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Review Articles

Multidisciplinary management of advanced ovarian cancer for an optimal therapeutic strategy

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Summary

The management of advanced ovarian cancer generally requires specialist multidisciplinary teamwork to achieve optimum outcomes. Preoperative computed tomography scans are the imaging modality of choice in determining the extent of disease and aiding in surgical planning. Histological classification is crucial to define various subtypes with their different behaviour and prognosis and to plan the best therapeutic strategy. Pathological prognostic factors, such as histological type, degree of differentiation, and FIGO stage must be described. To determine the ability to optimally cytoreduce advanced ovarian cancer, an experienced gynaecological oncologist needs to explore the entire upper abdomen and the pelvic and para-aortic lymph node regions to define the peritoneal cancer index (PCI). The final assessment is the completeness of cytoreduction (CC) score which is important in predicting prognosis and decision of post-surgical surgery. Ovarian cancer is the leading cause of death from gynaecologic cancers. Initial management is best provided by a specialist multidisciplinary team, including a radiologist, a pathologist, a gynaecologic oncologist, and a medical oncologist.

Key words: Advanced ovarian cancer; Initial staging; Multidisciplinary team.

Introduction

In 2012, the estimated number of new ovarian cancer cases in Europe, was 65,538 with 42,716 deaths [1]. Due to the fact that ovarian cancer remains asymptomatic for long periods of time, 75% of cases are not diagnosed until later stages, with invasion beyond the pelvis (FIGO Stage IIB to IV) [2].

According to French guidelines (RPC de Saint Paul, SFGO), the management of advanced ovarian cancer relies on initial complete surgical excision (nil-residue) [3]. Several recent studies have confirmed that postoperative tumour remnants are a major prognostic factor in advanced forms [4, 5]. If primary debulking surgery fails to achieve complete reduction of tumour volume without surgical risk or excessive sequelae, neoadjuvant chemotherapy may be implemented [3]. The choice of therapeutic strategy is guided by the initial workup, comprising of a clinical and biological evaluation, a radiological extension workup, an anatomo-pathological diagnosis, and surgical data. This management is thus necessarily multidisciplinary, requiring the formalisation of structured reports issued to all involved professionals, to facilitate exchanges during multidisciplinary meetings (MDMs). The purpose of this overview is to review the essential data required on the reports to allow therapeutic decisions to be made that grant patients the best possible management.

Radiological data

Imaging plays a major role in the initial workup, allowing pre-therapeutic assessment of peritoneal extension. It enables professionals to search for secondary supradiaphragmatic locations inaccessible to surgical exploration and to better plan the surgery when it appears possible.

Reference imaging

Computed tomography (CT) is the reference imaging system for the extension workup: (thoracic) abdominopelvic CT scan with injection of contrast agent is recommended [6].

Magnetic resonance imaging (MRI) may prove useful in the event of contraindication to CT scan (kidney failure, allergy to contrast agents, pregnancy). Moreover, a number of recent studies have shown that for small peritoneal carcinomatosis lesions in which CT is not very efficient, diffusion MRI could allow their detection with a sensitivity of

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91% [7-9]. In practice however, implementation is difficult and requires pelvic and abdominal MRI as the acquisition volume is smaller than for a CT scan. Thus, MRI is only indicated in specific situations.

Finally, positron emission tomography, PET-FGD, is not routinely indicated in the initial workup [6].

Reference CT technique

The examination must be performed correctly and the diagnostic reference level (DRL) must be a dose-length product (DLP) of 1,000 mGy.cm, according to the IRSN data (http://nrd.irsn.fr/). This figure must be mentioned in the radiologist's report. It is a single step with digestive marking that includes one litre, one hour before the examination. Multi-detectors include: liver without injection, thorax and liver passage (liver arterial transit time), abdominopelvic passage (liver portal vein and pelvic venous transit times), delayed bladder transit time, and opacified if necessary. Reading conditions include: five-mm axial plane, three-mm coronal plane, and ± sagittal plane.

Initial workup report

There is no reference ovarian CT scan report as it is highly complex: approximately 2,000 cross-sections to read. Moreover, the radiologist is faced with viewing difficulties (lesion < five-mm, miliary (micronodular peritoneal carcinomatosis), supramesocolic stage, bladder extension), and completeness difficulties (small intestine, mesentery, colon). It is, however, possible to draw up a check-list of locations to check with the most frequent peritoneal dissemination zones (paracolic grooves, greater omentum, douglas pouch, liver capsule, diaphragm, small intestinal surface), but also those rarer locations (mesentery, spleen capsule, hepatic pedicle, omental bursa, gastrosplenic ligament) that could complicate surgery.

For the oncologist or surgeon, the risks of perforation and anastomotic leak must be highlighted (occlusive syndrome risk zones). For this purpose, there are two essential requirements: 1) to opacify the entire digestive tract and 2) to specify the vascular ratios: the issue being located mainly in the pelvic area (for chemotherapy). The radiology workup report must thus be as extensive as possible to allow a collegial discussion between oncologist, surgeon, and radiologist.

Limitations of CT

The most significant limitation pertains to implant size. Scan sensitivity is high, between 85% and 93% for lesions greater than two cm in size, but drops to only 25-50% for peritoneal lesions smaller than one cm [10]. Moreover, it is difficult to obtain an absolute indication of radiological resectability criteria. Salani *et al.* [11] demonstrated that lesions considered by CT scan as predictive of sub-optimal resection were generally accessible to excision surgery. Their study involved a population of 180 patients presenting at least one non-resectability criterion by CT scan. They demonstrated that optimum resection was in fact possible in 92.2% of these patients. The Axell *et al.* study attempted to apply CT scan non-resectability criteria in one cohort of patients to another. It showed that the criteria were not reproducible between teams [12]. Patients may thus be wrongfully defined as non-operable and vice-versa. In both cases, this represents a loss of opportunities insofar as R0 resection surgery is the leading prognostic factor in late-stage cancer and remains the main goal. If primary surgery does not allow complete reduction, the Vergote *et al.* randomised trial (EORTC 55971) [13], showed that overall survival (OS) was equivalent between the "primary debulking surgery" group and the "interval debulking surgery" group (29 months *vs.* 30 months, RH: 0.98; 95% CI: 0.84-1.13; $p = 0.01$). The decision to initiate primary chemotherapy requires prior multidisciplinary discussion. Ultimately, the lack of radiological non-operability criteria imposes staging surgery.

Anatomo-pathological data

Anatomo-pathological report quality: where do we stand?

A European EORTC trial [14] conducted in 11 countries, traced anatomo-pathological report failings. Only 45.6% of reports mentioned all elements: diagnosis, histology, size, degree of differentiation, and origin of the tumour. The most frequently missing element was the size of the lesion. A French study [15] was also conducted by the AFAQAP, which coordinated a self-assessment of 230 reports in 2011. This study showed nonconformities greater than 10% for grading (15.9%), presence or absence of vascular emboli (48.2%), capsule status (20.2%), presence or absence of tumour at the ovary surface (13.5%), pT/pN extension stage (61.3%), classification year or UICC edition number used (80.9%), and FIGO extension stage (67.4%).

Recommendations for performing biopsies

It should first be noted that the quality of a report is determined by the anatomo-clinical information made available to the pathologist (generally by the surgeon). The essential elements are: age, tumour markers (CA 19-9, CA125), in young women: germ cell markers (alpha-fetoprotein, βhGC, LDH), inhibin B for sex cord tumours), family history (BRCA), along with the presence or absence of mass syndrome in the event of peritoneal carcinomatosis. Cytology alone is insufficient to determine the type and histological grade of the tumour. A histology sample (laparoscopy rather than percutaneous samples) is required.

It is also essential to ensure that the biopsy is collected under the following optimal conditions: multiple samples from different locations to ensure that tumour heterogeneity is represented, the largest possible volume: allowing comprehensive study of immunohistochemical markers, along with molecular biology analyses where necessary, and cryopreservation is not mandatory for ovarian cancer

Table 1. — *Histopathology report in the context of diagnostic laparoscopy.*

Histological type [19]:	
• Non-carcinoma: germ cell tumours (< 30 years), sex cord tumours	
• Carcinoma	
Histological subtype (for carcinoma)	Grade: the grading system differs according to subtype [20-22]
Serous	High (including the transitional cell variant) or low grade
Mucinous	Infiltrative or expansive mode Nuclear grade of 1 (regular nucleus) to 3 (pleomorphic nucleus)
Endometrioid	Grade 1/2/3 based on tumour architecture and atypical nuclei according to the FIGO grading used in endometrial cancer
Clear cells Undifferentiated cells	Still considered as high grade tumours and must not be graded

(no sanitary freezing), though it may be performed if the volume of material collected allows it.

Histopathology report in the context of diagnostic laparoscopy

The first step in the histopathology diagnostic process is to determine whether the tumour is a carcinoma, or a non-carcinomatous tumour (sarcoma, germ cell tumour or sex cord tumour). The second step in carcinomatous tumour diagnosis is to determine whether the carcinoma is of ovarian or gynaecological origin, or whether the origin is non-gynaecological (digestive tract, pancreaticobiliary system, breast, lung, or other), using various immunohistochemical markers in addition to morphological examination.

In the event of a tumour of ovarian origin, the aim is to confirm the diagnosis, to give its histological type and subtype, along with the grade of the histological subtype (Table 1). The grade can be determined from the laparoscopy sample (with reservations if only one sample is available), particularly as some data suggests that the grade may change after neoadjuvant chemotherapy. This issue occurs for other tumour types and the recommendation is to grade the tumour before treatment whenever possible [16-18]. It is important, however, to bear in mind that, considering the heterogeneity of the tumour, this grade may not be representative of the entire tumour.

Laparotomy report in the event of primary debulking surgery

The INCa and the Société Française de Pathologie (SFP) have jointly defined the minimum items to be included in anatomo-pathology reports [19]. These correspond to data essential for patient management for 21 tumour locations, including ovarian cancer. These reports list four types of information: patient and sampling physician identification information (under the responsibility of the authorised establishment at which the sample was collected), sampled organ-related information (under the sampling physician's responsibility), sample histopathology information, and information used to grade the tumour (pT/pN). The following data are provided by the surgeon: sample type – cystectomy/ovariectomy/annexectomy/total hysterectomy with bilateral annexectomy/total hysterectomy with bilateral annexectomy and lymphadenectomy/total hysterectomy with bilateral annexectomy, omentectomy, and lymphadenectomy/other; side – right/left/bilateral.

The histopathology description must include, at the least the following: histological type, histopronostic grading, criteria used to determine the pT/pN and FIGO Stage: uni- or bilateral- ovarian impairment, size, capsule (intact, broken), tumour on the surface of the ovary (presence/absence), tumour cells in ascites and/or peritoneal lavage, invasion of the uterus, fallopian tubes or other pelvic organs (rectum, bladder, other) by continuity and/or location, peritoneal metastases outside the pelvis (microscopic < two cm/ macroscopic > two cm), and number of invaded lymph nodes or number of lymph nodes examined at each location

Post-neoadjuvant chemotherapy laparotomy report

A laparoscopy may be performed, though for diagnostic purposes. In this case, the essential report items are: tumour remnants (yes/no): size of remnant and percent residual tumour cells, and vivacious tumour cells (yes/no)

As previously mentioned, the histological type and grading may be altered by chemotherapy; it is therefore preferable to use the pre-chemotherapy results. In conclusion, the elements required in the report are the WHO histological type and the differentiation grade, along with all elements required by the clinician to determine the FIGO classification (extension to neighbouring organs, invasive nature of implants, or lack thereof, nature of peritoneal fluid, etc.). Finally, the results must be discussed by the anatomopathologist and the oncologist.

Surgical data

It is essential for the surgeon that the preoperative workups include a number of data required to organise the surgical procedure. Similarly for the oncologist, the provision of a comprehensive surgical report, whether relating to the laparoscopy or the laparotomy, will enable this latter to select the optimum treatment strategy

Preoperative workup

Various elements of information must be shared between the oncologist and the surgeon: first the patient's general condition (age, co-morbidities) and nutritional status. According to SFAR/SFNEP recommendations [23], in patients

scheduled for surgery, preoperative undernutrition constitutes a risk factor independent of postoperative complications. Albumin level is a good marker: in the case of ovarian cancer, a correlation has been demonstrated between low preoperative albumin levels (< three g/dl) and digestive complications (anastomotic leaks) [24]. In the event of major surgery, preoperative serum albumin measurement is thus recommended (it should be determined prior to debulking, not after, as levels drop dramatically after surgery) [23]. In oncological digestive surgery, whether the patient is undernourished or not, preoperative immunonutrition should be prescribed for five to seven days.

The patient's thromboembolic context must also be discussed, particularly in the case of suggestive signs, along with the presence of occlusive or subocclusive syndrome. This notion must be shared between the oncologist and the surgeon to define the degree of severity and the need for intestinal bypass.

Diagnostic laparoscopy surgical report

In France, according to the Saint Paul de Vence guidelines, laparoscopy is the best tool available for evaluating initial resectability. It is complementary to imaging and biology and also allows histological diagnosis (biopsy). It is an essential procedure prior to treatment decision (Level 2, Grade A) [25]. It should be noted that in other countries, laparoscopy is not acknowledged as a required examination for the evaluation of resectability or for diagnostic purposes. The following items are required in the report: PCI score (with schematic representation of areas explored and possibly of inaccessible areas) [26, 27]; FIGO staging classification: laparoscopy enables an initial calculation of FIGO stage. A new classification was defined in January 2014 [28]; threat of perforation: to determine subsequent treatment, resectability status: for high or low PCI scores, the question is obvious. On the other hand, for intermediate scores, most frequently between 10 and 21, resectability is more difficult to evaluate: beyond the PCI score, histological date (subtype and grade) and the patient's general condition are important complementary data. Resectability status can be given with or without the Fagotti score (excision surgery is incomplete in 100% of patients with a score ≥ 8); incidents occurring during laparoscopy and impacting management (digestive wounds, conversion by laparotomy, serious ventilation disorders, etc.); the nature of the ascites (haemorrhagic or not): the presence of ascites and associated volume is a factor that impacts the resectability rate, but it is insufficient to establish a non-resectability indication.

Laparotomy surgical report

In the event of neoadjuvant chemotherapy, the patient's file must be discussed by the oncologist and surgeon after two or three sessions. Biological evaluation is performed by serum CA 125 levels: a correlation has been demonstrated between survival and normalisation (< 35 UI) or regression of CA 125 levels after neoadjuvant chemotherapy. The preoperative assay alone, however, is insufficient to make a therapeutic decision [29, 30].

Table 2. — *Residue size and CC - Sugarbaker score.*

Residue size	Sugarbaker score
Total absence of macroscopic residue CC-0	CC-0
Residue < 0.25 cm CC-1	CC-1
0.25 cm ≤ residue ≤ 2.50 cm CC-2	CC-2
Residue > 2.50 cm or confluence CC-3	CC-3

Beyond CA 125 levels, imaging is essential to make a decision concerning the feasibility of surgery: the CT scan is the reference. PET scan is not recommended as standard for FIGO Stage III tumours and remains optional for some Stage IV tumours [25]. The FIGO Stage must absolutely be reviewed at the time of excision surgery. The PCI score (with details of explored areas), along with the Sugarbaker score evaluating excision surgery quality (tumour residue) (Table 2) [31] must be specified.

The description of operations performed (surgical radicality) is essential: the type and number of resections must be described. The duration of the procedure must be specified and must match the surgical operations performed. Finally, the report must also mention any noteworthy peri- or postoperative events. In summary, the provision of a comprehensive surgical report, whether relating to the laparoscopy or the laparotomy, will enable the oncologist to select the optimum treatment strategy.

Conclusion

Currently, to be effective, the management of advanced ovarian cancer must be multidisciplinary. Indeed, beyond the surgeon's or oncologist's skills, the improvement of results also hinges on anatomo-pathological and radiological data.

The therapeutic strategy – primary debulking surgery or neoadjuvant chemotherapy – is decided according to all these elements. The aim is to achieve nil-tumour residue: this objective is currently consensual and has become the standard for surgical treatment of advanced ovarian cancer. The question arises however, concerning the time at which surgery should be performed: does neoadjuvant chemotherapy followed by interval debulking surgery offer the same survival rates as complete primary debulking surgery followed by the same chemotherapy regimen? EORTC 55971 [13] and CHORUS [32] trials demonstrated a non-inferiority in terms of OS between both surgical strategies: in the first trial, OS was of 29 months for the "primary debulking surgery" group *vs.* 30 months for the "interval debulking surgery" group (RH 0.98; 95% CI: 0.84-1.13; $p = 0.01$ for non-inferiority); in the second trial, OS was of 22.8 months

vs. 24.5 months (RH 0.87; 80% CI: 0.76-0.98). The trend would appear more favourable for interval debulking surgery in terms of observed side effects, quality of life, and postoperative morbidity and mortality. These trials also showed an increase in complete surgery after neoadjuvant chemotherapy, though with no increase in survival. If surgery is complete, however, interval debulking surgery is inferior to front line surgery in terms of OS . This latter point raises the question of the prognostic value of complete surgery after chemotherapy compared to primary complete surgery. Ongoing trials, such as JCOG0602 or TRUST, should provide some answers.

Given the current state of knowledge, the appropriate selection of patients eligible for neoadjuvant chemotherapy is difficult, thus fully justifying the discussion of each clinical situation during the MDMs. It has been demonstrated for other neoplastic diseases that discussing the treatment strategy before radical surgery tended to improve overall management compliance with guidelines [33]. A recent study conducted in the Rhône-Alpes region showed that the CC0 resectability rate is higher if the patient's case is discussed in the MDM prior to surgery, compared to patients whose case is not discussed (data submitted for publication). In the case of ovarian cancer, this compliance with guidelines improves the OS of these patients [34]. According to the available guidelines, the analysis of the balance between expected benefits and risks incurred, along with the resulting quality of life evaluation, should allow the best treatment strategy to be selected in each patient.

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