients aged ≥ 18 years presenting to the emergency department found severe hypocalcaemia in 716 patients (9.8%) within 48h of admission. Patients with severe hypocalcaemia had received more PRBC, more FFP and more platelet transfusions. Multivariable analysis revealed higher PRBC or FFP administered as an independent predictor of severe hypocalcaemia and severe hypocalcaemia as an independent predictor of mortality¹⁶². The retrospective analysis of patients prospectively enrolled in two institutions participating in randomized clinical trials for the use of prehospital plasma in traumatic haemorrhagic shock (control, standard of care; experimental, plasma), with ionized calcium collected before calcium supplementation, showed that prehospital plasma recipients had significantly higher rates of ionized calcium levels of ≤ 1.0 mmol/l compared with controls. Severe hypocalcaemia was associated with decreased survival and massive transfusion¹⁶³.

Management of bleeding complications in patients receiving direct oral anticoagulants (DOACs)

DOACs should be discontinued 48 hours before surgery. There is no routine monitoring of DOACs and aPTT and PT measurements are not useful to assess the anticoagulatory effect of these substances. Their incidental administration prior to surgery, inadequate dose regimen, excessive alcohol consumption, potential pharmacokinetics interactions (e.g. amiodarone, diltiazem) and lack of treatment reassessment might cause higher-than-expected DOAC levels in patients undergoing surgery. In patients with unexpected bleeding complications, plasma concentrations of rivaroxaban, apixaban and edoxaban can be measured by calibrated chromogenic anti-Xa assays. Lack of prolonged times in the anti factor Xa assays can reassuringly prove absence of any of DOAC activity in the patients' blood. However, rivaroxaban, edoxaban and apixaban have a substantially different impact on the anti-Xa-activity and especially low concentrations of apixaban at the treatment relevant threshold might cause only slightly elevated results in anti-Xa-assays. This means that even though commonly anti Xa assays 2-fold above the upper normal limit indicate relevant rivaroxaban plasma concentrations, for apixaban, the threshold is lower and any increase of the anti Xa assays means potentially effective anticoagulation and impairment of the clotting cascade perioperatively¹⁶⁴. During treatment with DOACs the current safe-for-treatment threshold is 30 ng/ml, Andexanet alfa is a recombinant modified inactive factor Xa that had been licenced as an antidote for rivaroxaban and apixaban, but not for edoxaban. It binds and sequesters oral factor Xa inhibitor molecules, thereby rapidly reducing the anti-factor Xa activity. There is a low and a high dosing regimen with 400 mg andexanet alfa given IV in 15 minutes followed by an infusion of 480 mg over 2 hours for patients with a rivaroxaban or apixaban intake more than 8 hours ago or within the recent 8 hours at low doses (≤ 10 mg rivaroxaban once daily or ≤ 5 mg apixaban twice daily). Patients that took more than 10 mg rivaroxaban or more than 5 mg apixaban in the recent 8 hours or an unknown dose in the recent 8 hours should be treated with 800 mg andexanet alfa IV in 15 minutes followed by an infusion of 960 mg over 2 hours. In a multicenter, prospective, open-label study of 352 patients with major bleeding (26% presented with gastrointestinal bleeding, 64% presented with intracranial hemorrhage) excellent or good haemostasis could be reached in 204 of 249 patients (82%) with andexanet alfa administration¹⁶⁵. In patients who had received apixaban, the median anti-factor Xa activity decreased from 149.7 ng/ml, at baseline to 11.1 ng/ml after the andexanet alfa bolus. In patients who had received rivaroxaban, the median baseline anti-factor Xa activity decreased from 211.8 ng/ml to 14.2 ng/ml.

Dabigatran has no effect on the anti-Xa-activity but a diluted thrombin time measurement is highly sensitive for the presence of dabigatran. Idarucizumab is a recombinant antibody fragment that specifically, rapidly, durably, and safely reverses the anticoagulant effect of dabigatran. In a multicenter, prospective, open-label study of 503 patients with either uncontrolled bleeding (302 patients) or in need of an urgent procedure (202 patients) 5g of intravenous idarucizumab was able to reverse the anticoagulant effect of dabigatran with a median maximum percentage reversal of 100%¹⁶⁵. In patients presenting with uncontrolled bleeding (45.5% presented with gastrointestinal bleeding, 32.6% presented with intracranial haemorrhage) the median time to the cessation of bleeding was 2.5 hours. In patients undergoing urgent procedures the median time to the initiation of the intended procedure was 1.6 hours;

periprocedural haemostasis was assessed as normal in 93.4% of the patients. There were no serious adverse safety signals. The IV application of idarucizumab is either a bolus injection of 5g or an infusion of 2 x 2.5 g over 5-10 minutes.

When there is no specific antidote available, prothrombin complex concentrates at high doses (50 IU/kg PCC) should be considered, although its clinical effect still is in question. There is no role of FFP in this setting^{167,168}.

Management of bleeding complications in the context of disseminated intravascular coagulation (DIC)

The incidence of disseminated intravascular coagulation in patients with ovarian cancer undergoing cytoreductive surgery is generally low¹⁶⁹. Signature feature is the loss of localized activation of coagulation and the inefficiency of natural coagulation inhibitors to downregulate thrombin generation. It is associated with a high risk of macro- and microvascular thrombosis and progressive consumption coagulopathy, which leads to an increased bleeding risk. Cancer anyway represents a prothrombotic state that may promote hypercoagulation via factor VII overexpression and plasma release of tissue factor (TF) resulting in an ongoing low-level thrombin generation¹⁷⁰. Thrombin generation is promoted by positive feedback-activation of the intrinsic pathway, and inhibiting natural anticoagulant pathways including tissue factor pathway inhibitor, antithrombin III and protein C do not neutralise this activation process sufficiently. The resulting availability of large amounts of thrombin results in platelet activation, fibrin generation and inflammation but also in the activation of fibrinolysis. The extent of this cascade depends on plasminogen activator inhibitor 1, thrombin-activatable fibrinolysis inhibitor, and other factors related to the underlying disease and the capacity of regulatory mechanisms. If not adequately counteracted by fibrinolysis, fibrin deposition may cause diffuse obstruction of the microvasculature while the consumption of platelets, coagulation factors and coagulation inhibitors result in hypocoagulability which might be worsened by additional hyperfibrinolysis¹⁷¹. Coagulation, anticoagulation and fibrinolysis can be stressed by major surgery or massive PRBC transfusion leading to decompensation of a before still controlled situation.

The International Society of Thrombosis and Haemostasis (ISTH) suggested a scoring system for the diagnosis of acute decompensated DIC based on platelet count, plasma fibrinogen concentration, PT and D-dimer levels on an 8-point scale with one point each for a platelet count below 100/nl but higher than 50/nl, fibrinogen levels lower than 1g/l and a PT of 40% to 70%. A platelet count below 50/nl and a PT lower than 40% is scored with two points each. Scoring of D-dimer levels has recently been modified with 2 points for D-dimer levels between 3 and 7 µg/ml and three points for D-dimer levels >7 µg/ml. With modified D-dimer levels an ISTH score ≥ 4 suggests overt acute DIC¹⁷². However, an appropriate underlying disease is required and low antithrombin III levels might further guide diagnosis in patients with otherwise elevated D-dimer levels.

The cornerstone of DIC management is treatment of the underlying disease and all patients with DIC and bleeding in need of volume therapy should receive FFP and PRBCs in a 1:1 ratio instead of crystalloid or colloid infusions right from the beginning. In patients with DIC and bleeding and a platelet count of <50/nl transfusion of platelets is suggested by the British Society of Haematology in recent guidelines. In bleeding patients with DIC and prolonged PT and aPTT, administration of FFP is considered useful, while there is no evidence that infusion of plasma stimulates the ongoing activation of coagulation¹⁷³. If transfusion of FFP is not possible in patients with bleeding because of fluid overload, factor concentrates (PCC) might be considered. Whereas acute decompensated DIC is a situation of global deficiency of coagulation factors and natural anticoagulants, the selective substitution of procoagulants using large amounts of PCC might shift the system towards a microcirculation defect. In cases of severe hypofibrinogenaemia (< 2 g/l), additional fibrinogen substitution is considered useful based on case reports. While patients with DIC should not be treated with antifibrinolytic agents by routine, patients with DIC and a suspected primary hyperfibrinolytic state who present with severe bleeding might benefit from treatment with tranexamic acid (e.g. 1g every 8h).

In the absence of prospective evidence from randomised controlled trials confirming a beneficial effect of antithrombin concentrate on clinically relevant endpoints in patients with DIC and not receiving heparin, the British Society of Haematology does not recommend the administration of antithrombin III¹⁷³. However, most clinical trials evaluating DIC treatment were done in patients with sepsis with multiorgan dysfunction due to diffuse microvasculature obstruction. The KyberSept trial applied a total of 30,000 IU antithrombin III or placebo over a total of 96 hours to patients with sepsis. While there was no difference in survival at days 28, 56 and 90, the rate of severe bleeding was increased in patients receiving antithrombin III. In a subgroup of patients that did not receive heparin in addition to antithrombin III, survival at day 90 was significantly improved, but the trial did not allow the identification of patients that might benefit from the application of antithrombin III alone²³². In a double-blind randomized trial of activated protein C (APC) and unfractionated heparin at a dose of 8 U/kg/h in the treatment of DIC aggravation of bleeding was seen in 8/55 patients receiving heparin, but in none of the 52 patients receiving APC²³³. While heparin clearly should not be given in patients with DIC and bleeding, substitution of antithrombin III to restore antithrombin III levels of up to 80% might be reasonable, especially in patients with additional microvasculature obstruction. The application of recombinant activated factor VII (rFVIIa) could have a potential role in the context of severe bleeding associated with DIC that cannot be controlled otherwise based on case reports²³⁴. The effect of any DIC treatment should be monitored by repeated analysis of the patient's blood count, PT, aPTT, fibrinogen and antithrombin III levels, at least every 6 hours.

13.4 Interventional radiology options

Computed tomography with an arterial phase acquisition is the preferred method to identify and quantify arterial bleeding; to define type of lesion (vessel rupture, pseudoaneurysm, arterio-venous fistula) and to guide percutaneous transcatheter embolization. Computed tomography angiography is more sensitive than digital subtraction angiography for detection of active extravasation²³⁵. Digital subtraction angiography should be employed preferably during endovascular treatment rather than for the actual diagnosis of bleeding.

Transcatheter embolization during digital subtraction angiography is a widely employed technique for vascular occlusion to treat acute or recurrent hemorrhage. The field of application of transcatheter embolization in the postoperative ovarian cancer surgery includes vaginal, bladder, gastrointestinal, muscular, parenchymal (liver, spleen, pancreas kidneys) peritoneal and retroperitoneal bleeding. The reported success rate for abdominal embolization for bleeding widely ranges from 62% to 100%. In hemodynamically stable patients, interventional radiological techniques are the gold standard and first choice of treatment to avoid relaparotomy²³⁶. All hospitals that routinely accommodate ovarian cancer surgery should have 24/7 access to interventional radiology either on site, or via a formalized referral pathway to another hospital.

Coagulopathy, sepsis, and renal failure are relative contraindications to transcatheter embolization, hence appropriate efforts should be made to correct or improve these conditions before the procedure if at all possible. Lack of safe or adequate access to the target is a further contraindication as is an inability to achieve a stable catheter position, which occurs only in a minority of patients. A vascular communication between the target and an adjacent vital structure is a further obstacle to a successful mobilisation technique.

If an arterial bleeding is suspected but not detected, there is no strong evidence to support the practice for a "blind" or "prophylactic" embolization, however in some vascular areas as gastroduodenal-, internal iliac- or muscular arteries, an embolization with re-absorbable agents is often performed even without an obviously visible bleeding target²³⁷.

Major intra- and post-operative bleeding

- A multidisciplinary major haemorrhage protocol should be in place in any centre performing ovarian cancer surgery. The protocol should be reviewed periodically [IV, B].

Surgical options

- There is a variety of different local haemostatic agents that should be considered and used appropriately as per their mechanism of action and the hereby related potential adverse effects [IV, C].
- Abdominal and pelvic packing is an effective option in uncontrollable intraoperative bleeding in ovarian cancer debulking surgery [IV, C].
- A successful abdominal packing should not be removed or replaced before the completion of the first postoperative day. Intervals to remove or replace the pack longer than 3 days increase the risk of infectious complications [IV, B].

Medical options

- Normothermia and the prevention of acidosis are critical to control bleeding effectively. A pH of 7.35-7.45 and a core body temperature of >34°C should be maintained [III, A].
- Replacement of combined blood and plasma products as well as pharmacologic agents to support coagulation pathways such as tranexamic acid are recommended in the management of intraabdominal blood loss in well defined algorithms [III, A].

Interventional radiology options

- Interventional radiology techniques such as percutaneous transcatheter embolization should be considered as a treatment option in an active arterial bleeding (or a suspected vascular lesion like pseudoaneurysm) in a stable postoperative patient to avoid a relaparotomy [III, B].

14 Prevention and management of upper abdominal complications

14.1 Liver resection and biliary leaks

Liver metastases in ovarian cancer patients are mainly capsular-peritoneal and/or parenchymal²³⁸⁻²⁴⁰. The most common type is in the form of a capsular or subcapsular infiltrative pattern²⁴¹. Complete liver mobilization is crucial to evaluate the whole capsule. In addition to the Glisson capsule, each sulcus, round ligament, gallbladder, porta hepatis, retrohepatic region and the hepatic bridge should be visualized carefully. During resection of the round ligament, 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, the root of round ligament is sutured or secured by hemoclip.

Resection of subcapsular liver metastases can be performed by electric devices and subsequent coagulation by bipolar forceps or argon beam cautery to avoid bleeding or biliary leaks. In case of hematogenous parenchymal metastasis adequate preoperative imaging and mapping are essential safe complete resection^{238,241,242}. Intraoperative ultrasonography can facilitate exact localization of the metastatic lesion within the liver together with the vascular anatomy to prevent unnecessary bleeding and bile leakage. The parenchymal metastases could be resected by using different techniques where necessary: wedge resection, segmentectomy, lobectomy and/or hepatectomy²³⁸. Although it is not always needed, Pringle manoeuvre may decrease the bleeding during liver resection. Nasser *et al.* analyzed the effect of extensive liver mobilization on hepatic function and liver failure by evaluating the results of 132 patients who underwent primary or secondary cytoreduction²⁴³. Although the liver enzymes elevated following an operation, they get normalized within seven days, and no significant morbidity was noted specifically related with liver surgery except for one patient who died due to fatal fulminant hepatic failure. Therefore, they suggested following elevated liver enzymes until normalization and to avoid hepatotoxic medication the first days postoperatively after extensive liver manipulation.

Postoperative biliary ductal injuries can result in significant morbidity, including biliary peritonitis, cholangitis, and sepsis. Postoperative bilomas can become colonized by bacteria and become infected if left undrained. Most evidence in literature is based on series published about postcholecystectomy leaks. The International Study Group of Liver Surgery established a uniform bile leak definition including a severity grading associated with postoperative morbidity and mortality²⁴⁴. Discharge from the abdominal wound or drain is being considered as of biliary origin if it has a total bilirubin level of > 5 mg/ml or 3 times the serum level.

Smaller biliary leaks that are adequately drained tend to spontaneously seal off without any further intervention necessary and so a watch and wait approach is appropriate if the patient is asymptomatic and otherwise well.

- The first-line treatment for clinically relevant biliary leaks is endoscopic retrograde cholangiopancreatography 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 sphincterotomy²⁴⁵.
- If sepsis and biliary peritonitis predominate, a percutaneous, endoscopic ultrasound assisted or surgical drainage is also necessary as first line treatment.
- The percutaneous transhepatic biliary drainage is a challenging option in case of non-dilated biliary tree and should be considered only when an endoscopic retrograde cholangiopancreatography is not feasible (e.g. for anatomical conditions) or has failed.

14.2 Spleen, pancreas

The International Study Group of Pancreatic Fistula classification has re-defined a clinically relevant postoperative pancreatic fistula as a drain output from the pancreatic resection bed with an amylase level >3 times the upper limit of normal serum amylase combined with a clinically relevant clinical picture. Therefore, the former "grade A postoperative pancreatic fistula" is redefined as a "biochemical leak," since it has no clinical importance and is therefore no longer considered as a true pancreatic fistula²⁴⁶.

Multicentre, retrospective evidence of 2,026 patients who have undergone distal pancreatectomy has failed to identify method of transection, suture ligation of the pancreatic duct, staple size, the use of staple line reinforcement, tissue patches, biologic sealants, or prophylactic octreotide as having any independent impact on the risk of clinically relevant postoperative pancreatic fistula²⁴⁷⁻²⁴⁹. The same study identified following risk factors as being independently associated with clinically relevant postoperative pancreatic fistula: age, obesity, hypoalbuminemia, absence of epidural anesthesia, neuroendocrine or nonmalignant pathology, concomitant splenectomy, and vascular resection²⁴⁸.

Retrospective cohort studies in tertiary high-volume pancreas centers have demonstrated that the postoperative pancreatic fistula rate seems to increase according to the thickness of the pancreatic stump. Group II staplers, i.e. closed height of 1.8mm, showed a significant reduction in the postoperative pancreatic fistula rate than other cartridges of closed height of ≤ 1.5 mm or ≥ 2.0 mm in pancreas with thickness <13 mm²⁵⁰. The type of cartridge did not appear to have any significant effect on pancreas thicker than 13 mm.

The application of Fibrin sealant patches such as Veriset or Tachosil to the pancreatic stump after distal pancreatectomy does not seem to provide any relevant benefit in terms of postoperative pancreatic fistula, mortality, reoperation rate, blood loss or length of hospital stay²⁵¹⁻²⁵³. Flowable hemostatic matrix on the pancreatic stump has been shown to be associated with significantly lower postoperative pancreatic fistula rates compared to thrombin-coated collagen patches, but in smaller studies²⁵⁴.

Somatostatin and its analogues have been evaluated in multiple studies in their value to reduce postoperative pancreatic fistula, but evidence is conflicting with no significant differences in mortality in several systematic reviews²⁵⁵⁻²⁶³. The heterogeneity of the studies has made any comparison difficult and also no clear subgroup for which prophylactic treatment might be potentially more beneficial has been identified²⁶⁴. For selected patients who develop high-output fistulas, somatostatin may be useful to control the volume of output.

A prospective randomised trial with pasireotide vs placebo, demonstrated decreased incidence of clinically significant postoperative pancreatic fistula, however recent studies have failed to replicate these results²⁶⁵. A large meta-analysis of five studies on 1,571 patients has shown that routine administration of pasireotide did not significantly decrease postoperative fistula rates at distal pancreatectomy²⁶⁶.

In case of pseudocyst/abscess formation at the pancreatic tail after tumour resection in that area, a conservative approach with drainage is recommended. There are two main ways of approach: the percutaneous radiological guided external drainage placement versus the endoscopic ultrasound-guided internal drainage. In the first option, the contents are being drained externally while in the second option the internal drain empties the content into the stomach and from there into the gastrointestinal tract. Multiple retrospective series have shown that the endoscopic ultrasound-guided drainage is at least equally feasible and effective compared to the radiological drainage and in some studies led to a more rapid resolution, while having the advantage of not requiring an external drainage apparatus²⁶⁷⁻²⁷⁰. A large meta-analysis of 10 studies (239 patients) demonstrated that endoscopic ultrasound had significantly better clinical outcomes, in terms of clinical success and disease recurrence, in the management of pancreatic fistula as compared to percutaneous drainage²⁷¹.

14.3 Diaphragm

Upper abdominal debulking procedures are a key to achieving complete cytoreductive surgery in advanced ovarian cancer²⁷². Crucial steps for achieving a complete tumor resection from the diaphragm/diaphragmatic peritoneum are knowledge of anatomical landmarks and mobilization of the liver adequate exposure of the surgical field. The sandwich technique is one of the many described to strip the diaphragmatic peritoneum²⁷³. The most frequently described post-operative complication across multiple prospective and retrospective studies is pleural effusion, with rates ranging from 10% to 60%, depending the setting and timing of the surgery, as well as the tumour burden, extent of diaphragmatic resection, amount of pre-existent ascites and pleural effusion²⁷⁴⁻²⁷⁶. The need for post-operative thoracentesis or chest tube placement is low. The routine use of intraoperative trans-diaphragmatic decompression of pneumothorax reduces these rates²⁷⁵. Diaphragmatic lesions at the time of interval debulking are less frequent and smaller in size. The morbidity of diaphragmatic surgery in this setting is lower as compared to a primary. Pneumonia and pneumothorax were the next most commonly reported morbidities²⁷⁷. The described rates of postoperative pleural drainage are not high enough to justify prophylactic chest tube placement for all the patients, however, patients who underwent full thickness diaphragmatic resection and high volume preoperative pleuraeffusion merited special consideration for intraoperative prophylactic drainage.

Phrenic nerve injury at diaphragmatic surgery for tumour debulking with clinically relevant consequences is very rare. The phrenic nerve provides the primary motor supply to the diaphragm, the major respiratory muscle. Phrenic nerve injury may more commonly occur from cardiothoracic surgery and can lead to diaphragmatic paralysis or dysfunction. The presentation of phrenic nerve injury is non-specific, and the diagnosis may easily be missed. Possible imaging modalities include ultrasound, electromyography, and fluoroscopy²⁷⁸.

Diaphragmatic hernia is also a further rare complication in patients after ovarian cytoreduction. The literature describes only a limited number of cases and is mostly left since the liver usually protects the right diaphragm against this event²⁷⁹⁻²⁸¹. The process may be multifactorial and may be caused not just due to direct injury and insufficiency of the diaphragmatic repair but also due to other reasons such as development of abdominal abscess for example after pancreatectomy that invades through the diaphragm²⁸¹. Diaphragmatic hernia with herniation of the abdominal organs into the chest may also occur delayed and months after the actual surgery. As a possible pathogenetic explanation is devitalization of the muscle with peripheral denervation and progressive thinning of the muscle wall and inducing fibrosis leading to diaphragmatic rupture.

14.4 Stomach

Gastric perforation after ovarian cytoreduction is rare, most likely the result of a multifactorial process and most commonly described in combination with hyperthermic intraperitoneal chemotherapy. Therefore careful tissue handling is key to safe tumor dissection and avoiding of overmanipulation of the affected organs. The injury happens usually at infragastric omentectomy with ligation of the gastroepiploic vessels on the surface of the greater curvature. Associated mechanisms of action are vascular compromise, delay in wound healing from any previous chemotherapy, seromuscular tears related to traction on the stomach wall and point pressure on the greater curvature from a long-term indwelling nasogastric tube. Surgical exploration has often revealed protrusion of the nasogastric tube through stomach wall defects which were either located at or near the greater curvature of stomach at omentectomy. To reduce the risk of gastric perforation, oversawing of the greater curvature, if seromuscular tears occur and avoiding nasogastric suction may reduce complications and morbidity^{282,283}.

Gastroparesis is a syndrome of objectively delayed gastric emptying of solids in the absence of a mechanical obstruction and main symptoms are nausea, vomiting, early satiety, bloating, and/or upper abdominal pain²⁸⁴. Risk factors include polypharmacy, frailty, comorbidities, diabetes. Gastric stasis is usually due to surgical injury to the vagus nerves. Vagal injury can be demonstrated by measurement of

the plasma pancreatic polypeptide response to modified sham feeding. Sham feeding, ie chewing but not swallowing food, results physiologically in cephalic vagal stimulation and thereby a rapid increase in plasma PP of at least 25 pg/ml in the first 20 minutes followed by a return to baseline. In patients with vagal injury, this mechanism is failed and no increase in PP over baseline occurs²⁸⁵. Foods that are fatty, acidic, spicy, and roughage-based increase the overall symptoms in individuals with gastroparesis²⁸⁶. Fat slows gastric emptying and nondigestible fiber (eg, fresh fruits and vegetables) require effective interdigestive antral motility that is frequently absent in patients with significantly delayed gastric emptying. Diet should be low in fat and in non-digestible (insoluble) fiber; in general, soluble fiber or fiber that is cooked and reduced in particle size by homogenization can be digested and emptied from the stomach except in the most severe patients with gastroparesis^{286,287}. Patients should also be advised to avoid carbonated beverages as they can 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.

Metoclopramide is usually the first-line therapy for gastroparesis. In patients whose symptoms fail to respond to metoclopramide or with side effects that result in its discontinuation, a further option is domperidone at a dose of 10 mg three times daily and increase to 20 mg three times daily with an additional dose at bedtime, if symptoms persist.

Macrolide antibiotics such as erythromycin would be the next step and also stimulate fundic contractility, or at least inhibits the accommodation response of the proximal stomach after food ingestion²⁸⁶⁻²⁸⁸. The liquid formulation is 40 to 250 mg three times daily before meals²⁸⁸. Oral erythromycin should be administered for no longer than four weeks at a time, as the effect of erythromycin decreases due to tachyphylaxis. Intravenous erythromycin is more effective than the oral form²⁸⁹. In a systematic review of five clinical trials involving oral erythromycin for gastroparesis, 43% of the patient had a significant clinical improvement²⁹⁰.

In cases of refractory gastroparesis ultima ratio is surgery including placement of an enterostomy tube (eg, gastrostomy, jejunostomy), pyloromyotomy, transpyloric stent and pyloroplasty²⁹¹⁻²⁹³. Intrapyloric injection of botulinum toxin is not recommended since randomized controlled trials failed to show any improvement in symptoms, even though some open-label trials have shown benefit^{294,295}. Endoscopic pyloromyotomy (gastric per-oral endoscopic myotomy) and laparoscopic pyloroplasty have been successful in small studies in treating gastroparesis²⁹⁶⁻²⁹⁸.

Gastric electrical stimulation is reserved for compassionate treatment in patients with refractory symptoms, particularly nausea and vomiting (eg, with persistence of symptoms despite antiemetic and prokinetic drug therapy for at least one year), without however proven benefit for postsurgical gastroparesis²⁹⁹.

14.5 Lesser sac, Porta hepatis, celiac region

The systematic evaluation of lesser omentum, lesser sac (bursa omentalis), porta hepatis, celiac trunk, gallbladder, liver and retrohepatic region is crucial to achieve complete tumor clearance in ovarian cytoreduction. The systematic visualization of the retrohepatic region including the anterior and posterior surface of caudate lobe after detachment of left triangular ligament up to the gastro-esophageal junction is relevant for adequate exposure. Common complications specific to these procedures are bleeding due to liver damage and due to left gastric injury. Tumor involvement of the porta hepatis/hepatoduodenal ligament, celiac trunk and lesser curvature of the stomach are common tumor sites that limit operability in various studies^{32,300-302}.

Following localizations should be assessed for tumor involvement:

- The peritoneal surface of hepato-duodenal ligament
- Peri-portal lymph nodes
- Celiac lymph nodes
- Gallbladder/gallbladder bed
- Hepatogastric ligament
- Lesser sac, lesser omentum, bursaomentalis
- Round ligament, hepatic bridge
- The entire surface of the liver including each sulcus
- The anterior and posterior surface of the caudate lobe
- The surface of diaphragmatic crus
- Retrohepatic surface down to inferior vena cava and up to gastro-esophageal junction

14.6 Cardiophrenic lymph node resection

The resection of bulky/suspicious cardiophrenic lymph node belongs in the armamentarium of the gynaecological oncology surgeon to achieve complete macroscopic tumor clearance in and outside of the peritoneal cavity³⁰³⁻³²⁰. The most commonly used access route is the transdiaphragmatic approach, which has been described as feasible and safe. The overall post-operative morbidity directly related to the cardiophrenic lymph node resection has been described as comparatively low with the most common being: pleura effusion, pulmonary embolism, chylothorax and acute respiratory distress syndrome^{304,307,309,313,314}. If during dissection the pericard is opened, this should not be closed, to avoid tamponade effects and infection. The defects should be left open and heal spontaneously. The management of chylothorax can be very challenging with no concrete treatment algorithm having been adopted and no well-conducted randomized trials comparing therapies are available^{303,321-422}.

For most patients with a persisting, high volume postoperative chyle leak (ie, >1 l per day) (more than 2-5 days) early invasive intervention with medical pleurodesis, percutaneous thoracic duct embolization/disruption, lymphangiography with highly viscous contrast or surgical thoracic duct ligation, should be considered early ie within the first few days after diagnosis, rather than prolonged conservative therapy with just chest tube drainage and dietary modification. The rationale for this approach is that these patients are likely to have major thoracic duct injury which is unlikely to close spontaneously, rather than leaks that originate from a smaller thoracic duct tributary which are more likely to undergo spontaneous closure.

Additional perioperative dietary modification for those high-volume leak patients consists of complete bowel rest by total parenteral nutrition, combined with somatostatin/octreotide to reduce the flow of chyle through the leak. For patients with low volume postoperative chyle leak (ie, <1 l per day) more conservative and minimally invasive approaches such as pleural drainage for symptom control and dietary modification (low-fat diet or total parenteral nutrition) could be followed. Success rates with conservative therapy are variable ranging from 25-80% with patients who have low-output leaks more likely to respond than those with high output leaks^{303,321-422}.

14.7 Postoperative pleura effusion

Postoperative pleura effusion is a common complication after upper abdominal and thoracic resection procedures. More than half of patients seem to develop ipsilateral pleural effusions after diaphragm peritonectomy for cytoreduction. The management depends mainly on the presence of associated cardiovascular symptoms and the volume, timing, progression, and persistence. Small to moderate effusions, not progressive and not associated with respiratory symptoms require only observation^{272,274-277}.

The incidence of symptomatic effusions does not appear high enough to recommend routine chest tube placement at the time of diaphragm peritonectomy or resection⁴²³. Drainage of postoperative pleura effusion usually occurs by the interventional radiologists or the thoracic physicians (pulmonologists, thoracic surgeons) or the gynaecological oncologists, depending on the expertise and availability of the team but also on medicolegal aspects and local guidelines^{272,274-277}. Thoracentesis without pleural drain placement is not recommended for the treatment of parapneumonic effusion or empyema. Any pleural drainage should be performed under imaging guidance to increase success rates and decrease complications^{424,425}; if ultrasound as a first step is not able to identify fluid collection due to its location, surrounding anatomic structures, or loculated nature, computed tomography can be an alternative option for localization of fluid and procedure guidance⁴²⁶.

A retrospective study by Gouy *et al.*, of 63 patients who underwent unilateral or bilateral diaphragmatic surgery, showed that a chest tube was routinely placed intraoperatively if there was a large resection (>5cm) of the diaphragm, including the muscle, or if there were many lesions resected from the same hemidiaphragm²⁷². With this approach, the authors reported a rate of 5% of pleural effusion and pneumothorax that required drainage, which is extremely low.

In 2013, Kato *et al.* presented a retrospective study of 37 patients who underwent a full-thickness diaphragm resection during cytoreductive surgery for advanced stage ovarian cancer⁴²⁷. All patients who had their thoracic cavity opened during diaphragmatic surgery routinely underwent an intraoperative tube thoracostomy, regardless of the size of the pleural opening. Post-operative chest x-rays demonstrated a higher density on the undrained side of the lung field than on the drained side in 24 patients, due to pleural effusion. However, the placement of the chest tube was correlated with the estimated blood loss, blood transfusion during surgery and the operative time. The authors stated that, in a multivariate analysis, an estimated blood loss of 2,500 ml was the only factor that was significantly associated with pleural drainage.

In a study by Sandadi *et al.*, the authors assessed the incidence of symptomatic pleural effusion between patients who underwent intraoperative chest tube placement and those who did not receive any intervention⁴²⁸. The study included 156 patients who underwent diaphragmatic surgery for advanced stage ovarian cancer, 49 of which had a resected specimen of 10 cm or more in largest dimension. The authors demonstrated that, in these patients, without intraoperative chest tube placement, recorded a postoperative complication rate of 57%, such as moderate or large pleural symptomatic effusion, compared to 19% in the chest tube group.

Exudate, empyema, chylothorax, pneumothorax and hemothorax are further indications for a drainage catheter placement. In complicated pleural fluid collections small size catheters (<14 Fr) are as effective as large (> 14F) catheters; moreover, patients with smaller drainage catheters experience less pain than those with large catheters. For Stage II and mixed (II/III) acute empyema video-assisted thoracoscopic surgery should be the first-line approach⁴²⁹.

Prevention and management of upper abdominal complications

- In patients with large volume ascites and extensive peritoneal and/or lymph node resections a placement of an intraabdominal drainage could be considered [III, C].

Liver resection

- A gynaecological oncology surgeon must be familiar with the anatomy of the liver and the biliary tree and also the various indications and anatomical borders of liver resection techniques (i.e. metastasectomy, segmentectomy and partial hepatectomy) [V, A].

Biliary leak

- The first-line treatment for biliary leaks includes conservative management with watch and wait and endoscopic/interventional radiology technics depending on the clinical picture of the patient and the extent of the leak [II, B].
- If sepsis and biliary peritonitis predominate, a percutaneous, ultrasound assisted or surgical drainage should be considered as additional treatment [II, B].

Spleen, pancreas

- There is no value of routine use of prophylactic somatostatin for patients undergoing splenectomy +/- distal pancreatectomy. Somatostatin analogues, especially its longer lasting derivates may be used for selected patients with high-output fistulas [II, C].
- Pancreatic pseudo abscesses due to pancreatic leak should be managed with percutaneous drains or with an internal endoscopically inserted drain to avoid reoperation [III, B].

Diaphragm, pleural effusion

- A prophylactic chest tube placement after diaphragmatic surgery is not routinely indicated [III, B].
- Prophylactic chest tube placement could be considered for those patients with high volume preoperative pleura effusion, frailty and hypoalbuminemia and large/full thickness diaphragmatic resection [III, B].
- Small to moderate postoperative pleura effusions, which are not progressive and not associated with respiratory symptoms should be managed conservatively [III, B].
- Thoracentesis alone without pleural drain placement is not recommended for the treatment of parapneumonic effusion or empyema [III, B].

Lesser sac-Porta hepatis-celiac region

- If postoperative gastric perforation occurs, reoperation is the mainstay of treatment [III, B].
- Postsurgical gastroparesis should be addressed with correction of electrolytes, appropriate diet and pharmacological support including metoclopramide, domperidone, and erythromycin [III, B].

Paracardiac lymph node resection

- Complications like chylothorax after cardiophrenic lymph node resection are rare and multidisciplinary management is required [V, B].
- In case of pericardial opening, no pericardial closure is recommended to avoid tamponade and infection [III, B].

15 Prevention and management of infective and urological complications

15.1 Postoperative sepsis, collection, drainage

Advanced, multivisceral cytoreductive procedures, especially in the upper abdomen and gastrointestinal tract increase the risk of postoperative sepsis, abscess formation, collections or lymphocysts. Computed tomography appears to be the most appropriate imaging modality to clarify symptoms of sepsis in a surgical patient. Ultrasonography is an easy and safe technique for image guided drainage of postsurgical collections with high success rates (>80%) and lower morbidity compared to relaparotomy. Close cooperation between surgeons and interventional radiologists is required to determine the best modality to perform image-guided percutaneous drainage. The success rate of image-guided percutaneous drainage is related to the interval between surgery and the onset of the abscess/collection as well as the number and septation of abscesses or collections.

15.2 Urological complications: hydronephrosis, ureteric fistulas, nephrostomies

The two major urological complications after gynecological oncologic surgery are urinary leaks/ fistulas and ureteric obstruction, mostly located at the ureterovesical junction. Pre- or intra-operative ureteric stenting has been shown to be associated with significantly lower urological complication rate especially in relapsed surgery and/or cases with preexisting hydronephrosis, even though the routine use of stents is not associated with a decreased risk of ureteral injury. They may make ureteric injury easier to detect intraoperatively by assisting with visualization and palpation of the ureters⁴³⁰. The most commonly used stent types include internal double-J (JJ) stents and externally draining percutaneous stents (PC). A small number of retrospective studies compared the outcomes of JJ stent versus PC stent placement in gynecological oncology surgery. All these studies support the use of a JJ stent, in terms of decreased urological complications, when compared to PC stents. None of these studies revealed a significant difference between the two groups in the number of urinary tract infections. These so-called JJ stents are placed typically using an antegrade approach through nephrostomy access; however, these need to be replaced every 3-6 months due to stent migration, encrustation, obstruction, and infection⁴³¹. Exchange may be performed using a retrograde or antegrade approach, with the former being preferred as the antegrade approach requires nephrostomy⁴³². Metallic stents can be considered as an alternative to long-term JJ stents and acute complications management of fistulas. The improvement in quality of life, reduction in the need to re-admit patients for repeated stent changes and effective maintenance of upper tract decompression are some of the benefits of metallic stents plastic stents. Metallic stents employed in the past were associated with epithelial hyperplasia and as such, plastic stents are preferred⁴³³. Metallic ureteric stents are not widely employed mainly due to lack of availability, higher costs as well as the complexity of management. Moreover, metallic stents may be an option for management of ureteric obstruction caused by chronic strictures⁴³⁴. Nevertheless, the wide acceptance of metallic stents would require well-designed clinical studies and long-term follow-up⁴³⁵.

Identification, careful dissection and careful handling of the ureters during cytoreduction are keys to avoid unnecessary ureteric complications. The adventitia of the ureters should be meticulously preserved to avoid devascularization and formation of strictures, fistulas and leaks. Ureteric injuries should be repaired immediately with the placement of a stent and catheter. Less often an urinary diversion via a nephrostomy tube may be necessary depending on the extent of the damage. Ureteric stenting after injury provides canalization and may decrease the risk of stricture. Benefit of stents must be weighed against the risk of accidentally worsening the severity of the ureteral injury during stent insertion.

In the event of ureteric transection, immediate reconstruction after mobilization of the ureteric ends and spatulation should be performed. End-to-end anastomosis is usually preferred. Ureteric stent placement is mandatory to avoid strictures and reduce anastomotic leak rates. The type of primary ureteric repair

depends on the distance from the insertion into the urinary bladder; in case of distal injuries close to the insertion of the ureter into the bladder (within the distal 2 cm from the ureterovesical junction), a ureteric reimplantation would be the preferred method. Even though in earlier years a submucosal tunnel was created to prevent reflux, nowadays nonrefluxing reimplantation techniques are usually preferred. When ureteric reimplantation cannot be performed without tension due to more extensive damage, we would recommend bladder mobilization and its anchoring to the psoas tendon (psoas hitch) as the most preferable approach. Placement of an intraabdominal drain is necessary in all these cases.

Management of ureteric strictures depends on the location and length of the affected segment. A percutaneous nephrostomy with delayed repair should be considered if ureteric stent has not been effective or not possible. If the nephrostomy does not resolve the urine leak, placement of a periureteral drain or immediate surgery with open ureteral repair should be considered to avoid the significant complications from uro-peritoneum. Ureteric JJ stents should be preferred compared to externally draining ureteric stents to shorten the length of hospital stay.

A more recent type of ureteric stents, the Allium Bulbar Urethral Stents is a self-expandable, large-caliber, round, metal urethral stent designed for urethral strictures treatment has however been successfully used for endoscopic management of iatrogenic ureteric injuries and or even transections. The stent is constructed of a coiled, super-elastic metal alloy (nitinol) and coated with a co-polymer which prevents mucosal hyperplasia and encrustations. It has been shown in studies to be an alternative to indwelling double J stents and although they are relatively high priced, they appear in some studies to show a financial benefit in the long-term; however large scale multicentre randomised evidence is lacking^{436,437}. For the adequate prevention of vesicovaginal fistulas the gynae oncology surgeon should ensure to adequately mobilize and expose the bladder, in order to provide a tension-free closure of any defects and help determine if there is any bladder injury. Bladder defects should be ideally repaired in 2 layers.

A preventive measure to avoid fistula formation is to avoid placing a suture line over any other suture line, such as those of the vagina and colon and to ensure interposition of viable tissue such as connective surrounding tissue. Vesicovaginal fistulas should be treated conservatively most commonly with adequate drainage via a bladder catheter. Other conservative management options may include:

- Endoscopic electrofulguration of the fistulous tract
- Occlusion of the fistulous tract

Surgical repair should be considered for complex vesicovaginal fistulas or for simple vesicovaginal fistulas refractory to conservative management, or due to patient preference/choice of surgical repair depending on surgeon experience, location and size of fistula. Options for surgical repair include transvaginal repair versus transabdominal repair (open, laparoscopic or robotic depending on intraabdominal situs and patients' picture and habitus). Postoperative bladder catheterization for at least 10-12 days is also here recommended. For bladder repair in case of partial bladder resection or cystotomy, there is no evidence that a two layer repair results in less complications than single layer repair' and it is at the discretion and expertise of the surgeon to choose the method of closure.

Prevention and management of infective and urological complications

Postoperative sepsis, collection, drainage

- Computed tomography scan is indicated as the best imaging modality in patients with septic symptoms and/or clinical symptoms evoking a collection or abscess after debulking surgery [III, B].
- Postoperative collections or intra-abdominal abscess should be managed with image-guided percutaneous drainage as the preferred option to avoid relaparotomy [III, B].

Urological complications: hydronephrosis, ureteric fistulas, nephrostomies

- Use of prophylactic ureteric stents could be considered in patients at high risk for ureteric injury such as previous urological operations and/or preexistent hydronephrosis [III, B].
- Immediate primary repair is recommended for any iatrogenic ureteric injury recognized during surgery [III, B].
- In the event of complete ureteral transection, immediate reconstruction after mobilization of the ureteric ends and spatulation should be performed. End-to-end anastomosis is usually preferred. Ureteric stent placement is mandatory [III, B].
- Type of ureteric repair (end to end anastomosis versus reimplantation) depends on the distance from the insertion into the urinary bladder [III, B].
- For iatrogenic ureteral injuries/fistulas diagnosed postoperatively, ureteric stent insertion or urinary diversion via nephrostomy tube is recommended [III, B]:
 - Internal stenting (with or without dilatation) can be performed either retrogradely or antegradely through a percutaneous nephrostomy
 - Surgical repair is necessary in cases of failure of conservative management
- In case of vesicovaginal fistulas we recommend adequate postoperative bladder drainage and delay of catheter removal until no contrast extravasation on cystogram is observed 7-21 days after leak/fistula diagnosis [III, B].

16 Management of bowel related morbidity, prophylactic stoma formation and stoma reversal

16.1 Anastomotic leak after colorectal resection

Average anastomotic leak rates at ovarian cytoreductive surgeries are approximately 6% even at a restrictive stoma policy^{438,439}. Early recognition of an anastomotic leak translates in lower mortality and overall morbidity. Advanced age, multiple bowel resections, low albumin serum levels and/or a short distance from the anastomosis to the anal verge have been described in one of the largest analysis of anastomotic leak in ovarian cancer patients as the most significant risk factors⁴³⁹. Also, other studies have confirmed that distance from the anal verge ≤ 7 cm but also previous neoadjuvant chemotherapy were associated with an elevated risk for anastomotic leak⁴⁴⁰.

A refined and meticulous surgical technique, careful tissue handling, adequate mobilization to achieve tension-free anastomosis and sufficient vascularization are keys for any successful and any safe anastomosis. Appropriate indication for the procedure itself is also crucial to reduce the risk of anastomotic leak. Preoperative oral antibiotics in combination with mechanical bowel preparation have been shown to contribute towards a reduced gastrointestinal morbidity.

Anastomotic leak is the most challenging complication after colorectal resection. In 2010, the International Study group of Rectal Cancer defined colorectal anastomotic leakage as the defect of the intestinal wall integrity at the colorectal anastomotic site leading to a communication between the intra- and extraluminal compartments⁴⁴¹. A pelvic abscess close to the anastomosis was also considered anastomotic leakage. Not all anastomotic leaks need immediate intervention. The same group classified the anastomotic leakage in three groups depending on the need of interventions:

- Grade A : No active therapeutic intervention
- Grade B : Active therapeutic intervention but manageable without re-laparotomy
- Grade C: Requiring re-laparotomy

Patients with anastomotic leaks frequently show pain, nausea, and fever, primarily if the leak is not contained⁴⁴². The diagnostic tool of choice is the abdominal computed tomography. The presence on the computed tomography of extraluminal contrast, free air perianastomotic air, perianastomotic fluid and a disrupted staple line are associated with anastomotic leak⁴⁴³. However, the sensitivity of the computed tomography is lower than 70%. A negative computed tomography does not rule out entirely a leak and may worsen the outcome of an undiagnosed leak or perforation⁴⁴⁴. The C-reactive protein and the procalcitonin have been proven very useful in discovering a potential leak, specifically between postoperative days three and five⁴⁴⁵. In some cases an endoscopic exam could be useful to check the integrity of the anastomosis. In view of the uncertainty of imaging to exclude an anastomotic breakdown it is critical to use all the available data (biochemical, clinical) to verify that the patient is advancing correctly and for ruling out a leak. Patients with suspected sepsis or unstable (Grade C) should be managed rapidly by intervention.

Colorectal anastomotic leaks without associated extensive peritonitis and critical clinical picture may be managed conservatively by keeping the patient nil by mouth and introducing parenteral nutritional support, broad-spectrum antibiotics, and percutaneous drainage. Surgery may be necessary in patients with continuing leakage of enteric contents or lack of clinical improvement following drainage. Various techniques have been described: repairing the anastomosis and performing a protective stoma proximally to the anastomotic site, taking down the anastomosis with end colostomy/ileostomy after stapling of the distal anastomotic end. A further option might be damage control surgery where the perforated bowel segment is resected and the 2 bowel segments proximally and distally to the anastomosis are left as blind

loops *in situ* and reanastomosed after improvement of the local peritonitis and clinical picture a few days later. Novel transanal endoscopic approaches help to manage anastomotic leaks in stable patients: coated stents, endoluminal staples, endo-sponges, and lately, transanal endoscopy to place sutures on the defect.

Intraoperative placement of abdominal drains based on the notion that they reduce perioperative fluid collections and simulate “an eye” in the abdominal cavity for the early detection of complications, such as bleeding or anastomotic leakage⁴⁴⁴. In a prospective randomized study by Merad *et al.*, in 712 patients that underwent bowel surgery, the authors assessed the intraoperative need for drain placement in the abdominal cavity⁴⁴⁶. A total of 314 patients had a drain placement and 391 did not, with the anastomotic leaks being 4.8% and 5.1%, respectively and so not statistically significantly different between the two arms. Therefore, in cases of low anterior resections, drain placement should be indicated based on the entire tumor dissemination, ascites and procedures performed and also on the surgeon's discretion, but not with the aim to prevent or reduce anastomotic leaks.

Intraoperative fluorescence angiography with indocyanine green has been shown to be a safe tool for assessing anastomotic rectal perfusion after rectosigmoid resection and anastomosis, associated with a reduction of anastomotic leakage rates following colorectal surgery for cancer reaching low anastomotic leak rates of 1.5%^{447,448}. Two meta-analyses showed that indocyanine green fluorescence angiography was associated with a lower anastomotic leakage rate after colorectal resection^{449,450}. The value of this technique should be assessed in randomized trials in patients undergoing ovarian cancer debulking surgery.

16.2 Stoma placement

Previous treatment with bevacizumab, multiple bowel resections, extended operating time and intraoperative red blood transfusion have been shown to be associated with diverting ileostomy formation⁴⁴⁴. An ileostomy at the time of cytoreductive surgery for advanced stage ovarian cancer has been shown to negatively affect survival, but this might be also just due to the bias of retrospective studies, where higher tumor burden patients with less favorable oncologic prognosis required higher ileostomy rates⁴⁴⁶. Even though diverting stomas are a low-risk surgical procedure from a technical stand point they carry substantial postoperative morbidity that can greatly hamper patients' quality of life and recovery. For that reason, the risks of a diverting loop ileostomy may outweigh its benefits and should not be routinely performed to prevent rectal anastomotic breakdown⁴⁴³.

There are no prospective randomized trials to assess the value of protective stoma formation after colorectal anastomosis especially in ovarian cancer patients. So, most of our prospective randomized experience is extrapolated from studies on patients with colorectal malignancies. A prospective multicenter study of 2,729 patients undergoing low anterior resection for low rectal carcinoma, has demonstrated similar anastomotic leak rates in patients with versus without a stoma: 14.5 versus 14.2%⁴⁵¹. However, patients with a protective stoma formation required significantly lower surgical interventions due to anastomotic leak: 3.6 versus 10.1% and had a lower mortality; 0.9 versus 2.0%. Data from a meta-analysis of four randomized trials including 358 rectal cancer patients showed that protective stoma formation could significantly reduce anastomotic leaks after low anterior resection, resulting in significantly fewer reoperations for leaks⁴⁵². In a randomized controlled trial of 234 patients undergoing a low anterior resection for rectal cancer that was included in the meta-analysis, the rate of anastomotic leakage with a protective stoma was significantly lower compared with no protective stoma in both men and women⁴⁵³.

Nevertheless, in all these colorectal cancer studies, the anastomotic leak rates in the patients without a protective stoma was with 14-29% significantly higher than the 6% anastomotic leak rate described in ovarian cancer patients and so attempts to reduce that with a protective stoma formation seem justified. To adopt however these strategies of routine stoma formation also to patients with ovarian cancer who appear to have much lower risk and incidence of anastomotic leak, needs careful consideration, especially

in view of the morbidity associated with bowel stoma such as herniation, electrolyte dysbalance etc. The lower incidence of anastomotic leak in ovarian cancer patients compared to colorectal cancer patients may be attributed to the fact that the anastomosis is usually higher after adequate mobilization of the en bloc pelvic package, patients are not previously irradiated and also the anatomy of the female pelvis is wider and shallower compared to the male pelvis⁴⁵⁴. Especially now, where most ovarian cancer patients are treated with maintenance regimens after completion of their cytotoxic treatment, such as antiangiogenetic agents; the reversal of any protective stoma appears challenging in terms of timing, since many of these maintenance treatments would have to be interrupted.

Morbidity rates following the creation of loop ileostomy were significantly decreased compared with loop colostomy at the cost of a risk for dehydration^{455,456}. There is increasing literature regarding the possible role of ghost ileostomy in ovarian debulking procedures⁴⁴⁴. High-risk patients such as those with low colorectal anastomoses, previous radiotherapy, technically difficult resections, abscess/infections in the pelvis, malnutrition and frailty seem to obtain the greatest benefit from fecal diversion. Appropriate support for patients following stoma reversal but also optimal preoperative preparation, to foster realistic expectations and subsequent adaptation are strongly encouraged⁴⁵³.

16.3 Stoma reversal

Reversal of temporary stomas is associated with significant complications, which can be minimizing by optimizing timing of closure and evaluating anastomotic integrity prior to stoma closure. A relevant number of patients are at risk of remaining with a permanent stoma after a bowel diversion, and therefore patients should be preoperatively informed of this possibility. There is no definition of the optimal time of stoma closure. This depends on multiple factors such as the patient's profile, targeted maintenance therapies planned and their impact on wound healing such as bevacizumab, integrity and risk factors of the actual anastomosis etc. Early closure of loop defunctioning ileostomy in patients undergoing distal colorectal resections is feasible with comparable outcomes to delayed closure⁴⁵⁷. A large meta-analysis has demonstrated that early stoma closure is asafe and feasible therapeutic approach in patients who have undergone colorectal surgery; early stoma closure was associated with reduced bowel obstruction but a higher wound complication rate⁴⁵⁸.

Incisional hernia of the previous stoma site appears common and frequently required surgical correction (6%)⁴⁵⁹. Insertion of a mesh to prevent incisional hernia has doubtful role and may cause complications/challenges in case of peritoneal carcinosis and future cytoreductive surgery⁴⁶⁰⁻⁴⁶². There has been described significantly lower prevalence of sepsis, prolapse, parastomal hernia and hospital stay after loop ileostomy compared to loop colostomy^{463,464}. Also, patients with colostomies demonstrated significantly more complications related to stoma reversal, such as wound infections and incisional hernias, than patients with ileostomies. Overall complications related to stoma formation and closure did not demonstrate significant differences⁴⁶⁵. However, patients with loop ileostomy had higher risk of electrolyte dysbalances and fluid losses. Further risk factors for surgical site infection are history of fascial dehiscence, thicker subcutaneous fat, colostomy, and Caucasian ethnicity⁴⁶⁶. In colorectal studies, 9% of patients who underwent a stoma reversal suffered a major complication requiring return to theatre⁴⁶⁷. The best available evidence demonstrates that the skin pursestring closure technique has significantly fewer surgical site infections and better cosmetic outcomes following stoma reversal than the conventional primary closure technique^{465,468,469}. Laparoscopy may be an option to implement the hernia repair at the time of stoma closure⁴⁷⁰.

16.4 Quality of life and low anterior resection syndrome

Low anterior resection syndrome is a common serious, long-term complication observed in patients after low anterior resection⁴⁷¹⁻⁴⁷⁴. Low anterior resection syndrome comprises a collection of intestinal dysfunction symptoms, such as diarrhea, fecal incontinence (gases or stool), increased bowel movements and frequencies of defecation, fecal urgency, constipation and incomplete emptying or accumulation of intestinal gases⁴⁷¹⁻⁴⁷⁴. The prevalence of major low anterior resection syndrome - described to impair patient's quality of life - is almost 40%⁴⁷⁴. Low anterior resection syndrome prevalence is stable irrespective of time interval between surgery and its evaluation. Multiple bowel anastomoses increase the risk for developing major low anterior resection syndrome. Potential therapeutic options for patients diagnosed with low anterior resection syndrome comprise medical treatment options (e.g. Loperamide Hydrochlorid, 5-HT3 antagonists), local supportive strategies (e.g. transanal irrigation, pelvic floor rehabilitation), as well as surgical treatment options (e.g. sacral nerve stimulation)⁴⁷¹. Diet modifications include intake of probiotics, adopt small frequent meals, plenty of fluids, avoid caffeine and alcohol, eat foods high in soluble fiber and use of fiber supplements, avoid lactose products in those who do not tolerate milk products etc. Of note, all of these modalities are based on individual physician's and patient's preference and severity of symptoms as none of these treatments has been evaluated in high-quality prospective studies.

Management of bowel related morbidity, prophylactic stoma formation and stoma reversal

Prevention and management of anastomotic leak

- Routinely applied protective stoma formation is not recommended to reduce risk of anastomotic leak in ovarian cancer patients with colorectal resection [III, B].
- Postoperative fasting does not prevent anastomotic leak and should not be recommended [III, B].
- Treatment of patients with gastrointestinal anastomotic leak should be assessed for conservative treatment with radiological and endoscopic interventional techniques if stable and appropriate. Those patients with extensive peritonitis through bowel content should be managed with reoperation, lavage, and repair and/or diversion [II, B].
- Endoscopic therapies, including self-expanding metal or covered stents, clips, glue, suturing, (alone or in combination), VAC systems could be considered as part of the management of gastrointestinal leak [III, C].
- Patients without symptoms but with incidentally detected small leaks/fistulas may be managed expectantly with close surveillance [III, C].

Stoma reversal and care

- Early versus delayed stoma reversal show comparable outcomes and timing should be chosen depending on patients-, surgery- and treatment related factors [III, B].
- Support by a dedicated stoma care team is recommended [V, B].

17 Antibiotic/microbiologic management and post-splenectomy management

17.1 Perioperative antibiotic prophylaxis

Optimal timing for administration of surgical antibiotic prophylaxis

Surgical antibiotic prophylaxis aims to the prevention of infectious complications through administration of an antimicrobial agent before exposure to bacterial contamination during surgery⁵⁴. Administration is therefore recommended to occur before the surgical incision. The half-life of the antibiotic, the underlying condition(s) of the individual patient (eg, body mass index, or renal or liver function), the time needed to complete the procedure and the protein binding of the antibiotic should be considered for timing, since successful prophylaxis requires delivery of the antimicrobial agent in effective concentrations to the operative site intravenously at the appropriate time to ensure adequate serum and tissue concentrations during the period of potential contamination⁴⁷⁵. Aim is the shortest effective period to minimize adverse effects and emergence of antibiotic resistance.

Low-quality evidence showed that the administration of surgical antibiotic prophylaxis after incision was associated with a significantly higher incidence of surgical site infection compared with administration before incision⁴⁷⁶⁻⁴⁸⁸. Moderate quality evidence showed that administration earlier than 120 min before incision was associated with a significantly higher prevalence of surgical site infection compared with administration within 120 min. Further comparisons of administration within 60 min before incision compared with 60-120 min, or within 30 min before incision compared with 30-60 min, showed no significant differences in the reduction of surgical site infections. On the basis of the available evidence, a more precise timing within this 120 min preoperative window before incision cannot be exactly defined. In general, administration should be closer to the incision time (<60 min before) for antibiotics with a short half-life, such as cefazolin and cefoxitin, and penicillins in general.

Postoperative routine surgical antibiotic prophylaxis

The preventive effect of the routine use of surgical antibiotic prophylaxis has long been recognized. However, the necessary duration of surgical antibiotic prophylaxis to achieve the desired effect has been a matter of debate. Most guidelines recommend maximum postoperative surgical antibiotic prophylaxis duration of 24 h, but increasing evidence shows that using only a single preoperative dose (and possible additional intraoperative doses depending on the duration of the operation) might be non-inferior. Despite this, surgeons still often routinely continue surgical antibiotic prophylaxis up to several days after surgery, which leads to serious concerns for the risk of antibiotic resistance.

A systematic review investigated whether prolonged surgical antibiotic prophylaxis in the postoperative period is more effective in reducing the risk of surgical site infections than perioperative prophylaxis (defined as a single dose before incision and possible intraoperative additional doses according to the duration of the operation)⁴⁸⁹. In total 69 randomized controlled trials were reviewed investigating the optimal duration of antibiotic prophylaxis in a variety of surgical procedures. The overall meta-analysis which pooled studies using any prolonged surgical antibiotic prophylaxis regimens, showed no benefit in terms of reducing the surgical site infection incidence compared with a single dose of antibiotic prophylaxis.

17.2 Post-splenectomy management

Ovarian cancer patients post-splenectomy are at a lifelong high risk for overwhelming infections with encapsulated bacteria (eg, *Streptococcus pneumoniae*), bloodborne parasites, and other infections that the spleen plays an important role in controlling. Key components of care for preventing such infections include patient and family education, vaccination against encapsulated bacteria and influenza, and low

threshold for antibiotic prophylaxis^{490,491}. Especially patient education has been associated with decreased rates of severe infections⁴⁹².

Post-splenectomy vaccination protocols

For protection against *S.pneumoniae* (pneumococcus), *H. influenza* type b, and *N.meningitidis* (meningococcus), ovarian cancer patients who have undergone splenectomy as part of their debulking require the following post-splenectomy vaccinations approximately 2 weeks after surgery (Table 1)^{491,493,494}. In regards to the timing with systemic chemotherapy; any vaccination should occur outside of the chemotherapy nadir which is usually expected 7-12 days post chemotherapy.

The 13-valent pneumococcal conjugate vaccine (PCV13) followed by the 23-valent pneumococcal polysaccharide vaccine (PPSV23) ≥ 8 weeks later. This should be repeated in 5 years.
The <i>H. influenzae</i> type b vaccine (Hib). No need for revaccination booster.
The quadrivalent meningococcal conjugate ACWY vaccine series (MenACWY). This should be repeated in 5 years.
The monovalent meningococcal serogroup B vaccine series (MenB-4C or MenB-FHbp).

Table 1. Post-splenectomy vaccination protocols

In addition to these vaccinations, post splenectomy patients should receive all routinely recommended age-appropriate vaccinations, including the annual vaccination against seasonal influenza virus, due to the increased risk of infection with *S. pneumoniae*. Splenectomy alone is not a contraindication for any other vaccination, including live vaccines. However, if additional immunocompromising conditions such as hematologic malignancies, immunosuppression under chemotherapy or HIV infection co-occur and can be contraindications to especially live vaccines.

Antibody responses to vaccination appear to be sufficiently protective in most post splenectomy patients but may be lower than in healthy persons⁴⁹⁵. In order to optimize the immune response, vaccinations should occur at least 2 weeks, and ideally 10 to 12 weeks, prior to splenectomy when possible. However, to realise this preoperative time frame in ovarian cancer patients is most of the times not feasible. Furthermore, due to the fact that we cannot predict with accuracy whether a splenectomy will be part of the debulking or not; most patients who will have had a splenectomy will end up being vaccinated rather two weeks after surgery and not before. Even in patients with clear splenic involvement at imaging, the spleen may not be removed if the rest of the disease is for example not fully operable and so the surgery is abandoned or it is often possible that lesions which are merely abutting the spleen are removed without associated splenectomy. Hence, an individualized approach should be followed whether vaccination should be performed before or after the operation, depending on the patients' profile and tumor dissemination patterns.

Post splenectomy patients should seek immediate medical care in suspect of sepsis or any animal bite. Dog bites, in particular, can transmit *Capnocytophaga canimorsus*, which can be rapidly progressive and fatal in patients with impaired splenic function. There are two main approaches regarding antibiotic prophylaxis in post splenectomy patients depending on their risk profile: routine daily antibiotic prophylaxis with Penicillin V 250 mg twice daily or Amoxicillin 500 mg twice daily or just empiric antibiotic treatment in case of fever and infection with Amoxicillin-clavulanate 875 mg/125 mg twice daily. Alternative antibiotic agents in case of intolerance or allergy, include Cephalexin, Cefdinir, fluoroquinolones (Levofloxacin) or a macrolide (eg, azithromycin or erythromycin). No matter the approach, post splenectomy patients should be provided with an emergency supply of antibiotics in case of acute infection, along with appropriate education about seeking medical advice when signs or symptoms of infection occur⁴⁹⁰⁻⁴⁹⁶.

The need for daily antibiotic prophylaxis and its duration is determined on an individual basis upon factors such as patient age, immune status, history of infections with encapsulated organisms, potential antibiotic side effects, local prevalence of antibiotic-resistant organisms, and patient values and preferences. Even though universal trend is to recommend daily antibiotic prophylaxis to asplenic or hyposplenic patients younger than 5 years of age, which of course does not apply in the ovarian cancer population, concurrent immunocompromising conditions, or history of sepsis caused by encapsulated bacteria, national guidelines vary substantially, since data supporting best practice are limited. The British guidelines for example recommend daily antibiotic prophylaxis for high-risk patients such as adults >50 years old, immunocompromised patients, and/or those with a history of sepsis⁴⁹⁷. In general an individualized decision-making approach is recommended for patients without high-risk features, where some experts recommend daily antibiotic prophylaxis only for 1-2 years post splenectomy due to the overall decline in incidence of pneumococcal disease⁴⁹³.

Antibiotic/microbiologic management and post-splenectomy management

Optimal timing for administration of surgical antibiotic prophylaxis

- Administration of surgical antibiotic prophylaxis is recommended in the 2 hours time window before surgical incision, while considering the half-life of the antibiotic [III, A].
- Repeat intraoperative dosing of the antibiotic prophylaxis should be performed depending on the half-life time of the antibiotic and the duration of the surgery [III, A].

Postoperative routine surgical antibiotic prophylaxis

- A routine prolonged surgical antibiotic prophylaxis after completion of the operation for the purpose of preventing surgical site infections is not recommended [III, A].
- In case of postoperative complications, antibiotic treatment should be considered depending on patients' clinical picture, biochemistry results, microbiological cultures, and previous treatments [III, B].

Post-splenectomy management

- All ovarian cancer patients post-splenectomy should receive vaccinations against *S. pneumoniae* (pneumococcus), *H. Influenzae* type b, and *N.meningitidis* (meningococcus) approximately 2 weeks after surgery [III, A].
- Annual vaccination against seasonal influenza virus is strongly recommended in post-splenectomy patients [III, A].
- Patient education regarding higher susceptibility to certain infections is strongly recommended in post-splenectomy patients, along with an emergency antibiotic supply in case of acute infection [III, A].

18 Postoperative pain management

18.1 Postoperative analgesia

Management of postoperative pain is an essential part of the peri-operative care of patients undergoing surgery for ovarian cancer. It is well established that optimal pain management improves the patient's experience and enhances recovery after surgery, for example by facilitating early mobilisation and establishment of enteral feeding, and may reduce the patient's length of stay. Analgesic techniques therefore form a key part of ERAS pathways.

The use of multi-modal analgesia in open abdominal surgery is well established⁴⁹⁸. This involves using several analgesics which target different nociceptive pathways, with the aim of reducing the requirement for opioids and therefore minimising their adverse effects such as reduced gastrointestinal mobility, postoperative nausea and vomiting, respiratory depression, sedation and urinary retention.

18.2 Systemic analgesia

Paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) are simple analgesics which have an opioid-sparing effect and are widely used in ovarian cancer surgery. Appropriate patient selection and dosing must be ensured to avoid hepatotoxicity with paracetamol, and nephrotoxicity and impaired platelet function with NSAIDs.

The N-methyl-D-aspartate receptor antagonist ketamine and magnesium may be used for pain relief in ovarian cancer surgery. Low dose ketamine has been shown to improve postoperative analgesia and reduce morphine consumption in major abdominal surgery, although the anaesthetist must be aware of its adverse psychomimetic effects including hallucinations⁴⁹⁹. Magnesium has also been shown in a meta-analysis to reduce postoperative pain and opioid consumption in patients undergoing a range of types of surgery⁵⁰⁰.

Pre-operative administration of gabapentinoids (gabapentin, pregabalin) has been shown in many clinical trials to reduce postoperative pain scores and opioid consumption, and there is also evidence that they might reduce the risk of development of chronic post-surgical pain^{501,502}.

The alpha-2 adrenoreceptor agonist clonidine exerts its analgesic effect by reducing central sympathetic outflow and noradrenaline release, inhibiting central and peripheral pain pathways, although its widespread clinical use is limited by hypotension⁵⁰³.

18.3 Non-neuraxial regional analgesia

Wound infiltration with local anaesthetic as part of a multimodal analgesia regimen is well described, but the main limitation is its short duration of action. In an attempt to prolong the duration of action, indwelling catheters that allow continuous infusion of local anaesthetic agents using elastomeric pumps have been developed. Wound infusion with local anaesthetic has been shown to produce a small reduction in pain intensity in patients undergoing gynaecological and obstetric surgery compared to placebo⁵⁰⁴.

The transversus abdominal plane block is a widely used technique in which local anaesthetic is placed bilaterally in the musculofascial plane between the internal oblique and transversus abdominis muscles, providing analgesia to the anterior abdominal wall from T10 to L1⁵⁰⁵. As transversus abdominal plane blocks only provide analgesia below the umbilicus, subcostal and rectus sheath blocks are adjuncts which can cover the upper abdomen. One major weakness of abdominal wall blocks is their short duration following a single injection of local anaesthetic; this may be prolonged with the use of infusion catheters.

In an attempt to prolong the duration of action of local anaesthetic drugs, liposomal bupivacaine has been developed which provides slow, sustained release of bupivacaine from multivesicular liposomes.

However, a recent review of 76 randomized controlled trials did not provide evidence to support the routine use of liposomal bupivacaine over standard local anaesthetics⁵⁰⁶.

18.4 Epidural/intrathecal analgesia

Epidural analgesia

Thoracic epidural analgesia remains the gold standard in patients undergoing major open abdominal surgery. It is well established that epidurals provide superior analgesia compared to systemic opioids for the control of postoperative pain, provided they are correctly inserted and managed^{507,508}. In addition, epidural analgesia may reduce pulmonary, cardiovascular and gastrointestinal complications after abdominal surgery⁵⁰⁹. A systematic review of epidural analgesia compared to systemic opioid-based analgesia in patients undergoing surgery showed that epidurals not only provided superior pain relief, but reduced the risk of respiratory depression, pneumonia, atrial fibrillation and supraventricular tachycardia, there was a decreased incidence of postoperative ileus and postoperative nausea and vomiting, accelerated return to normal bowel function, and mortality was reduced⁵¹⁰. Perioperative epidural use has also emerged as a potential prognostic factor in solid tumour malignancies. Epidural analgesia is thought to blunt the neuroendocrine and metabolic stress response to surgery, leading to decreased pro-tumorigenic cytokine and catecholamine release. In a retrospective analysis, Tseng *et al.* showed that perioperative epidural use in patients undergoing primary debulking surgery for advanced ovarian cancer was associated with improved progression-free survival and overall survival⁵¹¹. There are no prospective data validating this overall survival improvement.

A continuous epidural infusion of a mixture of low dose local anaesthetic and lipophilic opioids provides better analgesia than local anaesthetic alone⁵⁰⁷. Thoracic epidural analgesia should be initiated before surgery and continued in the intra- and postoperative period for up to 72 hours. Postoperative support from a dedicated acute pain team is important to troubleshoot issues and improve the efficacy of analgesia.

Epidural analgesia may be associated with adverse effects during the perioperative period. The most common problem is failure of the epidural as a result of incorrect placement, epidural catheter migration and/or suboptimal management⁵¹². Popping *et al.* found that this occurred in about 1 in 15 patients⁵¹⁰. Hypotension from sympathetic blockade may require increased fluid administration and/or require the use of vasopressors, motor block may delay mobilisation of the patient postoperatively and there is also a risk of urinary retention and pruritus. Although catastrophic permanent neurological complications such as vertebral canal haematoma and abscess formation are well described they are extremely rare⁵¹³.

A retrospective cohort study of 2,035 patients conducted using the American College of Surgeons' National Surgical Quality Improvement Program database, to identify the rate of postoperative complications after the use of epidural analgesia in women undergoing hysterectomy for gynecologic malignancy showed that the rate of 30-day complications and length of stay was higher for those women who received epidural analgesia, although there was no difference in 30-day mortality⁵¹⁴. Specific complications that were higher in the epidural group included: blood transfusion, wound disruption, surgical site infection, and delay in return of bowel function. Hospital length of stay was significantly longer, and readmissions were higher, in the epidural group compared to the no-epidural group, although there was no difference in 30-day mortality. The authors concluded that although epidural analgesia can provide a number of benefits when used for postoperative analgesia, the possible association with increased 30-day morbidity and hospital length of stay needs to be considered.

Intrathecal analgesia

Intrathecal or spinal analgesia is an effective and technically simple method of postoperative analgesia with a relatively low complication rate⁵¹³. Single-dose intrathecal morphine has been shown to produce effective analgesia following open abdominal surgery including for gynaecological malignancy and may reduce postoperative intravenous opioid requirements by up to six times⁵¹⁵⁻⁵¹⁹.

In addition to the analgesic effect, spinals have been shown to reduce the neuroendocrine and metabolic stress response to surgery, but only for the duration of the local anaesthetic⁵²⁰. Spinal analgesia has a lower side effect profile than epidural analgesia. For example, the patient is at less risk of postoperative hypotension from the sympathetic block induced by continuous epidural analgesia and may therefore require less intravenous fluids and/or vasopressors peri-operatively, and since the motor block wears off more quickly, the patient may be mobilised sooner after surgery⁵¹⁹. A study showed that length of stay following open gynaecological cancer surgery was significantly shorter following use of a single dose of intrathecal morphine compared to epidural analgesia⁵¹⁸. However, as intrathecal analgesia is a single injection technique, it has a shorter duration of action compared with epidural analgesia and the patient is likely to require systemic opioids in the postoperative period.

Commonly-used doses of intrathecal opioids are 300-500 µg diamorphine or 100-150 µg preservative-free morphine. The main concern of using intrathecal opioids is delayed respiratory depression (12 hours for diamorphine and 24 hours for morphine). Similar standards of monitoring of sedation and respiratory rate should therefore be used as for a patient using a patient-controlled analgesia pump.

Postoperative pain management

- **A multi-modal approach to postoperative analgesia including systemic and regional techniques should be used for ovarian cancer surgery [III, B].**
- **There is evidence that epidurals provide benefits in addition to analgesia and these should be considered [I, B].**
- **Prolonged use of opioids is not recommended [III, B].**

19 Perioperative thromboprophylaxis (pharmacological and mechanical) and management of postoperative thromboembolic events

To reduce and counterbalance the risks of thromboembolic events and bleeding, physicians must be aware of the distinct pharmacologic aspects of the different anticoagulants and antiplatelet drugs. Antiplatelet drugs belong to three different pharmacologic groups: (1) acetylsalicylic acid (aspirin), (2) thienopyrimidines (clopidogrel, prasugrel, ticlopidine) and (3) GPIIb/IIIa-antagonists (abciximab, tirofiban, eptifibatid). Aspirin has a serum half-life of less than 12 hours but irreversibly inhibits the enzyme cyclooxygenase of thrombocytes, permanently affecting their ability to synthesize thromboxan A2 and thus leading to an irreversible thrombocytic dysfunction. 50 to 75 mg aspirin is sufficient for a full antithrombotic effect. Recovery occurs about 7 days from the moment aspirin is stopped which is the time required for a sufficient production of new thrombocytes. While different NSAIDs can also affect thrombocyte function by interacting with their enzyme cyclooxygenase; their effect is reversible and limited by their half-life. Thienopyrimidines inhibit the ADP-mediated thrombocyte activation with a latency of hours and their effect usually decays within 5 days. GPIIb/IIIa-inhibitors inhibit the interaction of thrombocytes and fibrinogen which is the final step of thrombocyte activation. This is a reversible effect that decays with the substance's half-life.

On the plasmatic side of coagulation, warfarin and other vitamin K antagonists (VKA) inhibit the γ -carboxylation of different coagulation factors (II, VII, IX,X) and of anticoagulatory acting proteins (C, S, Z). In the initial phase of an anticoagulant treatment using VKA, there is an increased risk of thrombotic events due to the shorter half-life of protein C as compared to the half-life of factor II (50 hours). Moreover, due to the 50-hour half-life of factor II, VKA need some days to establish their full anticoagulatory effect, while INR values increase more rapidly due to an earlier decrease of factor VII levels. The individual half-life of different VKA affect the time for recovery of a patient's full coagulation potential from the moment that VKA are stopped. The range is between 3 to 5 days for warfarin and 5 to 7 days for phenprocoumon, but there is high interindividual variability.

Unfractionated heparin (UHF) and low-molecular weight heparins (LMWH) mainly inhibit coagulation by potentiating the ability of antithrombin III to covalently bind and inactivate activated thrombin (IIa) and factor Xa, thus inhibiting thrombin-formation and the thrombin-mediated final step of coagulation: the transformation of fibrinogen to fibrin. Unfractionated heparin (UFH) predominantly acts via factor IIa; has a short half-life of 1-2 hours but a difficult to predict dose-effect relation requiring dose monitoring by aPTT-measurement. It is inactivated by enzymatic degradation in the liver. Therapeutic doses (100 units/kg followed by 15-20 units/kg/h) are usually given intravenously and should result in a target aPTT-increase of about 100 to 150%. Prophylactic doses of UFH can be administered subcutaneously. Established regimens are 7,500 units twice daily or 5,000 units given every 8 hours. LMWH's have a more predictable anticoagulatory effect that involves mainly factor Xa; are administered subcutaneously in a fixed dose regimen in prophylactic, half-therapeutic and therapeutic doses, are (partially) eliminated from circulation by renal filtration, resulting in substantial accumulation in patients with renal impairment, and affect aPTT-measurements to a lesser degree. All these effects vary considerably between the different LMWHs and greatly depend on the LMWH's weight distribution curve.

DOACs act similarly to LMWHs, but bind directly to either factor Xa (rivaroxaban, apixaban, edoxaban) or IIa (dabigatran). Their mode of action is reversible, bypassing the need of antithrombin III for factor Xa or IIa inactivation, respectively. Anticoagulatory properties are reached within 2 to 3 hours after oral administration. aPTT and PT measurements are not useful to monitor the anticoagulatory effect, but the substances' predictable dose/effect relation makes monitoring dispensable in almost all situations. The half-life of dabigatran, rivaroxaban, apixaban and edoxaban is 7 to 14 hours, which is about 4-times longer than that of LMWHs (2-4 hours). Dabigatran is eliminated via the renal pathway by 80%, hence it is that only DOAK that requires a dose reduction when the creatinine clearance is less than 50 ml/min, while its

use is contraindicated in patients with a creatinine clearance below 30 ml/min. Rivaroxaban, apixaban and edoxaban are eliminated to a lesser degree via the renal pathway, and so can be safely administered till a creatinine clearance of 15 ml/min. As opposed to LMWH, DOACs carry no risk of heparin-induced thrombocytopenia.

19.1 Prophylactic anticoagulation in routine patients without thrombophilia or previous thrombosis

Abdominal surgery for cancer carries a high risk of venous thromboembolism and two double-blind, multicenter, placebo-controlled trials in patients undergoing planned curative open surgery for abdominal or pelvic cancer analyzed the optimal duration of postoperative thromboprophylaxis. In the prospective randomized phase III ENOXACAN II trial, patients received 40 mg enoxaparin daily for 6 to 10 days and were then randomly assigned to receive either enoxaparin or placebo for another 21 days⁵²¹. A total of 332 patients were included. VTE rates at the end of the double-blind phase were 12% in the placebo group and 4.8% in the enoxaparin group. The difference persisted at three months. There were no significant differences in the rates of bleeding or other complications during the interventional or follow-up periods. The FAME-study evaluated the efficacy and safety of thromboprophylaxis with 5,000 IU dalteparin administered for 28 days after major abdominal surgery compared to 7 days treatment. The first dose of dalteparin was administered on the evening prior to surgery, or a reduced dose of 2,500 IU was administered 2 hours prior to surgery and repeated 12 hours later. A total of 427 were randomized, and 343 reached an evaluable endpoint. The cumulative incidence of VTE was reduced from 16.3% with short-term thromboprophylaxis to 7.3% after prolonged thromboprophylaxis. Bleeding events were not increased through prolonged thromboprophylaxis⁵²². Even though no prospective randomized trials exist to compare pre- versus postoperative start of prophylactic anticoagulation, most randomized trials have started anticoagulation with LMWH the night before surgery. For that reason, most experts initiate prophylactic anticoagulation with LMWH the night before surgery.

A new prospective randomized trial evaluated the safety of DOACs for prophylactic postoperative anticoagulation in patients with gynecological cancer⁵²³. Postoperative bleeding- and VTE-rates were compared between apixaban versus enoxaparin as prophylactic postoperative anticoagulation during a 90-day follow-up period. Patients received 5,000 units unfractionated heparin sc 30 minutes before incision. Postsurgical care included 5,000 units of unfractionated heparin 3 times per day starting 6 to 8 hours after surgery until patients were deemed safe for randomization by the operating surgeon. Randomization had to occur within a maximal period of 7 days postoperatively. Postoperative major bleeding events, clinically relevant non-major bleeding and VTE events were an absolute contraindication for randomization. If epidural anesthesia was used, randomization occurred 8 hours after removal of the epidural catheter. Eligible patients were randomly assigned in a 1:1 ratio to 2.5 mg apixaban twice daily for 28 days or 40 mg enoxaparin once daily for 28 days. Four hundred women were enrolled and randomized. There were no statistically significant differences between the apixaban and enoxaparin groups in terms of rates of major bleeding events and clinically relevant non-major bleeding events. Even though the study was underpowered for the prevention of VTE, rates were slightly lower in the apixaban group, although the difference was not statistically significant.

19.2 Mechanical thromboprophylaxis

Intermittent pneumatic compression devices (IPC), graduated compression stockings (or else elastic stockings) and the venous foot pump represent the major mechanical methods of thromboprophylaxis and they contribute preventing thrombosis by stimulating the venous flow of the lower extremities and so avoiding venous stasis. Meta-analyses of smaller randomized trials of surgical patients across multiple specialties, have shown that IPC use is superior to no prophylaxis and to graduated compression stockings, and appear to offer additive benefit in combination with LMWH⁵²⁴⁻⁵²⁸.

The largest meta-analysis on 16,164 mostly surgical patients has identified IPC as an effective method to significantly reduce deep venous thrombosis (DVT) and pulmonary embolism (PE) compared to no prophylaxis without, however, any effect on mortality⁵²⁹. The addition of pharmacologic prophylaxis to IPC further reduced the risk of DVT, but had no effect on the incidence of PE. In a prospective study with 682 Korean patients with gastric adenocarcinoma and prophylaxis with IPC combined with LMWH the incidence of postgastrectomy VTE after was found to be 0.6% in the IPC + LMWH group, and mechanical methods are recommended in current clinical practice guidelines for VTE prophylaxis in high risk cancer patients undergoing surgery to improve efficacy over LMWH prophylaxis alone^{530,531}.

Major challenges with the IPC devices are compliance and appropriate fitting difficulties with common errors in their application resulting in lower efficacy. Moreover, IPC are contraindicated in those patients with skin leg conditions such as ischemia, skin ulceration etc like in peripheral arterial disease⁵³². Even though data about the optimal timing of mechanical prophylaxis are rather scarce, available evidence suggests applying the devices just before surgery and to continue until discharge. Occasional interruptions are allowed, but they devices should be reapplied when the patient is in seated or supine position^{524-529,532}.

19.3 Management of high risk patients with previous VTE already on anticoagulation (VKA, LMWH, DOACs)

The optimal perioperative management of patients receiving chronic anticoagulant therapy is anchored on four key principles: (1) risk stratification of patient-related and procedure-related risks of venous thromboembolism and bleeding, (2) the clinical consequences of thromboembolic or bleeding events, (3) pharmacokinetic properties of the various anticoagulants and (4) whether the risk reduction of VTE by bridging procedures outweighs the risk of bleeding increase. Several national and international societies have developed clinical guidelines to recommend on bridging of VKAs in patients on chronic anticoagulation due to previous/ recent VTE⁵³³⁻⁵³⁵.

Three bridging dose regimens have been studied extensively: (1) A high dose (therapeutic dose) heparin bridging regimen involves administering an anticoagulant dose that is similar to that used for the treatment of acute VTE (eg enoxaparin 1mg/kg twice daily or 1.5 mg/kg once daily; dalteparin 100 international units/kg twice daily or 200 international units/kg/day; tinzaparin 175 international units/kg/day; IV UFH to attain an aPTT 1.5 to 2 times the control aPTT). A low-dose (prophylactic dose) heparin regimen (2) involves administering a dose that is used to prevent postoperative VTE (eg enoxaparin 30-40 mg daily; dalteparin 5,000 international units daily; UFH 5,000-7,500 international units twice daily and (3) an intermediate-dose regimen of intermediate anticoagulation intensity between high- and low-dose regimens (eg enoxaparin 40mg twice daily). Most data are available for the therapeutic-dose regimen⁵³⁴.

Assessing risk for VTE during perioperative interruption of antithrombotic therapy is based largely on indirect evidence from studies outside the perioperative setting⁵³⁶⁻⁵³⁸. There is a clustering of recurrent VTE during the first 2 to 3 weeks after the start of any VTE treatment and therefore any dose interruptions or reductions during that period are to be strictly avoided unless absolutely necessary⁵³⁶. There is no difference in the rates of thromboembolic recurrence in patients with DVT versus PE, but recurrence is more likely to be fatal in patients who initially present with PE. Current guidelines of the American College of Chest Physicians assume a high recurrence risk in patients with a recent VTE in the last 3 months and in patients with VTE in the context of severe thrombophilia (eg protein C, protein S or antithrombin III deficiency, antiphospholipid syndrome or multiple abnormalities)⁵³⁴. In these patients, heparin bridging at a therapeutic level is recommended. In patients with VTE in the past 3 to 12 months or a moderate recurrence risk is assumed allowing heparin bridging at lower than therapeutic dose levels.

In cancer patients with newly diagnosed VTE, the VTE recurrence risk is 4% to 9% on anticoagulation with LMWH at therapeutic levels in the first 6 months with an absolute incidence of about 2% to 4% in the first month already⁵³⁹. In patients with proximal deep vein thrombosis and a recent VTE in need of

immediate ovarian cancer surgery therefore the use of IVCF should be considered in addition to bridging with LMWH or UFH at therapeutic doses. However, in those cases, other non-surgical alternatives such as neoadjuvant chemotherapy should be applied wherever possible, to reach a safer window to operate at a later time frame to allow anticoagulation to have been effective. Ideally, 3 months should elapse between VTE and cancer surgery.

In contradiction, a prospective cohort study demonstrated that the additional presence of inherited or acquired thrombophilia was not a significant predictor of the 3-month cumulative incidence of thromboembolism, major bleeding or mortality among chronically anticoagulated patients who had a temporary interruption of their chronic anticoagulation to undergo an invasive procedure. This applied also to those patients with severe thrombophilia, such as antiphospholipid syndrome⁵⁴⁰. However, in this study the majority of patients had experienced their VTE more than 3 months prior to their procedure.

Observational studies assessing LMWH bridging at therapeutic doses (i.e. 100 IU dalteparin/kg/twice daily) did not find an increased bleeding rate if the last dose of LMWH was given at least 12 hours before surgery^{541,542}. However, studies assessing anti-factor Xa levels found a detectable anticoagulant effect at surgery in more than 90% of patients who received their last LMWH dose around 12 hours before surgery with 34% of patients having still full therapeutic anti-Xa levels^{543,544}. Considering the extensive tissue defect of cytoreductive surgery in ovarian cancer, LMWH thus should be stopped at least 24 hours before surgery.

No studies have assessed the timing of interruption of IV UFH before surgery, but the dose-dependent elimination half-life of 30 to 120 minutes suggests that an infusion can be stopped 4 to 6 hours before surgery⁵⁴⁵.

Current guidelines of VTE treatment in patients with cancer suggest the use of LMWH and DOACs over VKAs for prolonged anticoagulation⁵³⁰. Most information on the management of patients on DOACs undergoing elective surgery and invasive procedures is from clinical trials for patients with nonvalvular atrial fibrillation receiving DOACs for stroke prophylaxis. In patients with high bleeding risk procedures and intermediate and high thromboembolic risk interruption of DOACs but no bridging with LMWH is suggested by guidelines⁵⁴⁶. Timing of stopping DOACs depends on their half-life; sufficient elimination requires 3 to 4 half-lives. The half-life of dabigatran, rivaroxaban, apixaban and edoxaban is 7 to 14 hours, which is about 4-times longer than that of LMWHs (2-4 hours). In patients with atrial fibrillation (and a glomerular filtration rate (GFR) > 50ml/min when receiving dabigatran) a bleeding risk of 0.9%-1.9% was found when apixaban, rivaroxaban or dabigatran were stopped 2 days prior to high bleeding risk interventions or 4 days prior to high bleeding risk interventions in patients receiving dabigatran with a GFR of 30-50 ml/min (PAUSE-trial)⁵⁴⁷.

Postoperative anticoagulation of patients with VTE should follow the recommendations for cancer-related VTE with LMWH at a 75% to 100% therapeutic level or DOACs for a total of 36 months as detailed in the section below.

19.4 Management of high risk patients with previous VTE not anymore on anticoagulation and in high risk patients with a thrombophilia but without previous VTE

In patients with a single recent VTE > 3 months but < 12 months ago the VTE might already have been cancer-associated and a moderate recurrence risk during ovarian cancer surgery is assumed. Perioperative VTE prophylaxis with LMWH at lower than therapeutic doses is recommended by different guidelines although clinical evidence is low⁵⁴³. We recommend a postoperative VTE prophylaxis with LMWH at at least a 50% therapeutic dose level for 28 days, provided there are no significant risk factors for bleeding.

In patients with a single recent VTE more than 12 months ago without thrombophilia, prophylactic pharmacological anticoagulation similar to routine patients without previous VTE is recommended. There is no data indicating that patients with inherited thrombophilia without previous VTE undergoing cancer surgery have an increased risk of VTE. These patients also should receive perioperative anticoagulation similar to routine patients without thrombophilia and previous thrombosis.

19.5 Bridging in patients on anticoagulation and/or antiplatelet drugs due to cardiovascular comorbidities: atrial fibrillation, biologic or mechanic valve replacement in mitral and aortic position, cardiac stents and stroke

Clinical guidelines recommending on bridging of VKAs in patients on anticoagulation because of atrial fibrillation, valve replacement, cardiac stents and strokes have been addressed by numerous national and international societies^{534,535}.

Nonvalvular atrial fibrillation

The risk of thromboembolic events in nonvalvular atrial fibrillation is assessed by specific scoring systems^{548,549}. Most widely used is the CHADS₂-Score, which includes the five predispositions (1) chronic heart failure, (2) arterial hypertension, (3) age > 75 years, (4) diabetes mellitus and (5) previous stroke on a 6-point scale with one point for each predisposition and two for a previous stroke⁵⁵⁰. The predicted risk of thromboembolic events is between 1.9%/year and 18.2%/year for patients with 0 and 6 points, respectively, while a high, moderate, or low risk for arterial thromboembolism and valve thrombosis refers to > 10%/year, 5% to 10%/year and < 5%/year.

Nonvalvular atrial fibrillation. patients receiving VKAs

The 3-month cumulative incidence of thromboembolism, bleeding, and death among patients with nonvalvular atrial fibrillation on chronic anticoagulation therapy with VKA with an intermediate and low CHADS₂-Score was analyzed in a prospective cohort study of 345 patients with AF that underwent 386 procedures. Patients receiving LMWH bridging were more likely to have prior thromboembolism and a higher CHADS₂-Score. Neither bleeding nor TE rates (1.1%) differed by anticoagulant management strategy suggesting that it might be safe to temporarily interrupt anticoagulant therapy with VKAs without the need of bridging anticoagulation in selected patients⁵⁵¹.

Observational studies including patients at high risk for thromboembolism typically applied bridging of VKA with LMWH at therapeutic doses. This bridging regimen was associated with a 1%-2% incidence of arterial thromboembolism^{542,543,551-554}. Bridging of high-risk patients with UFH at therapeutic doses was associated with a 0% to 5% incidence of arterial thromboembolism, but this data predominantly is based on patients requiring anticoagulation because of mechanic heart valves^{552,555,556}.

The BRIDGE trial addressed the question whether no-bridging would be noninferior to bridging with LMWH for the prevention of perioperative arterial thromboembolism in patients with atrial fibrillation on chronic anticoagulation with VKA in a randomized, double-blind, placebo-controlled clinical trial⁵⁵⁷. Patients with a recent stroke in the last 3 months had been excluded. After perioperative interruption of warfarin therapy, patients were randomly assigned to receive bridging anticoagulation therapy with dalteparin (100 IU/kg twice daily) or matching placebo from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. 1,884 patients were enrolled, with 950 assigned to receive no bridging therapy and 934 assigned to receive bridging therapy. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group. The incidence of major bleeding was 1.3% in the no-bridging group and 3.2% in the bridging group. The mean CHADS₂-Score was 2.3 with 38.3% of patients that had a CHADS₂-Score of 3 or higher. Only a few patients had a CHADS₂-Score of 5 or 6. Patients in whom arterial thromboembolism occurred had a mean CHADS₂-Score of 2.6. The median time to an arterial thromboembolism event after the procedure was 19.0 days.

The findings impressively show that the perioperative risk of arterial thromboembolism in patients with atrial fibrillation during interruption of warfarin treatment has been considerably overstated and that anticoagulation can safely be stopped perioperatively in most patients with a CHADS₂ score ≤ 4 .

Nonvalvular atrial fibrillation. patients receiving DOACs

Clinical trials for patients with nonvalvular atrial fibrillation receiving DOACs for stroke prevention included several patients that required temporary interruption of the study drug due to surgery. The RE-LY randomized trial compared dabigatran (150 mg or 110 mg twice daily) with warfarin (INR 2.0-3.0) in 18,113 patients with atrial fibrillation with a median CHADS₂-score of 2.1. 4,591 patients required therapy interruption for a surgery/procedure and a preprocedural dabigatran interruption protocol had been introduced during the trial based on the procedure bleeding risk and patient renal function⁵⁵⁸. Procedures included pacemaker/defibrillator insertion (10.3%), dental procedures (10.0%), diagnostic procedures (10.0%), cataract removal (9.3%), colonoscopy (8.6%), and joint replacement (6.2%). The rates of thromboembolism and bleeding were 0.5% and 3%, respectively, and were not significantly different between the treatment arms. The ROCKET AF trial compared 20 mg rivaroxaban once daily with warfarin (INR 2.0-3.0) in 14,264 patients with atrial fibrillation with a median CHADS₂-score of 3.4. 2,997 patients required therapy interruption for a surgery/procedure⁵⁵⁹. In most patients, rivaroxaban therapy was stopped at least 3 days preprocedure. The median duration of treatment interruption was 5 days. Only 6% (N=483) involved bridging therapy. Stroke/systemic embolism rates during the at-risk period were similar in rivaroxaban-treated and warfarin-treated participants. Risk of major bleeding during the at-risk period was also similar in rivaroxaban-treated and warfarin-treated participants (0.99% versus 0.79% per 30 days). The ARISTOTELE trial compared 5 mg apixaban twice daily with warfarin in 18,201 patients with atrial fibrillation with a median CHADS₂-score of 2.1. 4,692 patients required surgery/procedure⁵⁶⁰. In 62.5% of these the study drug was interrupted. Stroke/systemic embolism rates during the at-risk period were similar in both treatment groups. However, patients in whom therapy was interrupted had significant lower rates of stroke/systemic embolism and major bleeding than patients who continued to receive the study drug. Patients receiving apixaban had similar rates of major bleeding whether or not they had treatment interruption.

The PAUSE trial analyzed the timing of stopping DOACs in 3,007 patients with atrial fibrillation. Apixaban, rivaroxaban or dabigatran (patients were required to have a GFR > 50ml/min when receiving dabigatran) were stopped 2 days prior to high bleeding risk interventions or 4 days prior to high bleeding risk interventions in patients receiving dabigatran with a GFR of 30-50 ml/min. DOACs were resumed the second day after the intervention⁵⁴⁷. The risk for severe bleeding within 30 days was 1.35% for apixaban, 0.9% for dabigatran and 1.85% for rivaroxaban. 0.16% of patients receiving anticoagulation with apixaban, 0.60% of patients on dabigatran and 0.37% of patients on rivaroxaban had an arterial embolic event.

Patients with replaced cardiac valves

In patients with mechanical cardiac valves anticoagulation greatly depends on the type of valve and position. A high, moderate, or low risk for arterial thromboembolism and valve thrombosis refers to > 10%/year, 5% to 10%/year and < 5%/year risk, respectively, in the absence of anticoagulation. Patients receiving oral anticoagulation with VKA with a target INR of 2.5 to 4.5 for valve replacement with the St. Jude Medical device showed a linearized incidence of 0.75 thromboembolic events per 100 patient-years, of which 0.32% per patient year were minor, 0.15% per patient-year were moderate, and 0.28% per patient-year were severe. Thromboembolism following aortic valve replacement was significantly lower than after mitral valve replacement⁵⁶¹. A meta-analysis of 46 studies including 13,088 patients studied for 53,647 patient-years found an incidence of major embolism in the absence of antithrombotic therapy of 4 per 100 patient-years⁵⁶². With antiplatelet therapy this risk was 2.2 per 100 patient-years, and with coumarin therapy it was reduced to 1 per 100 patient-years. Mitral valve replacement increased the risk almost twice as compared to the aortic position. Tilting disc valves and bileaflet valves showed a lower

incidence of major embolism than caged ball valves. Although not validated prospectively, a high risk for arterial thromboembolism and valve thrombosis is assumed for any mechanical mitral valve prosthesis, any caged-ball or tilting disc aortic prosthesis and in all patients with mechanical heart valve replacement and a stroke within the recent 6 months. A moderate risk for arterial thromboembolism and valve thrombosis is assumed for bileaflet aortic valve prosthesis in the presence of at least one more risk factor (arterial fibrillation, prior stroke, hypertension, diabetes mellitus, congestive heart failure, age > 75 years), while a low risk is assumed for bileaflet aortic valve prosthesis without any of these risk factors⁵³⁴. In observational studies bridging of high-risk patients with therapeutic-dose UFH IV was associated with an incidence of 0-5% for arterial thrombotic events. Bridging of high-risk patients with therapeutic doses of LMWH showed an incidence of 1-2% for arterial thrombotic events, and the American College of Chest Physicians summarized the recommendations in their current evidence-based clinical practice guidelines⁵³⁴.

Patients on long-term aspirin medication and patients with cardiac stents

Despite evidence for the benefit of aspirin for secondary prevention, it is often discontinued in the perioperative period due to the risk of bleeding. A randomized, double-blind, placebo-controlled trial compared the effect of low-dose aspirin with that of placebo on myocardial damage, cardiovascular, and bleeding complications in high-risk patients undergoing non-cardiac surgery⁵⁶³. Aspirin (75 mg) or placebo was given 7 days before surgery and continued until the third postoperative day. Twelve patients (5.4%) had a major adverse cardiac event during the first 30 postoperative days. Two of these patients (1.8%) were in the aspirin group and 10 patients (9.0%) were in the placebo group ($p = 0.02$). Hence, treatment with aspirin resulted in a 7.2% absolute risk reduction for postoperative major adverse cardiac events. The relative risk reduction was 80%. Even though the study was not powered to evaluate bleeding complications, no significant differences were seen between the two groups.

An earlier meta analysis of 40,590 patients of whom 14,981 were on long-term aspirin medication prior to surgery, found that perioperative continuation of aspirin multiplied the overall bleeding risk by factor 1.5, but did not lead to a higher level of the severity of bleeding complications requiring medical therapeutic intervention⁵⁶⁴.

There are no randomized trials comparing different perioperative management strategies in patients with coronary stents and there is substantial uncertainty about whether the potential benefits of continuing dual platelet therapy outweigh the likely increased risk for bleeding. Indirect evidence from the non-perioperative setting indicates that premature discontinuation of dual antiplatelet therapy within 6 weeks of bare-metal stent placement or within 3 to 6 months of drug-eluting stent placement, increases the risk of stent thrombosis. In a retrospective study of 899 patients with bare-metal stent the frequency of major adverse cardiac events was 10.5% when non-cardiac surgery was performed less than 30 days after bare-metal stent placement, 3.8% when non-cardiac surgery was performed between 31 and 90 days after bare-metal stent placement, and 2.8% when non-cardiac surgery was performed more than 90 days after bare-metal stent placement⁵⁶⁵. In 600 surgeries on 481 patients with a mean time from drug-eluting stent placement to surgery of 1.1 ± 0.9 years the incidence of stent thrombosis was 2% and the incidence of a combined endpoint of 30-day post-operative risk of death, nonfatal myocardial infarction or stent thrombosis was 9%. The incidence of the combined endpoint decreased with time during the first 6 months after drug-eluting stent placement⁵⁶⁶. However, a single center retrospective trial from the Mayo clinic found a major cardiac adverse event rate of about 6% throughout the first year after drug-eluting stent placement in a total of 520 patients that underwent non-cardiac surgery within 2 years after drug eluting stent placement. Characteristics found to be associated with major cardiac adverse events in univariate analysis were advanced age, emergent surgery, shock at time of coronary intervention, previous history of myocardial infarction, and continuation of ticlopidine or clopidogrel into the preoperative period. The rate of transfusion seemed to be associated with antiplatelet therapy use⁵⁶⁷.

19.6 Management of postoperative VTE events

There is no difference in the treatment regimens of incidentally detected, asymptomatic VTE (PE or DVT) and symptomatic VTE. Patients with cancer-associated VTE are at a substantial risk of thromboembolic recurrence and should therefore receive prolonged anticoagulation for at least 6 months. A benefit/risk assessment at least every 3 months is required beyond these initial 6 months in all cancer related VTE. Anticoagulation beyond the initial 6 months should be offered to selected patients with still active cancer, especially those with metastatic disease and active treatment. Anticoagulation regimes include LMWH, DOACs or to a lesser degree VKA.

Patients with cancer have a substantial risk of recurrent thrombosis despite the use of anticoagulant therapy using VKA, and several prospective clinical trials evaluated the efficacy of a LMWHs with that of VKA in preventing recurrent thrombosis in that setting⁵⁶⁸⁻⁵⁷². The most important ones are the CLOT trial using dalteparin at a 75% therapeutic level for a prolonged anticoagulation of six months after initial full therapeutic doses of dalteparin for 1 month and the CATCH trial using a full therapeutic dose of tinzaparin (175 mg/kg/day) for 6 months^{569,572}.

In the CLOT trial patients with solid cancers who had acute, symptomatic proximal DVT, PE, or both were randomly assigned to receive dalteparin at a dose of 200 IU per kilogram of body weight subcutaneously once daily for five to seven days and a coumarin derivative for six months (target international normalized ratio, 2.5) or dalteparin alone for six months (200 IU per kilogram once daily for one month, followed by a daily dose of approximately 150 IU per kilogram for five months)⁵⁶⁹. Symptomatic VTE occurred in 27/336 patients in the dalteparin group and 53/336 patients in the VKA group. The Kaplan-Meier estimate of the probability of recurrent thrombosis at six months was 9% with LMWH and 17% with VKAs. Both Kaplan-Meier curves showed a plateau after 3 to 4 months with more than 50% of events occurring in the first 30 days in the warfarin group and more than 50% events occurring in the first 60 days in the dalteparin group. All recurrent DVT events were proximal. Of the 53 VTE events in the oral-anticoagulant group, 20 occurred when the INR was below 2.0. There was no significant difference between the dalteparin group and the oral-anticoagulant group in the rate of major bleeding or any bleeding.

The CATCH trial is the largest and most thoroughly planned trial comparing a 1:1 randomized treatment of 6 months with tinzaparin (175 mg/kg/day) to 6 months of warfarin with a target INR of 2.0 to 3.0 after an initial phase of tinzaparin at a dose of 175 mg/kg/day for 5 to 10 days in 900 patients with symptomatic VTE and active cancer⁵⁷². Patients were stratified according to tumor characteristics, the presence of metastasis, recurrent versus first VTE and region. Recurrent VTE occurred in 31/449 patients treated with tinzaparin and 45/451 patients treated with warfarin. More than half of the events had occurred in the first 60 days of treatment in both groups. There were no differences in major bleeding or overall mortality, but a significant reduction in clinically relevant non-major bleeding with tinzaparin.

LMWH monotherapy for the initial 6 months thus is considered a standard of care for the acute and long-term management of cancer associated thrombosis with a risk reduction for recurrent VTE of 44% with LMWH in the five randomized trials addressing this issue⁵³⁹. Dabigatran, rivaroxaban, apixaban and edoxaban became standard of care in the treatment of patients with VTE, but respective licensing trials included low numbers of patients with cancer and all used VKA in the comparator arm. However, a systematic review and meta-analysis of these trials found a lower VTE relapse rate for patients with cancer in the DOAC arms⁵⁷³.

The HOKUSAI VTE cancer trial was the first noninferiority trial that randomly assigned patients with cancer who had acute symptomatic or incidental VTE to receive either LMWH for at least 5 days followed by oral edoxaban at a dose of 60 mg once daily or subcutaneous dalteparin at a dose of 200 IU/kg once daily for 1 month followed by dalteparin at a dose of 150 IU/kg once daily⁵⁷⁴. Treatment was given for at least 6 months and up to 12 months. Recurrent venous thromboembolism occurred in 41/522 patients

(7.9%) in the edoxaban group and in 59/524 patients (11.3%) in the dalteparin group. Major bleeding occurred in 36/522 patients (6.9%) in the edoxaban group and in 21/524 patients (4.0%) in the dalteparin group. This difference was mainly due to the higher rate of upper gastrointestinal bleeding with edoxaban, which mainly occurred in patients with gastrointestinal cancer.

The SELECT-D trial randomly assigned 203 patients with active cancer who had symptomatic or incidental PE, or symptomatic lower-extremity DVT to rivaroxaban (15 mg twice daily for 3 weeks, then 20 mg once daily for a total of 6 months) or dalteparin (200 IU/kg daily during month 1, then 150 IU/kg daily for months 2-6)⁵⁷⁵. The primary outcome was VTE recurrence over 6 months. Safety was assessed by major bleeding and clinically relevant nonmajor bleeding. Twenty-six patients experienced recurrent VTE (dalteparin, n = 18; rivaroxaban, n = 8). The 6-month cumulative VTE recurrence rates and the 6-month cumulative rates of major bleeding were not significantly different among groups.

The ADAM-VTE trial randomly assigned 300 patients with cancer-associated VTE to apixaban 10mg twice daily for seven days followed by 5mg twice daily for 6 months or dalteparin 200 IU/kg daily during month 1 followed by 150 IU/kg daily for months 2-6⁵⁷⁶. 66% of patients had metastatic disease and 74% were receiving concurrent chemotherapy. Recurrent VTE was significantly higher in the dalteparin group than in the apixaban group. Major bleeding occurred in 0% of 145 patients receiving apixaban, compared with 1.4% of patients receiving dalteparin. Major bleeding or clinically relevant non-major bleeding rates were 6% for both groups.

Initial anticoagulation of patients with cancer-associated VTE thus includes apixaban, rivaroxaban or LMWH at therapeutic doses as a safe and effective treatment option based on results of multiple randomized clinical trials. Initial anticoagulation should be followed by LMWH at a 75% to 100% therapeutic dose level or by apixaban, rivaroxaban or edoxaban for up to 12 months. There is no role of oral anticoagulation using VKA in cancer patients in the first 12 months and only a very limited one thereafter.

19.7 Spinal/epidural anesthesia and anticoagulation

Concerns exist about the risk of neurological damage from compressive vertebral canal haematoma when central neuraxial blockade (spinal or epidural) is performed in a patient receiving antithrombotic drugs. Vertebral canal haematoma is a rare but potentially devastating complication and permanent neurological injury is likely unless it is rapidly diagnosed and treated. The Royal College of Anaesthetists national audit of major complications of central neuraxial blockade showed that the incidence of permanent harm from vertebral canal haematoma was approximately 1 in 20,000 for peri-operative epidurals and 1 in 140,000 for all types of central neuraxial blockade⁵¹³. Of the eight reported cases of vertebral canal haematoma, seven had received an antithrombotic drug around the time of epidural catheter insertion or removal. A number of countries have developed clinical guidelines to recommend “safe” time intervals between antithrombotic drug administration and performing central neuraxial blockade⁵⁷⁷⁻⁵⁷⁹. Spinal/epidural anesthesia is not recommended in patients with abnormal clotting or platelet/clotting disorders.

19.8 Indications and contraindications for insertion of an inferior vena cava filter

The indications of inferior vena cava filter placement have evolved over the last years by becoming more restricted due to the well recognized complications and long-term harm effects by an often-questionable benefit. Moreover, perioperative inferior vena cava filter placement may be associated with increased risk of hematogenous distant metastasis and decreased survival⁵⁸⁰. For that reason, the most recent ASCO guidelines do not recommend the insertion of an inferior vena cava filter with established or chronic thrombosis (more than 4 weeks ago), nor to patients with temporary contraindications to anticoagulant therapy such as surgery⁵³⁰. Moreover, there is no role for inferior vena cava filter insertion for primary prevention or prophylaxis of pulmonary embolism or deep venous thrombosis in high risk patients. A postoperative color-Doppler ultrasound examination of the lower limbs is rather encouraged in the early

postoperative period to assess status of a preexisting thrombus, since 50% of venous thrombo embolisms occur within 24 hours after surgery and an overall of 75% within 72 hours⁵⁸¹.

Only two randomized trials have addressed the value of inferior vena cava filter^{582,583}. It was demonstrated that in high-risk patients with proximal DVT, the initial beneficial effect of inferior vena cava filter for the prevention of PE gets counterbalanced by an excess of recurrent DVT, without any difference in mortality. Furthermore, among hospitalized patients with severe acute PE, the additional use of a retrievable inferior vena cava filter did not reduce the risk of symptomatic recurrent PE at 3 months compared with anticoagulation alone.

There is no evidence that free-floating thrombi are associated with a higher incidence of venous thromboembolism than thrombi which are adherent to the inferior vena cava. Moreover, most VTE had already occurred when the free-floating deep venous thrombosis is detected⁵⁸⁴. For that reason, there is no indication of a routine prophylactic inferior vena cava filter placement in this scenario.

In patients with a fresh deep venous thrombosis (diagnosis less than 4 weeks, particularly if femoro-popliteal or iliac) and/or venous thromboembolism, (particularly if symptomatic or with hemodynamic impairment or located in proximal pulmonary arteries) and a concomitant clear contraindication of anticoagulant therapy such as major bleeding diathesis (e.g., coagulation defects, severe thrombocytopenia [platelet count < 50,000/ μ l]), hemorrhagic stroke, recent or planned major surgery with persistent bleeding risk that can't be postponed, or active bleeding, inferior vena cava filter has a value and should be considered⁵⁸⁵. However, as discussed previously, cytoreductive ovarian cancer surgery should be - if possible - delayed in the setting with the use for example of neoadjuvant chemotherapy, to avoid high morbidity in terms of bleeding and thromboembolic events.

A further accepted indication is a DVT extension/ new VTE or recurrent DVT- without PE - despite adequate anticoagulant therapy and appropriate escalation^{530,586}. Due to the increased risk of caval thrombosis after inferior vena cava filter implantation, anticoagulation should be resumed in patients with an inferior vena cava filter once contraindications to anticoagulation or active bleeding complications have resolved⁵⁸⁷.

19.9 Types of inferior vena cava filter

Modern inferior vena cava filter can be classified into two categories: permanent and retrievable inferior vena cava filters. Permanent inferior vena cava filters are percutaneously placed intracaval filtration devices that trap migrating venous thromboemboli and prevent venous thromboembolism while allowing caval flow-through. As opposed to permanent inferior vena cava filters, retrievable inferior vena cava filters are designed with features that permit percutaneous removal if and when the risk of VTE resolves. It is important to note that all retrievable inferior vena cava filters have FDA and CE approval for permanent use. Current retrievable inferior vena cava filters are considered equivalent to definitive ones for long term efficacy, and should be employed as first option⁵⁸⁸. A permanent inferior vena cava filter could be considered in patients with limited life expectancy or long-term contraindication to anticoagulation.

The optimal timing for retrievable inferior vena cava filter removal is not always easy to determine. Average successful removal rates of 41.6% have been reported. Patients who receive retrievable inferior vena cava filter should be evaluated periodically for filter retrieval within the specific filter's retrieval window ideally within a multidisciplinary and systematic follow-up protocol to optimize filter retrieval rates⁵⁸⁹.

19.10 Value of cava filter implantation in case of lower limb DVT related to tumor compression/infiltration

No evidence is reported in literature. If in the surgical planning the ligation of the iliac veins is expected there is no need for inferior vena cava filter implant; however, in the case of a large thrombus extending above the lesion into the common iliac and/or vena cava axis, the filter implantation may be considered as a reasonable indication, if surgery cannot be delayed, for example via neoadjuvant chemotherapy, till the thrombus gets resolved/treated by effective anticoagulation. A multidisciplinary approach is here strongly recommended (surgeon, hematologist, and interventional radiologist).

Perioperative thromboprophylaxis (pharmacological and mechanical) and management of postoperative thromboembolic events

Prophylactic anticoagulation in routine patients without thrombophilia or previous thrombosis

- Patients undergoing cytoreductive surgery for ovarian cancer, without additional risk factors such as thrombophilia or prior thromboembolic events, should receive prolonged postoperative thromboprophylaxis with LMWH at prophylactic doses for 28 days [I, A].
- Perioperative mechanical thromboprophylaxis should be considered in addition to pharmacological thromboprophylaxis [IV, B].
- Postoperative thromboprophylaxis with 2.5 mg apixaban twice daily for up to 28 days after ovarian debulking procedures, could be considered as an equally effective alternative to the traditional thromboprophylaxis with prophylactic doses of LMWH in low risk ovarian cancer patients [II, A].

Management in high risk patients with previous VTE already on anticoagulation (VKA, LMWH, DOACs)

- In patients with recent VTE in the last 3 months, there is a high risk of VTE recurrence, requiring bridging of VKAs with heparin/LMWH at therapeutic doses [IV, B].
- In patients with recent VTE in the last 3-12 months, there is a moderate risk of VTE recurrence, allowing bridging of VKAs with heparin/LMWH at lower than therapeutic doses, for example in half therapeutic dose [IV, B].
- Therapeutic doses of LMWH should not be resumed sooner than 48 hours after surgery [III, A].

Management in high risk patients with previous VTE not anymore on anticoagulation and in high risk patients with a thrombophilia but without previous VTE

- Patients undergoing cytoreductive surgery for ovarian cancer with a previous VTE who are no longer on anticoagulation and patients with non-severe thrombophilia without previous VTE should receive preoperative (evening before surgery) and prolonged postoperative thromboprophylaxis for 28 days with LMWH at prophylactic doses similar to routine patients without thrombophilia or previous thrombosis [V, C].
- Patients with severe thrombophilia and previous VTE are already on long term anticoagulation and should be managed with bridging as per instructions above [V, B].

Bridging in patients on anticoagulation and/or antiplatelet drugs due to cardiovascular comorbidities: atrial fibrillation, biologic or mechanic valve replacement in mitral and aortic position, cardiac stents and stroke

- In patients at high risk for cardiovascular events due to for example previous ischemic heart disease, stents, or cerebrovascular disease who are receiving antiplatelet monotherapy with aspirin and require ovarian cancer surgery, aspirin should be continued peri- and intraoperatively [II, B].
- In patients at low risk for cardiovascular events who are receiving antiplatelet monotherapy with aspirin, aspirin should be stopped 7 to 10 days before ovarian cancer surgery [III, B].
- Surgery under dual antiplatelet therapy is not recommended [IV, C].

Management of postoperative VTE events

- Initial anticoagulation for cancer-associated VTE should be treated with UFH or LMWH at full therapeutic doses, or rivaroxaban (15 mg twice daily for 3 weeks) or apixaban (10 mg twice daily for 7 days). LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation in patients who do not have severe renal impairment (GFR <30 ml/min) [I, A].
- Edoxaban (60 mg once daily starting at day 5), or rivaroxaban (15 mg twice daily for 3 weeks followed by 20 mg once daily) or apixaban (10 mg twice daily for 7 days followed by 5 mg twice daily) can be used as a safe alternative to 75%-100% therapeutic dose of LMWH for prolonged anticoagulation of patients with cancer-associated VTE [I, A].

Spinal/epidural anesthesia and anticoagulation

- At least 12 hours should elapse after the last prophylactic dose of low-molecular-weight heparin before performing a spinal or epidural, or removing an epidural catheter [V, A].
- Therapeutic doses of LMWH should be discontinued at least 24 hours before performing a spinal or epidural, or removing an epidural catheter [V, A].
- Low dose aspirin (≤ 100 mg) is not a contraindication for spinal/epidural anesthesia [V, A].

Indications and contraindications for insertion of an inferior vena cava filter

- Routine prophylactic preoperative inferior vena cava filter placement is not recommended in patients at high risk for thrombosis such as history of thromboembolism or thrombophilia outside of specific indications [III, B].
- Retrievable inferior vena cava filters should be employed as first option over permanent ones, due to equivalent long-term efficacy and additional option of retrieval [IV, B].

20 Wound considerations/complications

20.1 Prophylaxis of impaired wound healing

Common practice for care of surgical incisions includes typically covering with a dry dressing that is held in place by an adhesive for the first 48 hours. This initial postoperative dressing can then be removed, provided the wound is dry⁵⁹⁰.

Implementation of an established surgical site infection reduction bundle is recommended to significantly decrease surgical site infection rates. A perioperative surgical site infection reduction bundle consisting of patient education, preoperative showering (with bar soap or 4% chlorhexidine), intraoperative normothermia, perioperative antibiotic administration, 2% chlorhexidine gluconate and 70% isopropyl alcohol coverage of incisional area, antibiotic redosing 3-4 hours after incision, sterile closing tray and staff glove change for fascia and skin closure, dressing removal at 24-48 hours, dismissal with 4% chlorhexidine gluconate, and follow-up nursing phone call, have been shown to significantly reduce surgical site infections. The surgical site infections relative risk reduction was 77.6% among ovarian cancer with bowel resection, 79.3% among ovarian cancer without bowel resection, and 100% among uterine cancer achieving an overall relative risk reduction of surgical site infection of 82.4%^{591,592}. There is no evidence to suggest that use of any particular wound dressing over a closed surgical wound has any effect on the rate of surgical site infection⁵⁹³.

A single-centre, single-blind prospective, randomized controlled trial of 456 elective laparotomies found demonstrated that a wound irrigation with 0.04% polyhexanide solution reduced surgical site infection rate compared with saline irrigation⁵⁹⁴. Special attention should be given to patients after targeted therapies and perform a comprehensive wound healing assessment to prevent and adequately manage potential wound healing complications.

20.2 Wound care in high risk patients

Frailty, obesity, medical comorbidities such as diabetes and polypharmacy are well established risk factors for impaired wound healing post surgery highlighting the need of identifying high risk surgical population^{595,596}. Patients with a higher risk profile for wound complications may benefit from a prophylactic subcutaneous wound drainage, especially when large potential dead spaces are created (ie, extensive sheeth mobilisation for hernia repair) to avoid creation of subcutaneous collections, seromas and haematomas that might lead to a wound breakdown⁵⁹⁷. Still, there is no clear systematic evidence that the use of subcutaneous closure for non-cesarean laparotomy reduces the risk of surgical site infections⁵⁹⁸. Meticulous attention to control of subcutaneous bleeding may additionally help prevent wound seroma, hematoma, infection or wound disruption, especially in obese patients⁵⁹⁹⁻⁶⁰¹.

Closed suction drain systems are preferred in the subcutis since they can achieve lower wound infection rate than Penrose wound drain⁶⁰². While the studies of cesarean section did not show any benefit; the series on gynecological surgery is controversial because of several different confounding factors and also only a few patients had a gynecological cancer⁶⁰³. A subcutaneous negative-pressure drain prevents wound dehiscence following a midline incision in obese patients undergoing extensive cytoreductive surgery. In the literature there are at least 3 randomized controlled trials regarding subcutaneous drains including both benign and malignant gynecologic patients with controversial results^{599,604,605}. Two randomized controlled trials published by Gallup *et al.* and Cardosi *et al.* did not show any benefit for the drain group contrary to the randomized controlled trial conducted by Panici *et al.* which showed benefit for overall wound complications and hospital stay^{599,604,605}. The drains were removed when the drainage was less than 50 ml/day, and the skin was closed by stapler in the former studies in contrast to the study published by Panici *et al.* in which the drains have remained *in situ* until the daily drainage is less than 20 ml and the skin is closed by a subcuticular method. A common belief that the drains may increase the wound infection is a complete surgical dogma, as demonstrated in several studies⁶⁰⁶⁻⁶⁰⁸.

Kim *et al.* evaluated a mixed group of general gynecologic and oncologic cases, and reported significantly better healing with a subcutaneous negative pressure drain in cancer patients⁶⁰³. This superiority remained significant after multivariate analysis with a shorter hospital stay. They have proposed that closed suction drains may be beneficial for obese advanced stage ovarian cancer patients who underwent long and complex surgical procedures. Further evidence investigating the value of negative pressure drains after cytoreductive surgery for ovarian cancer, has reported a lower rate of wound infection by comparing 163 patients with a drain to 37 women without a drain⁶⁰⁹. In multivariate analysis, disruption and infection were significantly less in the drain group. The drains were remained *in situ* until the time of stitch-out or if drainage was more than 1 ml/24 hr. By using the same methodology for drain placement and removal without subcutaneous tissue closure, Chung *et al.* recently compared 99 patients with a drain to 213 women without a drain at ovarian cancer setting⁶¹⁰. Although the drain group had worse baseline characteristics such as older age, more previous abdominal surgeries, more bowel surgery and higher surgical complexity scores, they had more clean wound healing and a lower rate of seroma formation. This difference was also significant in multivariate analysis. On the other hand, no significant difference was noted for infection, dehiscence, hematoma or reoperation.

There is only one retrospective study addressing ovarian cancer patients undergoing major cytoreduction which showed a benefit for those that had a negative pressure subcutaneous drain versus those that did not⁶⁰⁹. Finally, the SAWHI randomized controlled trial published in 2020 is the only randomized trial showing that negative-pressure wound therapy is superior to conventional dressings and achieves better wound closure⁶¹¹.

The vacuum assisted closure is a form of negative-pressure wound therapy and is the application of subatmospheric pressure across a wound bed to create an environment that promotes wound healing by secondary or tertiary intention. The continuous negative pressure keeps together the edges of the wound and removes all the potential infectious agents and fluids, which in turn can lead to contamination of the wound. It provides moist environment, increases blood perfusion, accelerates the formation of granulation tissue and removes excess exudate from the site of the injury, thus indirectly reducing the risk of infection. Although today there is not enough randomized controlled trials to justify the cost of the use of vacuum assisted closure in all obese patients with wound complications who undergo major cytoreductive surgery, this method may prevent surgical site infection and reduce hospital costs when individualized⁶¹². This applies particularly for patients who have meshes as vacuum assisted closure has been shown to decrease the rates of wound complications⁶¹³.

Finally, an algorithm for selecting the cases that will benefit most from vacuum assisted closure should be developed and factors as pressure level, dressing type, dressing time intervals and duration of treatment should be standardized.

20.3 Surgical necrotizing fasciitis

Postoperative necrotizing fasciitis is a rare condition and often challenging to manage due to the usual and unexpected rapid onset with rapid progression. It is an aggressive subcutaneous infection that tracks along the superficial fascia, which comprises all the tissue between the skin and underlying muscles⁶¹⁴. The term “fasciitis” sometimes leads to the mistaken impression that the muscular fascia or aponeurosis is involved, but in fact it is the superficial fascia that is most commonly involved⁶¹⁵. Prompt recognition and optimal timely surgical debridement has been shown to reduce morbidity and improve overall outcome. Clinical signs include crepitus, skin discoloration/ necrosis, foul-smelling wound discharge, pain and clinical deterioration^{615,616}. The presentation is variable with respect to the etiology, anatomic location, and extent of required initial and subsequent debridement, and the manner and complexity of reconstruction. The extent of the disease is frequently underestimated at initial presentation. Necrotizing fasciitis may involve any or all layers of the skin and soft tissue, including dermis, subcutaneous fat, fascia, and muscle, as well as other structures⁶¹⁶. The diagnosis may not always be apparent upon first seeing the patient. Overlying cutaneous inflammation may resemble cellulitis. However, features that suggest

involvement of deeper tissues include (1) severe pain that seems disproportional to the clinical findings; (2) failure to respond to initial antibiotic therapy; (3) the hard, wooden feel of the subcutaneous tissue, extending beyond the area of apparent skin involvement; (4) systemic toxicity, often with altered mental status; (5) edema or tenderness extending beyond the cutaneous erythema; (6) crepitus, indicating gas in the tissues; (7) bullous lesions; and (8) skin necrosis or ecchymoses. In the monomicrobial form, the usual pathogens are *S. pyogenes*, *S. aureus*, *V. vulnificus*, *A. hydrophila*, and anaerobic *streptococci* (*Peptostreptococcus*). Infection with *staphylococci* and hemolytic *streptococci* can occur simultaneously. There is often a predisposing condition, such as diabetes, arteriosclerotic vascular disease, venous insufficiency with edema, venous stasis or vascular insufficiency, ulcer, or injection drug use. The mortality in patients with group A streptococcal necrotizing fasciitis, hypotension, and organ failure is high, ranging from 30% to 70%^{617,618}.

Computed tomography or magnetic resonance imaging may show edema extending along the fascial plane, although the sensitivity and specificity of these imaging studies are ill defined. In practice, clinical judgment is the most important element in diagnosis.

Surgical exploration is crucial not just for debridement but also for confirmation of diagnosis and to obtain cultures for optimal antimicrobial treatment. Empiric antimicrobial therapy is recommended as a first step, until the responsible organisms are isolated from debridement specimens. In the absence of definitive clinical trials, antimicrobial therapy should be administered until further debridement is no longer necessary, the patient has improved clinically, and fever has been absent for 48-72 hours. Empiric treatment of polymicrobial necrotizing fasciitis should include agents effective against both aerobes, including methicillin-resistant *Staphylococcus aureus*, and anaerobes. These could be vancomycin, linezolid, or daptomycin combined with one of the following options: (1) piperacillin-tazobactam, (2) a carbapenem (imipenem-cilastatin, meropenem, and ertapenem), (3) ceftriaxone plus metronidazole, or (4) a fluoroquinolone plus metronidazole. Once the microbial etiology has been determined, the antibiotic coverage should be appropriately modified. Necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A *streptococci* should be treated with both clindamycin and penicillin. Clindamycin suppresses streptococcal toxin and cytokine production. Clindamycin was found to be superior to penicillin in animal models, and 2 observational studies show greater efficacy for clindamycin than β -lactam antibiotics^{619,620}. Penicillin should be added because of potential resistance of group A *streptococci* to clindamycin.

Patients may appear initially well, but often experience rapid deterioration later. Therefore, failure to recognize the severity of disease resulting in delays of the initial debridement is associated with worse outcomes and higher mortality rates⁶²¹⁻⁶²³. Collective data from the American Association for Surgery of Trauma demonstrate an overall lower mortality rate of 14% vs 26% in 341 patients when managed with early compared with late debridement⁶²⁴. Initial surgical debridement should be undertaken aggressively without compromise to remove all the necrotic tissue starting at the most severely involved region and progressively working outwards until healthy soft tissue is encountered. The risk of multiorgan failure and mortality increases with incomplete initial debridement⁶²³.

Optimal care is on a multidisciplinary level including ideally plastic surgery colleagues and intensive care team. Repeated aggressive debridement in a supportive critical care setting is usually required due to an often prolonged and complex process of reconstruction^{615,616}.

No covering of the area is recommended until all necrotic areas have been debrided. Once achieved, temporary coverage may be very valuable to protect the wound from desiccation and further infection, reduce evaporative heat and fluid losses, limit the inflammatory and hypermetabolic response, thus enabling the patient to recover physiologically before it can be exchanged for definitive coverage. During this period, and once allograft is adherent, definitive wound covering and closure should be planned and undertaken, which may include autografting, fasciocutaneous flap, or muscle flap coverage.

Medical photographic documentation with the consent of the patient is recommended for recording and medicolegal purposes.

20.4 Hernia repairs, use of mesh

Incisional hernias are a frequent complication following abdominal operations and can reach an incidence of 38% in specific groups. Suturing of the fascia after abdominal midline incision with a continuous small bites technique reduces the incidence of incisional hernia compared with suturing with the conventional large bites technique. The technique is applied with tissue bites of 5mm and intersuture spacing of 5 mm. The rationale for this is to apply as many stitches as the length of the incision trying to incorporate only the aponeurosis and not muscle or fat. There are two randomized controlled trials showing that this is the safest way of closing midline abdominal incisions^{625,626}.

Use of mesh for abdominal wall hernia repair should be avoided in case of extensive cytoreductive surgery with bowel resection, long surgery and large hernia defects due to the higher risk of wound infection⁶²⁷. Intraoperative risk factors associated with a wound infection following hernia repair include: bowel resection/injury/fistula, emergency procedure, prolonged operative time, perioperative blood transfusion, ventral hernia defects (>10 cm)⁶²⁷.

The risk of prosthetic mesh-related infections is higher in case of contamination during or after the mesh insertion. Main reason is that it is difficult for the host to eradicate mesh-related infections related to the formation of a biofilm around the inserted mesh⁶²⁸. In a systematic review that included 2,418 patients from six cohort studies, predictors of mesh infection included steroid or other immunosuppressive drug use, urgent repair, and postoperative surgical site infection; while predictors of mesh explantation were polytetrafluoroethylene mesh, onlay mesh position, and associated enterotomy in the same procedure⁶²⁹.

In case of creation of a large dead space subcutaneously after sheeth mobilisation and hernia repair, a drain with negative suction might be appropriate to reduce seroma and hematoma formation⁶³⁰. Fluid collections as those, that are not associated with signs of infection should generally not be aspirated, unless the patient is symptomatic, due to risk of introducing infection into a sterile site⁶³¹.

Also, in view of the fact that ovarian cancer patients may undergo multiple cytoreductive attempts during their disease journey to achieve longer remission, the risks and benefits of use of mesh should be counterbalanced with potential challenges in future relaparotomies with abdominal entry and adhesions especially in the presence of peritoneal carcinosis. The sublay mesh position (ie. below the fascia and muscular layers but above the peritoneum) has been demonstrated to have the lowest risk of infection, and the underlay position (directly beneath the peritoneum) had the second lowest risk for surgical site infections⁶³².

Wound considerations/complications

- Implementation of an established surgical site infection reduction bundle is recommended to reduce surgical site infection rates [IV, B].
- In extensive sheeth/subcutaneous mobilisation with creation of large dead space and in largely obese patients, a closed suction drainage and subcutaneous closure may be recommended [IV, C].
- Meticulous hemostasis at abdominal closure especially in the subcutis is strongly recommended to prevent postoperative wound haematomas and seromas [IV, B].
- A continuous closing technique of a midline fascial incision using a slowly absorbable suture material is the best way for closing the abdomen in the elective setting. The small bites suture technique seems to be more effective than the traditional large bites suture technique for the prevention of incisional hernia in the midline incisions [I, B].
- Negative pressure wound treatment is an option for patients in wound management of perioperative infections and/or wound breakdown [II, B].

Surgical necrotizing fasciitis

- Immediate surgical exploration in case of suspected necrotizing fasciitis is recommended for confirmation of diagnosis, wound debridement and to obtain cultures for optimal antimicrobiological treatment [IV, B].
- Initial broad empiric antibiotic therapy that covers both gram-negative and gram-positive organisms (eg., vancomycin or linezolid plus piperacillin-tazobactam or carbapenem, or ceftriaxone and metronidazole) is recommended as the etiology maybe polymicrobial (mixed aerobic-anaerobic microbes) [IV, B].
- Second-look surgery should be considered within 24 hours after the initial debridement. On average, three to four debridements may be needed [IV, C].

21 Nutritional management

Patients with peritoneally disseminated ovarian cancer have a high risk of malnutrition and hypoalbuminemia through the extensive volume losses with ascites and pleura effusion and impairment of bowel function⁶³³. Malnutrition increases in ovarian cancer patients the risk of treatment related toxicity and impairs overall outcomes while increasing length of postoperative stay⁶³⁴⁻⁶³⁸. Studies have interestingly shown, that ovarian cancer patients are more likely to have a body mass index classified as overweight, while they have at the same time low serum protein levels and high malnutrition scores⁶³⁹. In under- and overweight patients alike, sarcopenia is associated with higher incidence of chemotherapy related toxicity, shorter time to tumour progression, physical disabilities, poorer surgical outcomes, and reduced survival⁶³³.

Decreased albumin is significantly associated with more postoperative complications, hospital readmissions, reoperations, intensive care admissions, and cancer recurrence⁶⁴⁰. Up to 40% of all cancer patients die from causes related to cancer induced malnutrition. Outcomes depend on (a) patient characteristics, (b) tumor biology, and (c) the quality of treatment. Whereas the first 2 factors are non-modifiable, the latter can be. Nutrition represents an important aspect of patients' management that impacts on patient outcomes; hence, strategies to support and ensure maintenance of adequate nutrient intake throughout the patients' journey are warranted⁶⁴¹. Identification of those who are at risk for malnutrition relied traditionally on low body weight (or body mass index) and a history of weight loss. This approach, however, has become increasingly ineffective in the face of the global obesity epidemic and the new understanding of the metabolic alterations that occur prior to any measurable change in body weight. Evolving definitions of cachexia and sarcopenia aim to identify and quantify signs/symptoms of malnutrition or its risk, including evidence of inflammation as well as loss of muscle mass and function. The Glasgow Prognostic Score, based on serum concentrations of C-reactive protein and albumin as markers of inflammation, is an easy-to-use and highly predictive tool for the assessment of inflammation in cancer patients⁶³³.

Screening for malnutrition before major surgery is essential to identify patients at risk who may benefit from a nutritional intervention preoperatively while increasing overall awareness^{642,643}. Baseline nutritional assessment should be ideally carried out by a professional expert in artificial nutrition taking into consideration the nutritional status and estimated duration, benefits and side effects of potentially needed artificial nutrition on an individual basis^{644,645}.

Use of validated malnutrition screening tools is associated with better nutritional care and lower malnutrition prevalence rates in hospitalized patients⁶⁴⁶. Various nutritional screening scores have been used such as: nutritional risk screening score, subjective global assessment, patient-generated subjective global assessment, Malnutrition Universal Screening Tool, and preoperative nutrition screen^{643,647}. Regardless of the actual screening tool applied, centres should define and implement an appropriate and validated screening and assessment protocol, and subsequent action plan⁶⁴⁸. For the nutritional screening to be efficient, it should be brief, inexpensive, with a high specificity and sensitivity. For this purpose, body mass index, weight loss, and an index of food intake may be obtained directly, or via validated nutrition screening tools, e.g. nutritional risk screening score, Malnutrition Universal Screening Tool, Malnutrition Screening Tool, Mini Nutritional Assessment Short Form Revised⁶⁴⁹. The Global Leadership Initiative on Malnutrition (GLIM) has introduced a two-step approach for the malnutrition diagnosis, i.e., first screening to identify "at risk" status by the use of any validated screening tools, and second, assessment for diagnosis and grading the severity of malnutrition⁶⁵⁰.

21.1 Measures and principles of perioperative nutritional support

The main objective of preoperative carbohydrate loading is to stimulate the metabolism like a full breakfast would do. For non-diabetic patients, administration of oral carbohydrate drinks containing 100 g of carbohydrate (maltodextrin) the evening before and 50g of 2-4h before surgery is recommended to

improve insulin sensitivity, post-operative muscle function, and to reduce the hunger and anxiety. After their intake the metabolism enters into a carbohydrate-storing state. When the trauma of surgery occurs, a release of mediators shuts off glucose uptake in the muscles while increasing glucose production. These two components lead to a state of insulin resistance⁶⁵¹. Carbohydrate metabolism is activated by preoperative carbohydrate fluids given up to 2 hours prior to surgery in contrast to the traditional midnight preoperative fasting and so are hypothesized to help the body to overcome surgery induced insulin resistance, to reduce patients catabolism, and also having a positive impact on perioperative glucose control and muscle preservation^{643,651-655}. For that reason, carbohydrate loading is an established practice in many countries and a key component of ERAS programs, yet its independent effects on clinical outcomes remain unclear⁶⁵⁶. In contrast to that, preoperative fasting has significant side effects including thirst, hunger, headaches, and increased anxiety⁶⁵⁴. Following ingestion of carbohydrate drinks, no adverse events such as apparent or proven aspiration during or after surgery were reported^{642,657-659}. Several randomized studies on early feeding have been performed in gynecologic oncology and ovarian cancer. Maintenance of appropriate nutritional status post-operatively has led to improvements in return of bowel activity, reduced length of hospital stay, and equivalent complication rates as measured by wound healing, anastomotic leaks, or pulmonary complications^{654,660-663}. Currently, ERAS protocols for colorectal surgery recommend oral intake of regular solid food within 24 h of the operation, based on the evidence that gastrointestinal function tends to resume almost immediately postoperatively, and provision of enteral nutrition promotes bowel hypertrophy, improved wound healing and healing of the anastomotic site, leading so to decreased intensive care unit length of stay^{643,654,661,662}. Postoperative diet should be tailored to the patients' nutritional habits and intolerances to avoid diet related side effects.

The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines suggest that severely malnourished patients are supplemented before any elective surgery. Seven to 14 days of preoperative nutritional support is indicated even if surgery has to therefore be delayed. Equally, the ERAS recommendations also suggest 7 to 10 days of preoperative supplementation in severely malnourished patients with oral nutritional supplements⁶⁵⁴.

In general, although perioperative nutritional support is useful in modulating the stress response, the extent to which this is accomplished depends not only on the medical care provided, but also the timing, route of delivery, and composition of the nutritional support regimens provided.

A further important message is that since anabolism cannot be achieved in the postoperative period when glucose is administered alone, inadequate protein intake is associated with loss of lean mass, which in turn can impair physiologic function. Provision of protein, regardless of whether or not energy requirements are met, are strongly recommended in the form of oral nutritional supplements in addition to regular meals to maintain adequate intake of protein⁶⁶⁴. Evidence shows that this approach maintains lean mass and reduces the risk of incident frailty⁶⁵⁴. Wischmeyer *et al.* recommended reaching an overall protein intake goal is more important than total calorie intake in the postoperative period⁶⁴². Higher post-operative protein intake is also associated with earlier discharge⁶⁶⁰. Currently there are no definitive guidelines for surgical patients in regards to protein needs; however, in the acute care setting guidelines have recommended up to 2.0 g of protein/kg/day and 25-30 kcal/kg/day^{653,660}. Without adequate dietitian support, many patients do not meet protein their needs with oral nutrition alone in the immediate postoperative period⁶⁵⁴. The ESPEN Clinical Nutrition in surgery guidelines suggest that the energy and protein requirements can be estimated with 25-30 kcal/kg and 1.5 g/kg ideal body weight⁶⁶². Protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day, and Muscaritoli *et al.* 1 g/kg and aiming for 1.2–1.5 g/kg body weight per day^{633,665}.

There is no specific data for the perioperative requirements of lipids in ovarian cancer patients. It should therefore be tailored to the patients' needs. In weight-losing cancer patients with insulin resistance, ESPEN recommends to raise the ratio of fat to energy from carbohydrates. This is intended to increase the energy density of the diet and to reduce the glycemic load⁶⁴⁹.

Vitamins and trace elements should be generally substituted in parenteral nutrition unless there are contraindications. The supplementation of vitamins and trace elements is obligatory after a parenteral nutrition of more than 1 week⁶⁴⁹.

The current ESPEN guidelines for nutritional support therapy during adult anticancer treatment recommend the use of immune-modulating EN formulas containing arginine, nucleic acids, and essential fatty acids for 5-7 days preoperatively for malnourished patients undergoing gastrointestinal or head and neck surgery. Benefits of such use have resulted in improved immune parameters, including infectious and wound healing complications, even if without differences in overall mortality^{653,661,662}. According to Bisch *et al.* immunonutrition may be most beneficial in the preoperative period and may be more important than post-operative immunonutrition in all but the most complex surgeries^{633,643}. Several large randomized trials in colorectal patients compared an immune nutrition/high protein diet to a high calorie supplement and found a lower rate of infection and length of stay in the immune nutrition group.

When the energy needs cannot be met by normal feeding, oral nutritional supplements are recommended. The next step would be feeding through nasogastric tube. Parenteral nutrition, which results in more side effects, is only started when enteral nutrition is insufficient to ensure adequate nutritional status or in contraindications of enteral feeding, post-surgical complications or short bowel syndrome⁶⁶⁶. The ESPEN and the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines define following circumstances as beneficial for parenteral nutrition in the surgical patient: in undernourished patients in whom enteral nutrition is not feasible or not tolerated, and in patients with postoperative complications impairing gastrointestinal function who are unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days⁶⁶². Wischmeyer *et al.* recommended for patients who are not anticipated to meet nutritional goals (>50% of protein/kcal) through oral intake to start early enteral nutrition or tube feeding within 24h⁶⁴². Where goals are not met through enteral nutrition, they suggested early parenteral nutrition, in combination with enteral nutrition if possible. They also recommended starting patients on enteral nutrition and/or parenteral nutrition, who are not able to take in at least 60% of their protein/kcal requirements via the oral route⁶⁴². For patients with nutritional need, the route of administration should be tailored to the patient's physical condition⁶⁶⁵. Enteral nutrition and parenteral nutrition have to be considered equally effective in maintaining or improving nutritional status in cancer patients. However, use of parenteral nutrition is not without risks, including increased infections, increased surgical complications, and increased costs⁶⁶¹.

21.2 Refeeding syndrome

If oral food intake has been decreased severely for a prolonged period of time, ESPEN recommend increasing (oral, enteral or parenteral) nutrition only slowly over several days and to take additional precautions to prevent a refeeding syndrome⁶⁴⁹. Refeeding syndrome describes the biochemical changes (electrolyte abnormalities), clinical manifestations (fluid retention), and potential complications (cardiorespiratory dysfunction) that can occur as a consequence of suddenly feeding a severely malnourished person. The hallmark biochemical feature of refeeding syndrome is hypophosphataemia. However, the syndrome is complex and may also feature abnormal sodium and fluid balance; changes in glucose, protein, and fat metabolism; thiamine deficiency; hypokalaemia; and hypomagnesaemia⁶⁶⁷. Indeed, this complication may occur only in extreme cases, such as in cancer patients with a body mass index less of 14 kg/m² or a starvation longer than 15 days. In these patients, refeeding syndrome can be prevented by a stepwise and tailored refeeding protocol as well as providing optimal management and monitoring⁶⁴⁴.

In postoperative patients with minimal food intake for at least 5 days, it has been recommended that no more than half of the calculated energy requirements be supplied during the first 2 days of reintroducing normal feeding. If depletion is severe, initial energy supply should not exceed 5-10 kcal/kg/day and then a slow increase of energy intake over 4-7 days can be provided until full substitution of requirements is reached^{633,649}.

21.3 Dietary management of the patients with a bowel stoma

A colostomy usually passes soft, formed stool approximately once daily, depending on diet and physical activity, whereas normal output for an ileostomy is approximately 600-800 ml/day of loose feces of porridge-like consistency. Patients with an ileostomy, and even more so with jejunostomy, are at greater risk of nutritional deficiencies than people with a colostomy due to removal of the colon and varying amounts of the ileum⁶⁶⁸. When considering stoma output, generally the more proximal the stoma is formed the less viscous or formed the effluent. When the output is more liquid, there is an increased likelihood of nutritional and pharmacologic malabsorption and, therefore, the preferred location for the formation of ileostomies is often the distal ileum, just proximal to the cecum. Although there is no universal definition of high stoma output, it's often considered when the volume exceeds 1,200 ml/24 h. In some patients, restricting hyper- or hypotonic fluids may reduce the volume of stoma output, however, many require ant motility medications to prevent dehydration, electrolyte dysbalances such as hyponatremia, hypomagnesemia, and vitamin (B12, A, D, E, and K), micronutrient deficiencies and acute kidney injury. When assessing a patient's hydration status, urinary sodium or urine urea if the patient is taking diuretics, can be considered as a source of objective information⁶⁶⁹.

High output stomas are normally managed by oral or/and intravenous replacement of water and electrolytes, antisecretory and antidiarrheal medication, nutritional and psychological support⁶⁷⁰. Dietary advice involving high energy/protein diet and oral nutritional supplement drinks may be required to prevent or resolve malnutrition. People with less than 200 cm of small intestine remaining for digestion and absorption of nutrients may require artificial feeding (enteral or parenteral nutrition) to prevent malnutrition. Dietary management is recommended for the following complications associated with having a stoma: high output, loose output, constipation, blockage, wind and odour. High and/or loose output and obstruction are common complications in people with an ileostomy or jejunostomy. Constipation and odour are more common complications of a colostomy. Aspects of dietary management include: fibre restriction to prevent blockage and high output; oral rehydration solutions and/or fluid restriction for high output; added salt for people with high output ileostomy; white, starchy carbohydrates and gelatine containing sweets to thicken output; increased fibre and fluid for constipation; and avoidance of onions, beans and carbonated drinks to reduce wind. Acceptability of, and adherence to, dietary interventions for stoma management is important in improving clinical and patient reported outcomes⁶⁶⁸.

Nutritional management

- Patients should be screened and assessed for nutritional status with validated nutritional screening tools for malnutrition [III, B].
- Preoperative nutritional supplementations should be considered [III, B].
- Carbohydrate preloading prior to surgery is recommended [II, A].
- Early oral feeding adapted to patients' habits and tolerances is recommended within the first 24 hours after ovarian cancer surgery [II, A].
- High protein diet/immunonutrition and oral nutritional supplements may be considered in early feeding [III, C].
- Parenteral nutrition is recommended in undernourished patients in whom enteral nutrition is not feasible or not tolerated, and in patients with postoperative complications, impairing gastrointestinal function rendering them unable to receive and absorb adequate amounts of oral/enteral feeding for at least 7 days [II, A].
- If oral food intake has been decreased severely for a prolonged period of time, nutritional support should be initiated slowly to prevent refeeding syndrome [III, B].
- Patients with bowel stoma should receive specialist dietary advice tailored to the type of stoma and length of residual small bowel, to avoid stoma related complications such as high/loose output, constipation, blockage, flatulence and odour [III, B].

22 Prehabilitation, enhanced recovery, postoperative ileus prevention

22.1 Prehabilitation and ERAS concepts

The ERAS concepts in gynecological oncology have led to a standardization of perioperative care and focused on reducing perioperative morbidity and shortening the length of stay without increasing readmission rates, in an overall effort to improve patients' surgical stress response^{660,671}. This multimodal and patient-educative concept is now being extended to include the aspect of prehabilitation⁶⁷². The concept of prehabilitation focuses on proactively modulating the patients' resilience. By improving the baseline condition, the stress and tissue damage caused by surgery is supposed to be reduced and the time to recovery is expected to be improved⁶⁷³. Elderly and/or fragile patients will especially benefit from the pre-surgical, tailored improvement of their baseline physical capacity⁶⁷⁴. Although no definitive and validated prehabilitation concept has been established to date, trimodal strategies appear to be the most effective⁶⁷⁵. Multimodal prehabilitation concepts consist of patient education, nutritional assessment and improvement, physical exercise and psycho- (oncological), anxiety reducing support.

Various studies have evaluated the effect of prehabilitation programs in patients with colorectal cancer colorectal surgery⁶⁷⁶⁻⁶⁷⁹. The Charité Berlin and the Kliniken Essen Mitte working group introduced a concept of a bicentric prospective trial enrolling ovarian cancer patients who will participate to a multimodal prehabilitation concept and standardized perioperative care following the ERAS guidelines in order to reduce postoperative morbidity⁶⁷². Nevertheless, the implementation of an ERAS program alone is not sufficient; equally important is the verification of protocol adherence of the healthcare team as well as the individual patient⁶⁸⁰⁻⁶⁸². Newer and previous surveys in Germany for example have revealed an extremely heterogeneous picture with less than half of the gynecological centres surveyed following the recommendation of the ERAS guidelines^{69,683}.

The ERAS® Society group for major gynecology published guidelines for perioperative care in gynecologic oncology surgery based on the best available evidence and updated them recently^{660,684,685}. To date, several initiatives have been developed to integrate ERAS into clinical care of gynecological oncological patients^{672,679,686-689}.

A recent review by Schneider *et al.* evaluated the implementation of ERAS protocols in gynecologic oncological patients scheduled for major surgery in 12 observational studies; except one of them, all were single center analyses demonstrating that evidence for ERAS programs in gynecologic oncology is still based on rather heterogeneous data^{672,679}. Still, the constant work of the ERAS® Society including the publication of guidelines and instruments that help to implement ERAS protocols (like Recover- checklist) and their emphasis on the relevance of adherence monitoring, help to generate more homogeneous data and have demonstrated the crucial importance of adherence monitoring.

22.2 Physical exercise

It is recommended that physical exercise strategies consist of both: moderate aerobic training and resistance exercise and patients follow a tailored program in order to improve their postoperative recovery⁶⁹⁰. Commonly used guidelines in the Anglo-American region are Physical Activity Guidelines for Americans and American Cancer Society guidelines⁶⁹¹⁻⁶⁹⁴. The description of preoperative exercise as part of multimodal prehabilitation programs is heterogeneous: type, duration, intensity and supervision of the interventions differ⁶⁹⁵. Moran *et al.* described in their systematic review that prehabilitation strategies consisting of aerobic exercise and resistance training decrease postoperative complications after surgery⁶⁹¹. Some of the multimodal concepts, resulted in a faster recovery to baseline functional capacity, but these trials failed to prove a positive impact on postoperative complication rates^{676,696-698}. Contradictory to these results, Soares *et al.* reported a small single center trial wherein in 16 patients who participated to a prehabilitation program before abdominal surgery, surgical complication rates were

significantly reduced compared to the 16 patients in the control group⁶⁹⁹. Similar results were shown by Barberan-Garcia *et al.* in a single centre randomized controlled trial of 143 patients with high-risk for perioperative morbidity (>70 years and/or ASA III/IV)⁷⁰⁰. After drop out due to changes in surgical plan, 62 patients underwent a personalized prehabilitation program (patient education, endurance training, promotion of physical activity) versus no prehabilitation (n = 63) before elective major abdominal surgery. Patients in the interventional group had significantly lower perioperative complication rates.

22.3 Nutritional interventions

Malnutrition, sarcopenia and hypoalbuminemia are well described risk factors for increased perioperative morbidity in gynecological oncological patients and especially for ovarian cancer patients^{136,701-705}. It is highly recommended to perform a preoperative nutritional assessment to avoid and compensate malnutrition^{635,662,706}. Several screening tools like the Nutrition Risk Screening 2002, the Subjective Global Assessment, the Malnutrition Universal Screening Tool and the evaluation of the bioelectrical impedance analysis (BIA)-derived phase angle are validated for preoperative assessment in cancer surgery^{702,707-709}. Several trials investigated the effect of preoperative nutritional intervention in patients scheduled for abdominal cancer surgery⁷¹⁰⁻⁷¹². Within the context of multimodal concepts, a synergistic effect of physical exercise and nutritional intervention has been demonstrated^{695,713-715}.

The European working group on sarcopenia in older people characterizes sarcopenia as an acute or chronic muscle disease with low muscle quality and quantity resulting in low muscle strength and physical performance⁷¹⁶. Multiple markers (e.g. skeletal muscle index or muscle attenuation, measured in Hounsfield units) with different cut offs and diagnostic instruments (e.g. computed tomography scans, magnetic resonance imaging, bioelectrical impedance assay and dual energy X-ray absorptiometry) exist to describe sarcopenia⁷¹⁷. The impact of sarcopenia in ovarian cancer is controversially discussed. In a retrospective analysis of 216 ovarian cancer patients undergoing primary debulking surgery, Rutten *et al.* found no significant correlation between sarcopenia (defined as skeletal muscle index $\leq 38.73 \text{ cm}^2/\text{m}^2$) and severe postoperative complications or poor overall survival⁷¹⁸.

A very recently published prospective single center trial investigated the role of sarcopenia and malnutrition in ovarian cancer patients undergoing debulking surgery⁷¹⁹. However, three retrospective trials found that low muscle quality (skeletal muscle attenuation) is associated with poorer overall survival in patients with ovarian cancer^{703,705,720}. Recently, two meta-analyses described the impact of sarcopenia on overall survival of ovarian cancer patients^{721,722}. McSharry *et al.* published a meta-analysis of six trials and concluded that sarcopenia was not significantly associated with improved 3 or 5 year survival rates but normal muscle attenuation in comparison to low muscle attenuation showed a significant correlation to an improved 3 and 5 year survival rate⁷²¹. Ubachs *et al.* published a meta-analysis of eight studies describing that low skeletal muscle index and muscle attenuation were associated with poorer overall survival but emphasize that low data quality does not allow a definitive conclusion⁷²².

Up to date, assessment of sarcopenia is not yet a standardized part of a clinical routine in preoperative diagnostics of ovarian cancer patients. But frailty assessments become increasingly important in order to predict the risk of severe postoperative complications and poor overall survival. Prospectively run multicenter trials are warranted to investigate if evaluation of sarcopenia should be part of a multimodal frailty assessment. Especially the question which markers and cut-offs are feasible to describe clinically relevant sarcopenia should be addressed in the future.

22.4 Psychological, anxiety reducing support

Oncology patients have been shown to benefit from psycho-oncological support on multiple levels; from postoperative pain and behavioural recovery to length of stay and overall coping mechanisms in various series. Especially relaxation methods seem to have additional positive impact on postoperative pain levels⁷²³. Still, from various prospective randomized data there is no clear evidence regarding the exact impact of psychological interventions during prehabilitation on the postoperative outcome of

gynecological cancer patients. Further research is necessary to answer this question. For patients with apathogenic germline BRCA mutation, which is prevalent in about 20 % of the cases, additional genetic counselling and psychological support, is required for the patient and her family⁷²⁴. This should be therefore provided as soon as the results are communicated.

22.5 Proactive measures for postoperative ileus prophylaxis

The pathogenesis of postoperative ileus is multifactorial^{678,681}. In a retrospective single center study of 578 patients who underwent primary ovarian cytorreduction between 2003 and 2008, Bakkum-Gamez *et al.* reported an incidence of 30.3%⁷²⁵. A higher risk for postoperative ileus is observed in patients with relapsed as compared to those with primary epithelial ovarian cancer. This might be attributed to patients being operated due to preoperative ileus and or to a higher small bowel resection rate at cytoreductive surgery for relapse⁷²⁶. Tumor related factors like involvement of the mesentery and the extent of peritoneal tumor spread as well as surgery related aspects such as surgical complexity and anaesthesiological interventions (transfusion, pain management using ibuprofen) influenced the risk of postoperative ileus⁷²⁵. Therefore, decreasing the rate of postoperative ileus is one of the goals of interventions that are part of ERAS pathways. Some of them are simple, like coffee consumption or early feeding within 24h after surgery and early mobilization; others like opioid sparing pain management or goal-directed fluid therapy are more complex^{642,660,727}.

A prospective randomized trial by Sanchez-Iglesias *et al.* demonstrated a 10% decreased rate of postoperative ileus in the ERAS intervention arm in patients undergoing ovarian cancer cytoreductive surgery⁷²⁸. A Cochrane review, confirmed that early postoperative feeding after major abdominal gynecologic surgery appears to be safe and supports faster recovery of bowel function without increasing postoperative complications⁷²⁹. Moreover, patients' satisfaction increases and length of stay is shortened. In any case, routine postoperative fasting till the time of first flatus or bowel movement is outdated and not recommended. Additional measures like chewing gum have shown controversial effects in various prospective randomized trials⁷²⁸⁻⁷³⁵. Even though some trials have shown a positive impact of chewing gum on time of first flatus and time to first bowel movement and even length of stay; the largest randomized multicenter trial on 2,000 patients after major abdominal surgery, could not confirm this benefit⁷³⁰.

Coffee consumption is an additional simple measure that has been shown to be beneficial in terms of faster recovery of bowel function. A randomized controlled single center in 114 patients with gynecological cancer demonstrated a reduced time to flatus, mean time to defecation and mean time to tolerate food in the coffee intervention arm⁷³⁶. The addition of milk and sugar seems not to be beneficial in this context^{737,738}.

Prehabilitation enhanced recovery, postoperative ileus prevention

- **Prehabilitation and enhanced recovery programs should be applied as a new and relevant global concept in ovarian cancer surgery [II, A].**
- **Trimodal concepts consisting of physical exercise, nutritional assessment and intervention and psychological support and patients education are key elements to this program [III, B].**
- **The implementation of ERAS protocols in gynecological oncology is recommended, whereby adherence monitoring is of fundamental importance [II, A].**
- **A multimodal approach, comprising of early feeding, goal directed/balanced fluid therapy, physical activity, opioid-sparing pain therapy and early mobilization is recommended for the prevention of postoperative ileus [III, B].**

23 Postoperative physiotherapy and mobilisation

Despite the general concerns about robustness of evidence in the various physiotherapy trials, numerous studies have demonstrated the benefit of postoperative physiotherapy on perioperative pain, bowel obstruction, deep vein thrombosis, respiratory complications, as well as early mobility and formation of lymphedema^{38,739-748}. Early physiotherapy in patients with surgery associated critical illness may have a significant impact on physical and functional outcomes and length of intensive care stay⁷⁴³.

In an analysis of 283 Cochrane reviews, Momosaki *et al.* reported that physiotherapy trials are commonly (94%) inconclusive and not providing any definitive answers or insight, while nearly all emphasize the need for further research⁷³⁹. However, few articles included in this review address its value perioperatively.

A systematic review on the impact of physiotherapy on postoperative pain has demonstrated a positive impact on a range of outcomes including pain, quality of life, physical function and depression scores, even though caution is needed due to the lack of uniformity and some methodological concerns⁷⁴⁰. Studies reporting on the use of physiotherapy, often include reference to analgesic pain relief as a supporting measure to accompany or facilitate physiotherapy^{743,749}. There is no evidence for the routine use of physiotherapy techniques Clear Passage Approach in the management of ovarian cancer related bowel obstruction⁷⁵⁰.

Regarding the impact of chest physiotherapy on postoperative pulmonary complications, there are some evidence suggesting that postoperative pulmonary complications can be reduced after abdominal surgery with a range of perioperative physiotherapy modalities. However, no single physiotherapy treatment has been identified as more effective than others. Although incentive spirometry is used widely in clinical practice, there is mixed evidence on the benefit of this in the management of surgical patients⁷⁴³.

Mobilization of hospital patients brings benefit in physical functioning and reduction of complications, and in emotional and social well-being⁷⁴³⁻⁷⁴⁵. Early mobilization is accepted as a positive outcome of physiotherapy programs and can be delivered by the entire team that cares for the patient including nurses and doctors and not just dedicated physiotherapists⁷⁴⁴⁻⁷⁴⁷. Psychological effects include positive effects on anxiety, depression and symptom distress, and social outcomes include increased independence and reduced length of stay^{744,745}. Patients decline in walking ability within two days of hospital admission and interventions such as MOVEON are designed to ensure mobility is recognized as a vital part of inpatient care^{744,745}. MOVEON is a large multisite educational intervention to improve mobilization of older patients in hospital in Ontario, the initial targets were not surgical patients but the aim is to upscale to other units in hospitals⁷⁴⁶. Some adopters of MOVEON use “mobility champions” who act as role models to facilitate the mobilization of patients and dispel the myth of “the sick role” and an expectation for patients to remain sedentary⁷⁴⁷.

Lower limb lymphedema is one of the most frequent postoperative complications of retro-peritoneal lymphadenectomy and can affect quality of life and activities of daily living³⁸. In a study of 126 patients having lymphadenectomy for gynecological cancer (about one third ovarian), the rate of stage 1 and stage 2 lower limb lymphedema was 45% and adjuvant chemotherapy increased the risk of lower limb lymphedema. Assessing patients at risk for lower limb lymphedema provides an opportunity for education and physiotherapy input in the form of complex decongestive therapy, which includes manual lymphatic drainage, limb compression, skin care and exercise^{38,748}. Providing complex decongestive therapy routinely for patients having systematic retroperitoneal lymphadenectomy has been shown to reduce risk of lower limb lymphedema.

Improving preoperative status with physiotherapy as part of pre-habilitation programs has been shown to improve postoperative outcomes and complication rates for patients undergoing major abdominal surgery, including cytoreductive surgery, although the evidence may be weak^{743,744,751}. In a retrospective

study of 124 patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcinosis, the 67 patients who had preoperative physiotherapy and patient controlled epidural anesthesia, incurred benefit in the form of reduced length of stay in the intensive care unit and earlier mobilization⁷⁴⁹. Boden *et al.* studied 441 adults within 6 weeks of upper abdominal surgery who had either an information booklet or a booklet and a 30 min preoperative physiotherapy session, concentrating on early mobilization and breathing exercises⁷⁵¹. They found the combined approach halved the incidence of post-operative pulmonary complications. In a sub-group of this study, 29 patients were assessed for memorability of, and compliance with, the education provided. The experimental group was 6 times more likely to remember the breathing exercises, some of the participants reported not reading the information sheet and a preference for face-to-face information delivery⁷⁵². However, and importantly in a post covid-19 landscape, telerehabilitation (providing services to patients at a distance using information and communication technologies) in the postoperative setting has been shown in a systematic review and meta-analysis to be feasible, with the potential to improve quality of life by providing a more flexible, patient centered way to deliver care⁷⁵².

There is growing evidence showing that physical activity has value at all stages of the cancer care pathway; prehabilitation, during treatment and in rehabilitation after treatment⁷⁵³. Studies have demonstrated that patients are receptive to advice about lifestyle factors, particularly soon after diagnosis or at the end of treatment, in what is often termed a teachable moment⁷⁵⁴. The main areas for lifestyle change are around physical exercise, diet and nutrition, weight management and smoking cessation and these form a significant part of the survivorship agenda.

Postoperative physiotherapy and mobilisation

- **Physiotherapy should be offered as part of routine perioperative care for women with ovarian cancer [III, B].**
- **Early mobilisation after surgery is recommended [III, B].**

24 Frailty scores/Management of the fragile patient

Frailty is associated with poor outcomes in a number of disease processes and therapeutic interventions. It performs better than age alone as a predictor of these outcomes and can be measured by a number of tools. Studies have shown that frail patients are more likely to experience postoperative higher grade 3-4 complications or death within 90 days of surgery, admissions to intensive care unit, readmissions, are less likely to initiate chemotherapy within 42 days of surgery and have an overall less favorable outcome^{595,596}. For that reason, frailty assessment and screening tools should be applied to improve tolerability and outcome of any medical and surgical interventions.

Frailty is an age-related process; certainly, there are non-frail patients over the age of 70 that may have outcomes similar to their younger counterparts as well as vice versa. The benefit of a frailty deficit index is that subjectivity can be removed from assessment of a patient while the index may provide precise objective measures of comorbidities and functional status⁷⁵⁵. These objective measures can be incorporated into a gynecologic oncology practice via simple questionnaires, so that geriatric assessment goes alongside with the oncologic assessment as an established strategy.

Frailty is a state of vulnerability to poor resolution of homeostasis following a stress and is a consequence of cumulative decline in multiple physiological systems over a lifespan. This cumulative decline erodes homeostatic reserve until relatively minor stressor events trigger disproportionate changes in health status, typically a fall or delirium. Comprehensive geriatric assessment has become the internationally established method to assess older people in clinical practice. It is a multidisciplinary diagnostic process to determine an older person's medical, psychological and functional capability to develop a plan for treatment and follow up. The practical limitation of comprehensive geriatric assessment is the time and expertise required for the process⁷⁵⁶.

A systematic review of systematic reviews was performed in order to investigate assessment tools of the most commonly included geriatric assessment domains and their predictive ability regarding the adverse postoperative outcomes. The authors demonstrated that frailty seems to be the most important predictor, which underpins the importance of an integrated approach. Tailoring the "optimal geriatric assessment" should be taken into consideration expertise, and resources available in daily clinical practice as well as the patient population⁷⁵⁷.

Geriatric assessment can be valuable in oncology practice for following reasons: detection of impairment not identified in routine history or physical examination, ability to predict severe treatment-related toxicity, ability to predict overall survival in a variety of tumors and treatment settings, and ability to influence treatment choice and intensity. Geriatric assessment has been shown to predict the risk of treatment-related complications (e.g. chemotherapy toxicity or surgical risk), but toxicity prediction at the individual level remains moderate⁷⁵⁸. A prospective study of older women with advanced ovarian cancer and frailty demonstrated that cytoreductive surgery can be performed safely in a tertiary care center with preoperative/postoperative geriatric and surgical co-management and may play a role in outcomes⁷⁵⁹.

In a quantitative systematic review identifying diagnostic accuracy and predictive ability of frailty measures in older adults, only a few frailty measures seem to be demonstrably valid, reliable and diagnostically accurate, and have good predictive ability. Among them, the Frailty Index and gait speed emerged as the most useful in routine care and community settings⁷⁶⁰.

Increasing cooperation between geriatricians and physicians will lead to a more personalized treatment strategies and directed interventions for older patients. Baseline geriatric assessment parameters may predict functional decline and chemotherapy-related toxicity. Education of physicians treating older patients with cancer has been shown as an essential step in the implementation of geriatric assessment and subsequent interventions⁷⁶¹. Assessment of frailty syndrome should be added in the preoperative risk assessment in older individuals⁷⁶².

The Dutch risk assessment tool is for hospitalized older adults and includes a short evaluation of four geriatric domains: risk for delirium, risk for undernutrition, risk for physical impairments, and fall risk. In a prospective cohort study this geriatric sum score has strong associations with long-term outcome and morbidity after colorectal cancer surgery⁷⁶³. Still in various randomized controlled trials, a preoperative geriatric assessment and tailored interventions did not reduce the rate of complications grade II-V, reoperations, re-admittance or mortality in frail older patients electively operated for colorectal cancer^{764,765}.

Older individuals (≥ 65 years) undergoing major elective gastrointestinal surgery identified following red flags for higher risk patients: age ≥ 75 years, eating soft food, reported hypertension, weight loss > 3 kg in the previous 3 months, fair-to-weak grip strength, sleeplessness, perceived health as no better than that of same-age peers, and short-term inability to recall two of three common words⁷⁶⁶.

The Multidimensional Frailty Score based on a preoperative comprehensive geriatric assessment is a useful tool for predicting postoperative complications and prolonged hospital stay, even in low risk elderly women who are undergoing cancer surgery⁷⁶⁷. In a prospective observational cohort study it has been found that clinical frailty scale is an accurate, sensitive screening tool, with good face and content validity to measure frailty in the perioperative setting. Higher risk patients should be screened for frailty prior to anesthesia with a cut-point of a Clinical Frailty Scale ≥ 4 selecting those for more comprehensive measurement⁷⁶⁸.

In a retrospective observational analysis using Fried's 5-point preoperative frailty assessment of elderly patients, identified pre-frail and frail subgroups to have the highest rate of postoperative complications, regardless of age, surgical discipline, and surgical risk. Significantly increased length of hospitalization and discharges to care facilities were also observed. Implementation of routine frailty assessments appears to be an effective tool in identifying patients with increased risk⁷⁶⁹. Inci *et al.* showed that Fried frailty score could be useful for the surgeon to estimate the risk of postoperative complications⁷⁷⁰.

A cohort study from Memorial Sloan Kettering, to evaluate the association of the Memorial Sloan Kettering-Frailty Index with established geriatric assessment and surgical outcomes. included prospectively evaluated patients with cancer 75 years and older before undergoing surgery⁷⁷¹. The Memorial Sloan Kettering-Frailty Index appeared to be associated with the previously validated geriatric assessment and postoperative outcomes in older patients with cancer and was shown to be a feasible tool for perioperative assessment of older surgical cancer patients.

Frailty scores/Management of the fragile patient

- **Preoperative frailty assessment is recommended to improve tolerability and outcome of any medical and surgical interventions [II, B].**

25 Psycho-oncological and social support

The diagnosis of cancer may cause enormous distress in face of a life-threatening condition. Between 20% and 50% of patients with cancer suffer from distress, which can be impacted by physical symptoms (e.g. fatigue, pain), psychological symptoms (depression, anxiety), social/financial problems (childcare, unemployment), spiritual and existential concerns^{772,773}. Therefore distress has been identified as the 6th vital sign in cancer care⁷⁷⁴. Around one third of cancer patients have a perceived need for psychosocial support and younger age, female sex and higher education are associated with more needs⁷⁷⁵. Women with early stage disease have been shown to have as much risk of distress as those with later stage disease, or recurrence^{776,777}. Evaluation for psychological distress, sexual dysfunction, psychiatric comorbidity, and psychosocial needs should be offered at the time of diagnosis, during treatment, follow-up and survivorship to all patients^{778,779}. Perioperative counselling should be part of a surgical prehabilitation concept and has been shown to improve patients' reported outcome measures including quality of life and somatic symptoms⁷⁸⁰. The National Comprehensive Cancer Network® distress thermometer serves as an easily manageable first stage screening tool to evaluate a patient's distress in areas such as practical, family, emotional, spiritual, sexual and physical problems⁷⁸¹. A cut off of ≥ 4 is recommended to identify patients with clinically elevated levels of distress⁷⁸²⁻⁷⁸⁴. Further scales like the Hospital Anxiety and Depression Scale can supplement the diagnostic process and patient reported outcomes may help to monitor treatment side-effects^{785,786}.

Patients with low level of distress should be offered patient-orientated information and psychosocial consultation^{778,787}. Patients with high distress should be seen by specialized caregivers (physicians, nurses, psycho-oncologists, social workers, creative therapist) for psycho-oncological and psycho-social support. This can improve quality of life as well as overall experience of patients facing the threat of cancer⁷⁸⁸. An armamentarium of interventions including counselling, psychoeducation, dignity-based therapy, relaxation-, all creative therapies including art-, music-, creative writing and movement therapies, and guided imagery techniques can help to reduce patient's anxiety⁷⁸⁹. Furthermore, psychotherapy offers an approach to empower the patient with the goal to improve coping skills and resilience, to decrease emotional distress, reduce feelings of depression, encourage a positive body image and help the patient to regain self-esteem. Additionally, psychological support enhances personal growth, strengthens personal and social resources of the patient and caregivers, and helps to improve quality of life^{790,791}. Exercise has the strongest evidence to decrease fatigue⁷⁹². Increasing body mass index and inactivity are associated with poorer quality of life⁷⁹³⁻⁷⁹⁵. Psychosocial interventions may support the management of various physical symptoms like pain, fatigue, nausea and include discussion of symptom management, all of which are of major importance in a surgical setting^{788,790}. Treatment approaches should be tailored to individual needs and availability of interventions.

Love, affection and sexuality are essential elements of life. Type and radicality of surgical treatment can influence sexual function and quality of life, which may be impaired by cancer itself or surgical treatment, with subsequent hormonal loss and side-effects of systemic therapy. Almost 50% of women with cancer lack information about sexual dysfunction in the course of cancer therapy, such as vaginal dryness, dyspareunia and impairment of orgasm⁷⁹⁶. Therefore, prior to surgery and during treatment the patient and her partner should be counseled regarding potential sexual problems and options of support (lubricants, vaginal dilators or local or systemic hormone replacement therapy depending on the type of cancer)^{9,790,797-799}. Overall, to strengthen the ability of our patients to cope with the diagnosis of the disease and side-effects of treatment, they should receive continuous evaluation for psycho-social needs and psycho-oncological support.

The concept of cancer survivorship has become established in clinical care and political strategies⁸⁰⁰. Cancer survivorship focuses on health and well-being of a person with cancer from the time of diagnosis until the end of life as a care continuum. This includes the physical, mental, emotional, social, and financial effects of cancer that begin at diagnosis and continue through treatment and beyond. A diagnosis of cancer can have significant adverse effects on both patients and their families and many more people are

living with incurable cancer but are not yet in the last 12 months of life. Undertaking a holistic needs assessment is one way to support a structured discussion of a wider range of patients' needs within a clinical consultation. There are several tools available e.g. Sheffield Profile for Assessment and Referral to Care, distress thermometer, Pepsi-Cola Aide Memoir and the requirement to complete such an assessment has been embedded in cancer care in many settings⁸⁰¹. Internationally, there is a growing focus on long-term survivors. In 2020, the Gynecological Cancer InterGroup defined in Athens a specific charta of cancer survivorship and include cancer-survivor as well patients with relapsed ovarian cancer with a cancer history at least 5 years. Structured survivorship programs should include information about cancer diagnosis and (performed) therapies, possible somatic and non-somatic symptoms, information on late and long-term effects as well as future-oriented aspects of health promotion and prevention. Long-term survivors also need information on psychosocial issues. These programs should support interdisciplinary and interprofessional communication and cooperation between medical and non-medical healthcare providers. The focus on long-term survivor is the consequence of an increase in cancer incidence as well as medical advances in diagnosis and treatment leading to declining mortality rates⁸⁰².

In addition to fear and risk of tumour recurrence, long-term survivors have an increased risk of physical, cognitive, emotional and social limitations due to disease and oncological treatment. Approximately 30% of long-term survivors are in a moderate or poor health condition, 17% are unable to work and more than half of all survivors suffer from at least one physical limitation^{803,804}. Depending on tumour entity and type of oncological therapy, late and long-term repercussions such as cardiovascular, intestine, neurological, endocrine (including infertility) dermatological and cognitive sequelae as well as psychosocial limitations (including early retirement, financial problems, anxiety, depression, post-traumatic stress disorder and a reduced quality of life (including fatigue, sexual dysfunction) occur in different frequencies⁸⁰³. These effects can occur months to years after the completion of treatment. Special attention should also be given to bone health (osteopenia, osteoporosis) and cardio-vascular diseases (hypertonia, cardio-myopathy) due to the fact that many cancer therapies can induce these late toxicities.

Secondary malignancies, including hematologic malignant neoplasms, develop months or years after diagnosis. Because of the poor long-term survival rate for patients with ovarian cancer this was up to now seldom of concern. With the new treatment options for ovarian cancer e.g. PARP inhibitors and improved overall survival even after secondary debulking surgery for recurrence, long term survival and long-term side-effects are coming into focus^{805,806}. Myeloid dysplastic syndrome/acute myeloid leukemia were reported with an incidence of around 1.5% in PARP inhibitor studies. In the Surveillance, Epidemiology and End Results the incidence of secondary malignancies for patients with ovarian cancer was assessed with 3.1 %⁸⁰⁷. Therefore, patients have to be counselled prior to systemic treatment for a low chance of secondary malignant neoplasms and they have to be closely monitored for alerting symptoms.

Cancer survivors report special needs for additional information about their diagnosis and therapy, as this often could not be adequately provided at the time of diagnosis and during the course of treatment. In the transition from treatment to follow up with the shift of responsibilities from doctors to themselves, patients experience a loss of their safety net. They are looking for a normal life again, but might find a restricted one which requires the definition of a new "normal"⁸⁰⁸. Cancer survivors profit from information about persistent symptoms as well as about future-oriented aspects of health promotion and secondary disease prevention. Long-term survivors also need information about psychosocial issues including financial and legal aspects, options for rehabilitation, psycho-oncological support and the recommendation of facilitating support groups. Interdisciplinary communication and cooperation between medical and non-medical healthcare providers is of great importance to ease the way for a coordinated holistic approach^{801,809}. Initial evaluations have shown that participants of survivorship programs profit from better health condition and a greater knowledge of their disease, therapy and possible risk factors^{810,811}.

Every cancer patient should receive an individualized survivorship care plan with information about diagnosis, therapy, possible long-term side-effects, recommended check-ups, health promotion like

physical activity, healthy eating, weight management, nicotine and alcohol abstinence, options for psychosocial and psycho-oncological support including stress reduction, mechanism of resilience, relaxation and creative therapies. As cancer is a “WE” disease, family and caregivers should also routinely be integrated in survivorship aftercare. Based on the high-prevalence of genetic background, such as BRCA and Lynch-syndrome and the possible PARP-induced hematological malignancies screening of secondary malignancies should also be part of every cancer survivorship program.

Finally, every patient should receive information about patient advocacy groups or support organizations.

Psycho-oncological and social support

- **Every woman with ovarian cancer should be screened for distress in a holistic approach as early as possible and should be offered professional psycho-oncological support [III, B].**
- **Screening should be repeated in regular intervals during the course of treatment, follow-up and survivorship programs. For every woman the individual need for psycho-oncological support should be evaluated [IV, B].**
- **Besides evaluation by the treating clinician, women should be screened with validated and standardized screening tools such as the National Comprehensive Cancer Network® distress thermometer or the Hospital Anxiety and Depression Scale [III, B].**
- **Scores that require intervention should be identified in whatever tool is used and women offered psycho-oncological counselling to evaluate distress and psychological/psychiatric comorbidity [IV, B]:**
 - **Women with low level of distress should be offered patient-orientated information and psychosocial consultation including creative therapies.**
 - **Women with high level of distress should be offered psycho-oncological interventions (therapy, escort), in addition.**
- **Women should be counseled for sequelae of diagnosis and treatment on sexual function and for options of support [IV, B].**
- **Survivorship care should support survivors beyond their cancer treatment and regular follow-up care, throughout a lifetime [IV, B].**
- **Every cancer patient should receive an individualized survivorship care plan with information about diagnosis, therapy, possible long-term side effects, recommended check-ups and health promotion as well as psychosocial and psycho-oncological support [III, B].**

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27 Appendices

27.1 Appendix 1 - List of the international development group

Christina Fotopoulou (chair), gynecologic oncologist, Imperial College London, London (United Kingdom) ; **François Planchamp**, methodologist, Institut Bergonié, Bordeaux (France) ; **Tugce Aytulu**, oncology specialist dietician, American Hospital, Istanbul (Turkey) ; **Jeremy Campbell**, anaesthetist, Imperial College London, London (United Kingdom) ; **Luis Chiva**, gynecologic oncologist, University Clinic of Navarra, Madrid (Spain) ; **Alessandro Cina**, interventional radiologist, Fondazione Policlinico Universitario Agostino Gemelli, Rome (Italy) ; **Onder Ergonul**, microbiologist, American Hospital, Istanbul (Turkey) ; **Anna Fagotti**, gynecologic oncologist, Fondazione Policlinico Universitario Agostino Gemelli, Rome (Italy) and Catholic University of Sacred Heart, Milan (Italy) ; **Dimitrios Haidopoulos**, gynecologic oncologist, Alexandra Hospital, University of Athens, Athens (Greece) ; **Annette Hasenburg**, gynecologic oncologist, Medical Center Johannes Gutenberg University, Mainz (Germany) ; **Cathy Hughes**, consultant nurse, Imperial College London, London (United Kingdom) ; **Pawel Knapp**, gynecologic oncologist, Medical University of Bialystok, Bialystok (Poland) ; **Philippe Morice**, gynecologic oncologist, Institut Gustave Roussy, Villejuif (France) ; **Stephanie Schneider**, gynecologic oncologist, Evangelical Hospital Essen-Mitte, Essen (Germany) ; **Jalid Sehouli**, gynecologic oncologist, Charite-Universitätsmedizin Berlin, Berlin (Germany) ; **Emmanouil Stamatakis**, anaesthetist, Alexandra General Hospital, Athens (Greece) ; **Stephanie Suria**, anaesthetist, Institut Gustave Roussy, Villejuif (France) ; **Cagatay Taskiran**, gynecologic oncologist, Koc University School of Medicine, Koc (Turkey) ; **Ralph Trappe**, haematologist, Christian Albrechts University of Kiel, Bremen (Germany).

27.2 Appendix 2 - Identification of scientific evidence

Literature search in MEDLINE

Research period	2010/01/01 - 2020/07/15
Indexing terms	abdominal bleeding, abdominal closure, abdominal packing, absorbable agent, acetaminophen, acute respiratory distress syndrome, albumin, alcoholic chlorhexidine, allogenic transfusion, analgesia, analgesic management, analgesic techniques, anastomotic leak, anastomotic leakage, anemia, anesthesia, antiangiogenic therapy, antiangiogenic treatment, antibiotic management, antibiotic prophylaxis, antibiotic therapy, antibiotic treatment, anticoagulant agent, anticoagulant therapy, anticoagulation, antimicrobiological treatment, antisepsis, antithrombotic drugs, anti-VEGF monoclonal antibody, anxiety, anxiety reducing support, apixaban, arm positioning, arterial bleeding, aseptic technique, bevacizumab, biliary leak, biological agent, bleeding, blind embolization, bloating, blood loss, blood transfusion, bowel preparation, bowel stoma, cachexia, carbapenem, carbohydrate drinks, carbohydrate carbohydrate loading, preloading, cardiophrenic lymph node resection, ceftriaxone, celecoxib, cell salvage, central neuraxial blockade, chlorhexidine gluconate, chlorhexidine gluconate bathing, chlorhexidine gluconate shower, chronic thrombosis, chronic pain, chylothorax, clindamycin, clips, closing technique, coffee consumption, collagen-based agent, colloid, colorectal resection, comorbidities, complication, comprehensive package, computed tomography, continuous suture, conventional dressing, covered stent, crystalloid, daptomycin, deep venous thrombosis, depression, dexmedetomidine, dextran, diabetes, diaphragm, diaphragmatic peritoneum, diathermy, dietary management, dignity-based therapy, distress, distress thermometer, domperidone, drainage, drainage catheter placement, draining ureteric stent, elective colonic resection, electromyography, electrothermal device, embolization, empyema, endoscopic retrograde cholangiopancreatography, endoscopic vacuum therapy, endoscopic ultrasound, endoscopic interventional technique, endotracheal tube, enhanced recovery, enteral nutrition, epidural, epidural anesthesia, epidural catheter, ertapenem, erythromycin, euvoemia, exudates, fatigue, ferritin saturation, fibrin sealant, fibrin sealant patch, fluoroquinolone, fluoroscopy, fragile patient, fragility, fragility score, frailty, frailty assessment, frailty management, frailty score, frailty syndrome, free-floating thrombus, gabapentin, geriatric assessment, goal-directed hemodynamic therapy, gastric electrical stimulation, gastric perforation, gastrointestinal complications, gastroparesis, gelatin-based product, glue, <i>H. influenzae</i> type b vaccine, haemorrhage protocol, haemostatic agents, hair removal, hair shaving, head-down tilt, hemodynamic stability, hemostasis, hemothorax, hernia repair, holistic approach, hospital stay, hydronephrosis, hydroxyethyl starch, hypoalbuminemia, hypothermia, iatrogenic ureteral injury, ileus prevention, image-guided percutaneous drainage, imaging modalities, imipenem-cilastatin, immediate repair, immunonutrition, inferior vena cava filter, infiltration, influenza virus, inotrope, internal iliac artery, internal stenting, interventional radiology, intra-abdominal abscess, intraoperative bleeding, intraoperative chest tube placement, intrathecal analgesia, iron administration, iron deficiency, iron supplementation, iso-osmolar bowel preparation, JJ stent, length of stay, lesser sac-Porta hepatis-celiac region, levantinib, linear stapling closure, linezolid, lithotomy, liver resection, Lloyd Davies positions, local analgesic techniques, local haemostatic agents, low anterior resection syndrome, low-molecular-weight heparin, lower limb deep venous thrombosis, macrolide antibiotics, magnetic resonance imaging malnutrition, maltoextrin, management, mechanic thromboprophylaxis, medicamentous thromboprophylaxis, meditation, meningococcal conjugate vaccine, meningococcal serogroup B vaccine, meropenem, mesh, metoclopramide, metronidazole, microbiologic management, microbiologic therapy, mobilisation, monoclonal antibody, multidisciplinary approach, nausea, negative-pressure wound therapy, negative pressure wound treatment, nephrostomy, neomycin, neoplastic tissue, nerve injury, neurological damage, niraparib, non-steroidal anti-inflammatory drugs, normovolemic hemodilution, nutrition, nutritional assessment, nutritional care, nutritional intervention, nutritional screening tool, nutritional status, olaparib, oncologic outcome, operating table, oral antibiotic, oral nutritional supplement, ovarian carcinoma, ovarian cancer, oxidized cellulose-based haemostatic agent, pain, pain management, pain medication, pain score, pancreas, pancreatic fistula, pancreatic tail, parastomal hernia, parenteral nutrition, paracentesis, patient coaching, patient education, patient positioning, pelvic packing, pembrolizumab, penicillin, peri-firing compression, perioperative antibiotic prophylaxis, perioperative care, perioperative counseling, perioperative management, perioperative nutritional support, perioperative thromboprophylaxis, permanent inferior vena cava filter, permanent neurological injury, peripheral nerve injury, pharmacologic therapy, physical exercise, physical symptom, physiotherapy, piperacillin-tazobactam, pleura drains, pleura effusion, pneumococcal conjugate vaccine, pneumococcal polysaccharide vaccine, pneumothorax, poly(ADP-ribose) polymerase inhibitor, polyethylene glycol, polymicrobial necrotizing fasciitis, postoperative bleeding, postoperative collection, postoperative drainage, postoperative ileus, postoperative ileus prevention, postoperative ileus prophylaxis, prolapse, prophylaxis, protein diet, postoperative muscle function, postoperative pain management, postoperative physiotherapy, postoperative pleura effusion, postoperative sepsis, post-splenectomy management, prehabilitation, preoperative bowel preparation, preoperative patient education, prevention, primary prevention, prophylactic dose, prophylactic drainage, prophylactic embolization, prophylactic stoma formation, prophylaxis, proximal deep-vein thrombosis, psychiatric comorbidities, psychoeducation, psychological distress, psychological support, psychological symptom, psycho-oncological support, psycho-oncology, psychosocial consultation, psychosocial needs, pulmonary embolism, quality of life, radical debulking surgery, radiologic intervention, refeeding syndrome, relaxation, replacement, retractors, retrievable inferior vena cava filter, risk stratification, rivaroxaban, rolled laparotomy sponge, routine antibiotic prophylaxis, routine postoperative fasting, rucaparib, sarcopenia, screening tool, self-expanding metal, sepsis, sequelae, sexual dysfunction, silver dressings, skin antisepsis, social support, sphincterotomy, spinal anesthesia, spleen, spinal catheter, spinals, spontaneous closure, stapled closure, stent, stenting, stoma placement, stoma reversal, stomach, stump closure, supplementation, surgical drainage, surgical hand antisepsis, surgical internal iliac artery ligation, surgical ligation, surgical necrotizing fasciitis, surgical retraction, suturing, targeted agents, synthetic agent, telerehabilitation, tetracycline, thromboembolic events, thromboprophylaxis, timing of surgery, titrating fluids, thoracic epidural analgesia, tranexamic acid, tranexamic administration, transcatheter embolization, transferrine saturation, transversus abdominis plane block, Trendelenburg position, ultrasonography, ultrasonography technique, ultrasound, upper abdominal complications, upper abdominal pain, ureteric fistula, urinary catheter, urological complications, ureteric JJ stent, vaccination, vaccination protocol, vaccine, vancomycin, vasopressor, veliparib, vertebral canal haematoma, vesicovaginal fistula, vomiting, weight loss, wound closure, wound complications, wound considerations, wound debridement, wound healing, wound infiltration.
Language	English
Study design	Priority was given to high-quality systematic reviews and meta-analyses but lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, case reports and <i>in vitro</i> studies

27.3 Appendix 3 - List of the 117 international reviewers

Patriciu Achimas-Cadariu, gynecologic oncologist (Romania) ; **Giovanni Aletti**, gynecologic oncologist (Italy) ; **Jose Alvarez Avello**, anaesthetist (Spain) ; **Lukas Angleitner-Boubenizek**, obstetrician & gynecologist (Austria) ; **Maria Aymerich**, anaesthetist (Spain) ; **Manel Barahona Orpinell**, gynecologic oncologist (Spain) ; **Desmond Barton**, gynecologic oncologist (United Kingdom) ; **Anne-Sophie Bats**, gynecologic oncologist (France) ; **Claudia Bessa Pereira Chaves**, gynecologic oncologist (Brazil) ; **Andreas du Bois**, gynecologic oncologist (Germany) ; **Mareike Bommert**, gynecologic oncologist (Germany) ; **Rebecca Bowen**, medical oncologist (United Kingdom) ; **Robert Bristow**, gynecologic oncologist (United States of America) ; **Ulrich Canzler**, gynecologic oncologist (Germany) ; **Vlad Catalin**, gynecologic oncologist (Romania) ; **Hüsnü Celik**, gynecologic oncologist (Turkey) ; **Dennis Chi**, gynecologic oncologist (United States of America) ; **David Cibula**, gynecologic oncologist (Czech Republic) ; **Ovidiu Florin Coza**, radiation oncologist (Romania) ; **Antonino Ditto**, gynecologic oncologist (Italy) ; **Gaetano Draisci**, anaesthetist (Italy) ; **Osnat Elyashiv**, gynecologic oncologist (United Kingdom) ; **Nicole Erickson**, nutritionist (Germany) ; **Henrik Falconer**, gynecologic oncologist (Sweden) ; **Aarne Feldheiser**, anaesthetist (Germany) ; **Annamaria Ferrero**, gynecologic oncologist (Italy) ; **Anne Floquet**, medical oncologist (France) ; **Jose Fonseca-Moutinho**, gynecologic oncologist (Portugal) ; **Dirk Michael Forner**, gynecologic oncologist (Germany) ; **Prafull Ghatage**, gynecologic oncologist (Canada) ; **Ronny Goethals**, gynecologic oncologist (Belgium) ; **Mikel Gorostidi**, gynecologic oncologist (Spain) ; **Dan Grisaru**, gynecologic oncologist (Israel) ; **Murat Gultekin**, gynecologic oncologist (Turkey) ; **Frédéric Guyon**, gynecologic oncologist (France) ; **Bjorn Hagen**, gynecologic oncologist (Norway) ; **Philipp Harter**, gynecologic oncologist (Germany) ; **Erik Hartmann**, anaesthetist (Germany) ; **Florian Heitz**, gynecologic oncologist (Germany) ; **William Helm**, gynecologic oncologist (United Kingdom) ; **Gines Hernandez-Cortes**, obstetrician & gynecologist (Spain) ; **Barbara Hucs**, patient (Hungary) ; **Ahmet Iyibozkurt**, gynecologic oncologist (Turkey) ; **Ibon Jaunarena**, gynecologic oncologist (Spain) ; **Päivi Kannisto**, gynecologic oncologist (Sweden) ; **Dionyssios Katsaros**, gynecologic oncologist (Italy) ; **Vesna Kesic**, gynecologic oncologist (Serbia) ; **Ruth Kilcawley**, nutritionist (United Kingdom) ; **Katalin Koblos**, anaesthetist (Hungary) ; **Jacob Korach**, gynecologic oncologist (Israel) ; **Paul Kubelac**, gynecologic oncologist (Romania) ; **Kersti Kukk**, gynecologic oncologist (Estonia) ; **Bjoern Lampe**, gynecologic oncologist (Germany) ; **Kimseng Law**, gynecologic oncologist (Taiwan) ; **Fabrice Lecuru**, gynecologic oncologist (France) ; **Birthe Lemley**, patient (Denmark) ; **Christianne Lok**, gynecologic oncologist (The Netherlands) ; **Domenica Lorusso**, gynecologic oncologist (Italy) ; **Anamaria Luca**, anaesthetist (Romania) ; **Nicola Mac Donald**, gynecologic oncologist (United Kingdom) ; **Tiziano Maggino**, gynecologic oncologist (Italy) ; **Susanne Malander**, gynecologic oncologist (Sweden) ; **Gemma Mancebo**, gynecologic oncologist (Spain) ; **Fabio Martinelli**, gynecologic oncologist (Italy) ; **Sara Martinez**, patient (Spain) ; **Mehmet Mutlu Meydanli**, gynecologic oncologist (Turkey) ; **Lucas Minig**, gynecologic oncologist (Spain) ; **Milena Mitrovic**, obstetrician & gynecologist (Serbia) ; **Milos Mlyncek**, gynecologic oncologist (Slovakia) ; **Berit Jul Mosgaard**, gynecologic oncologist (Denmark) ; **Francesco Multinu**, gynecologic oncologist (Italy) ; **Jamie Murphy**, colorectal surgeon (United Kingdom) ; **Eva Myriokefalitaki**, gynecologic oncologist (United Kingdom) ; **Shibani Nicum**, medical oncologist (United Kingdom) ; **Ernst Oberlechner**, gynecologic oncologist (Germany) ; **Felipe Ojeda**, gynecologic oncologist (Spain) ; **Adeola Olaitan**, gynecologic oncologist (United Kingdom) ; **Cristina Olivieri**, anaesthetist (Italy) ; **Peter Oppelt**, obstetrician & gynecologist (Austria) ; **Gitte Ortoft**, gynecologic oncologist (Denmark) ; **Maja Pakiz**, gynecologic oncologist (Slovenia) ; **Patricia Pautier**, medical oncologist (France) ; **Fedro Peccatori**, gynecologic oncologist (Italy) ; **Jacobus Pfisterer**, gynecologic oncologist (Germany) ; **Jurgen Piek**, gynecologic oncologist (The Netherlands) ; **Klaus Pietzner**, gynecologic oncologist (Germany) ; **Felicity Plaat**, anaesthetist (United Kingdom) ; **Karl Podratz**, gynecologic oncologist (United States of America) ; **Denis Querleu**, gynecologic oncologist (France) ; **Friederike Rawert**, obstetrician & gynecologist (Germany) ; **Isabelle Ray-Coquard**, medical oncologist (France) ; **Nicholas Reed**, clinical oncologist (United Kingdom) ; **Alexander Reinthaller**, obstetrician & gynecologist (Austria) ; **Alexandros Rodolakis**, gynecologic oncologist (Greece) ; **Stuart Rundle**, gynecologic oncologist (United Kingdom) ; **Henk Schreuder**, gynecologic oncologist (The Netherlands) ; **Bernadette Adele Sewell**, patient (United

Kingdom) ; **Clare Shaw**, nutritionist (United Kingdom) ; **Tayup Simsek**, gynecologic oncologist (Turkey) ; **Spela Smrkolj**, gynecologic oncologist (Slovenia) ; **Linda Snoep**, patient (The Netherlands) ; **Erik Soegaard-Andersen**, gynecologic oncologist (Denmark) ; **Artem Stepanyan**, gynecologic oncologist (Armenia) ; **Eva-Maria Strömsholm**, patient (Finland) ; **Sudha Sundar**, gynecologic oncologist (United Kingdom) ; **Monica Terenziani**, pediatric oncology (Italy) ; **Kassiani Theodoraki**, anaesthetist (Greece) ; **Dimitros Tsolakidis**, obstetrician & gynecologist (Greece) ; **Jacobus van der Velden**, gynecologic oncologist (The Netherlands) ; **Ignace Vergote**, gynecologic oncologist (Belgium) ; **René Verheijen**, gynecologic oncologist (France) ; **Claire Verschraegen**, medical oncologist (United States of America) ; **Calogero Virgone**, paediatric surgeon (Italy) ; **Pauline Wimberger**, gynecologic oncologist (Germany) ; **Vanna Zanagnolo**, gynecologic oncologist (Italy) ; **Oliver Zivanovic**, gynecologic oncologist (United States of America) ; **Paolo Zola**, gynecologic oncologist (Italy).