Guidelines

European Society of Endocrine Surgeons (ESES) and European Network for the Study of Adrenal Tumours (ENSAT) recommendations for the surgical management of adrenocortical carcinoma

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Abstract

Background: **Radical surgery provides the best chance of cure for adrenocortical carcinoma (ACC), but perioperative surgical care for these patients is yet to be standardized.**

Methods: **A working group appointed jointly by ENSAT and ESES used Delphi methodology to produce evidence-based recommendations for the perioperative surgical care of patients with ACC. Papers were retrieved from electronic databases. Evidence and recommendations were classified according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, and were discussed until consensus was reached within the group.**

Results: **Twenty-five recommendations for the perioperative surgical care of patients with ACC were formulated. The quality of evidence is low owing to the rarity of the disease and the lack of prospective surgical trials. Multi-institutional prospective cohort studies and prospective RCTs are urgently needed and should be strongly encouraged.**

Conclusion: **The present evidence-based recommendations provide comprehensive advice on the optimal perioperative care for patients undergoing surgery for ACC.**

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Introduction

Adrenocortical carcinoma (ACC) is a rare and highly aggressive malignancy. Interest in this condition has increased in recent years[1,2], and the first international multicentre RCTs on chemotherapy in advanced ACC were published in 2012[3] and 2015[4]. There is a consensus that surgery provides the best chance of cure for patients with ACC, but evidence-based protocols are lacking as the small number of patients operated on in each hospital, and the complex challenges related to the operations, have hampered attempts to standardize the surgical management of these tumours. In this context, a collaborative working group was appointed as a joint initiative from the European Network for the Study of Adrenal Tumours (ENSAT) and the European Society of Endocrine Surgeons (ESES), with the aim of providing standards for the perioperative surgical care of patients with ACC.

Methods

The scientific committees of ENSAT and ESES appointed as panelists surgeons with a dedicated interest in adrenal surgery who are part of a multidisciplinary team managing patients with ACC. Clinicians from several European countries were invited to participate in order to achieve a broad knowledge base and ensure the international validity of the conclusions.

As reported previously[5–7], a Delphi methodology[8], incorporating consecutive rounds of voting, feedback and open discussion, was used. A computerized search of the PubMed database was conducted using the following

*Members of the joint working group of ESES and ENSAT are co-authors of this study and can be found under the heading Collaborators

terms: 'adrenocortical cancer', 'adrenocortical carcinoma', 'adrenal cancer', 'adrenal carcinoma' and 'adrenal surgery'. Only studies published in English were included. Cross-checks for further publications were made based on reviews written by members of ESES[9], reviews from the European Society of Medical Oncology (ESMO)[10] and other recent reviews[2,11].

The invited experts defined the questions to be addressed and subsequently issued a draft consensus statement. Key single-sentence statements were taken from this document and circulated to all members for anonymous online voting. Statements with at least 80 per cent agreement were considered to have reached consensus and to be strong. Statements with less than 80 per cent agreement were reported to have achieved low consensus and were forwarded for discussion at the second consensus meeting held in November 2014. After further rounds of e-mail communication, agreement was reached for all statements.

The quality of evidence and strength of recommendations were categorized according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system[12–14]. When recommendations were rated as 'strong', the phrase 'the panel recommends' was used (indicating that the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects). When recommendations were rated as 'weak', the phrase 'the panel suggests' was used (indicating that the desirable effects of adherence to a recommendation most likely outweigh the undesirable effects, but the panel is less confident).

The quality of evidence was rated as 'high' (further research is very unlikely to change the panel's confidence in the estimate of the effect), 'moderate' (further research is likely to have an important impact on the panel's confidence in the estimate of the effect and may change the estimate), 'low' (further research is very likely to have an important impact on the panel's confidence in the estimate of the effect and is likely to change the estimate) or 'very low' (any estimate of the effect is very uncertain).

The level of evidence and final recommendations were evaluated and adjusted until consensus was achieved. The evidence is presented in the text, and the recommendations are summarized in *Table 1*.

Preoperative assessment before adrenalectomy for suspected ACC

Clinical history and examination

ACCs present with symptoms associated with hormonal oversecretion or local or regional manifestations triggered by mass effect, or are discovered as incidentalomas on imaging when unrelated symptoms are being investigated[15–17].

Clinical history and examination should assess the following: symptoms related to excess hormone production, including cortisol, Cushing's syndrome, androgen/oestrogen excess (virilization in females, feminization in males), signs or symptoms suggestive of multiple hormone secretion, and high BP[16–18]; local compressive symptoms of a large mass, usually non-secreting, including abdominal or flank pain, abdominal distension, early satiety, nausea/vomiting, weight loss, quick onset of symptoms and leg oedema[16–19]; and the genetic context[20–23] (Li–Fraumeni syndrome, multiple endocrine neoplasia type 1, Lynch syndrome, familial adenomatous polyposis, Gardner syndrome and Beckwith–Wiedemann syndrome).

Recommendation 1

Before adrenalectomy for suspected ACC, the panel recommends that the clinical history and examination assess at least:

1 *Symptoms related to hormone excess*
2 *Symptoms related to local compression by a large mass*
3 *A detailed family history for familial forms of cancer*

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Biochemical assessment

The rigorous biochemical and imaging assessment of an adrenal incidentaloma is outwith the scope of this article. This section focuses only on the information required by the surgeon to plan for the surgical intervention and perioperative care[24].

Before operating on a patient with ACC it is imperative to exclude the diagnosis of phaeochromocytoma by measuring 24-h urinary metadrenalines (metanephrines). Plasma metadrenalines can be measured, but the assay is not always available. The possibility of excessive secretion of steroids/precursors, aldosterone (extremely rare) and, in particular, cortisol should be assessed (*Table S1*, supporting information) in order to differentiate non-functional from functional tumours, and to decide whether the patient will require postoperative steroid replacement.

A promising approach for differentiating adenomas from ACCs uses mass spectrometry-based steroid profiling of 24-h urine samples[25]; clinicians are encouraged to contribute to the recruitment of patients into the prospective multicentre trial EURINE-ACT, which is exploring the feasibility of this new approach (http://www.ensat.org).

Table 1 Summary of the European Society of Endocrine Surgeons and European Network for the Study of Adrenal Tumours consensus guideline

		Summary and recommendations	Recommendation grade	Evidence level
Optimal preoperative investigation				
R1	Preoperative assessment before adrenalectomy for suspected ACC	Before adrenalectomy for suspected ACC, the panel recommends that the clinical history and examination assess at least: 1 Symptoms related to hormone excess 2 Symptoms related to local compression by a large mass 3 A detailed family history for familial forms of cancer	Strong	Moderate
R2	Biochemical assessment	The panel recommends a biochemical assessment to exclude the diagnosis of phaeochromocytoma, and that clinicians should investigate the excessive secretion of steroids/precursors (especially cortisol) before adrenalectomy for ACC or suspected ACC	Strong	Moderate
R3	Imaging	The panel recommends thoracoabdominal CT with contrast injection within at least 6 weeks before adrenalectomy for suspected ACC. MRI with gadolinium enhancement is required in patients with doubtful diagnosis, suspected vascular invasion or liver metastasis	Strong	Moderate
R4	Nuclear medicine	The panel recommends ^{18}FDG-PET within a maximum of 6 weeks before adrenalectomy for suspected ACC	Weak	Low
R5	Definition of an adrenal mass at increased risk of malignancy	The panel recommends considering the adrenal mass at increased risk of malignancy when it presents with: 1 Multiple hormonal, steroid precursor or sex hormone oversecretion, and/or 2 Intratumoral radiological signs of malignancy and/or a diameter greater than 6 cm, and/or 3 Evidence of local invasion, suspected metastatic lymph nodes, distant metastasis and/or high ^{18}FDG-PET uptake	Strong	Strong
R6		The panel recommends against preoperative biopsy of suspected ACC if surgical radical excision is feasible	Strong	Moderate
Optimal surgical approach				
R7	Referral centres	The panel recommends that care of patients with ACC should be limited to referral centres – those with established multidisciplinary teams consisting of surgeons, endocrinologists, oncologists, radiologists, pathologists, nuclear medicine physicians, biologists and geneticists. The surgery should be performed by surgeons with expertise in adrenal surgery (open and laparoscopic) and with a volume of more than 15 adrenalectomies per year (benign and malignant)	Strong	Low
R8	Oncological standards of ACC resection	The panel recommends complete *en bloc* resection of the ACC with the peritumoral/periadrenal retroperitoneal fat. Enucleation and partial adrenal resection are contraindicated for suspected ACC. Intraoperative tumour capsule rupture or spillage must be avoided for ACC and the suspected malignant adrenal mass	Strong	Moderate
R9		The panel does not recommend neoadjuvant chemotherapy in patients with resectable ACC	Strong	Low
R10	Optimal surgical route: open *versus* laparoscopic approach	The panel recommends the open approach as the standard of surgical care for confirmed or highly suspected ACC	Strong	Moderate
R11		The panel does not recommend the laparoscopic approach for an adrenal mass with evidence of local invasion or suspected metastatic lymph nodes (ENSAT stage III)	Strong	Moderate

Table 1 Continued

		Summary and recommendations	Recommendation grade	Evidence level
R12		The panel suggests the laparoscopic approach for a suspected malignant adrenal mass with a diameter of less than 6 cm (ENSAT stage I or II) without evidence of local invasion or suspected metastatic lymph nodes, as an option, should be restricted to high-volume centres. If a laparoscopic approach is used, the transperitoneal approach in the flank position might be preferable	Weak	Very low
R13		The panel recommends, if the adrenalectomy is performed laparoscopically, that the principles of oncological surgery be respected, with immediate conversion to open operation if there is an increased risk of spillage or capsular disruption. In that setting, the specimen should be retrieved in a plastic bag and care taken to avoid crushing the specimen within the bag	Strong	Moderate
R14	Regional lymphadenectomy	The panel suggests that routine locoregional lymphadenectomy should be performed with adrenalectomy for highly suspected or proven ACC. It should include (as a minimum) the periadrenal and renal hilum nodes. All suspicious or enlarged lymph nodes identified on preoperative imaging should be removed	Weak	Low
R15		The panel suggests that removal of the coeliac axis, superior mesenteric artery, para-aortic node and/or paracaval lymphadenectomy ipsilateral to the tumour be additionally considered in ACC	Weak	Very low
R16	Need for adjacent organ resection or extended resection	The panel recommends extended *en bloc* multivisceral resection of the invaded adjacent organ(s) to avoid tumour rupture or spillage for stage III ACC	Strong	Moderate
R17		The panel cannot recommend routine resection of the ipsilateral kidney in the absence of direct renal invasion	Weak	Low
Quality criteria of operative note and pathological report				
R18	Operation note	The panel recommends that an operation note should be standardized with detailed preoperative and surgical information (*Table 2*), and should ideally be included in a prospective collaborative database	Strong	Very low
R19	Pathology report	The panel recommends the use of a standardized pathology report including several macroscopic and microscopic features (Weiss score, ENSAT stage and Ki-67 proliferation index), ideally included in a prospective collaborative database	Strong	Very low
Optimal follow-up after surgery for ACC				
R20	Modality and frequency	The panel recommends that follow-up should include clinical evaluation, hormonal evaluation, thoracoabdominal CT and ^{18}FDG-PET every 3 months for the first 2 years and, thereafter, every 4–6 months based on the risk of recurrence	Strong	Very low
Surgical management of metastatic and/or recurrent ACC				
R21	Local recurrence	The panel recommends, when feasible, complete resection of locally recurrent ACC. The best results after surgery for recurrent ACC are found in patients with delayed recurrence (more than 12 months), low Ki-67 status and R0 complete resection. The panel recommends that laparoscopic resection be contraindicated in the management of recurrent ACC	Strong	Low

Table 1 continued

		Summary and recommendations	Recommendation grade	Evidence level
R22	Metastatic disease	The panel suggests that surgical resection of liver and/or pulmonary metastases be considered for metastatic ACC if R0 resection is achievable, and can be performed with low morbidity and mortality rates. The best results are observed in highly selected patients with favourable biological behaviour (low Ki-67 index and long disease-free interval)	Weak	Low
Debulking or palliative surgery				
R23	Palliative surgery	The panel cannot recommend the routine resection of asymptomatic primary ACC in the presence of unresectable metastasis	Strong	Low
R24		The panel cannot recommend routine debulking or R2 resection for primary, recurrent or metastatic ACC	Strong	Low
Need for inclusion in collaborative and/or prospective database				
R25	Perspective	The panel recommends the inclusion of patients and tumours in collaborative prospective databases and biobanks	Strong	Low

R, recommendation; ACC, adrenocortical carcinoma; ^{18}FDG, [^{18}F]fluorodeoxyglucose; ENSAT, European Network for the Study of Adrenal Tumours.

Recommendation 2

The panel recommends a biochemical assessment to exclude the diagnosis of phaeochromocytoma, and that clinicians should investigate the excessive secretion of steroids/precursors (especially cortisol) before adrenalectomy for ACC or suspected ACC.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Cross-sectional imaging

The goals of preoperative imaging are as follows: to determine whether an adrenal mass is at increased risk of being an ACC (see also Definition of an adrenal mass at increased risk of malignancy, below); and to plan the surgical procedure. Thoracoabdominal CT with contrast injection provides information regarding the size, shape, margins, internal structure, vascular distribution, venous thrombus, lymph node involvement, adjacent organ invasion (of kidney, distal pancreas, spleen, liver or diaphragm), the presence of intravascular thrombus in the inferior vena cava (IVC) or left renal vein, and distant spread of tumours[16,18,26].

Usually, ACCs are large at presentation, with a diameter greater than 6 cm in more than 90 per cent of patients[16,26]. The median size reported in large series is 10–11 (range 240) cm, whereas most benign adrenal tumours are usually smaller than 5 cm[16]. Non-enhanced CT usually identifies a heterogeneous but well defined suprarenal mass that displaces adjacent organs[16]. A spontaneous density of more than 10 Hounsfield units (HU) has a high sensitivity, but relatively low specificity to define an adrenal mass as malignant[16,26,27]. After contrast injection, the periphery typically shows greater enhancement with relatively low central enhancement owing to areas of haemorrhage and necrosis. In contrast to benign lesions, ACCs retain intravenously administered contrast materials and exhibit slow washout after administration, with relative and absolute percentages of less than 40 and 50 per cent respectively at 10 min, or 40 and 60 per cent respectively at 15 min[26]. Calcifications (small punctate or coarse) are relatively common, and usually located centrally[16,26]. Vascular invasion with a thrombus extending within the left renal vein and/or IVC is not uncommon (9–19 per cent of patients), and occurs more often in right-sided ACCs[16,26]. Metastases are frequently found at presentation; the most common sites are regional or para-aortic/paracaval lymph nodes (25–46 per cent), lung (45–97 per cent), liver (48–96 per cent) and bone (11–33 per cent)[18].

MRI with gadolinium enhancement and chemical-shift MRI can further characterize ACCs, with high sensitivity and specificity. Magnetic resonance angiography is superior to CT in the diagnosis of venous tumoral thrombus or venous invasion[16,28]. The typical feature of ACC is a heterogeneous mass owing to haemorrhage and foci of necrosis. On T1-weighted imaging, ACCs are isointense or hypointense compared with liver parenchyma. On T2-weighted imaging, ACCs appear hyperintense compared with liver, with a heterogeneous texture. Contrast enhancement is generally avid with slow wash-out[16,28].

Recommendation 3

The panel recommends thoracoabdominal CT with contrast injection within at least 6 weeks before adrenalectomy for suspected ACC. MRI with gadolinium enhancement is required in patients with doubtful diagnosis, suspected vascular invasion or liver metastasis.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Nuclear medicine

[^{18}F]fluorodeoxyglucose (FDG) is taken up by ACCs[29,30]. The specificity of ^{18}FDG-PET is lowered by the fact that the tracer is also actively taken up by some benign adrenal neoplasms and phaeochromocytomas. However, the most important ability of PET is to detect distant metastasis, which makes it a valuable tool in the staging and follow-up of patients with ACC undergoing treatment[29,30].

A new tracer for adrenocortical cells, [^{11}C]metomidate, has been developed and is currently under evaluation[31]. Imaging with metomidate labelled with ^{123}I (iodometomidate, [^{123}I]IMTO) can identify adrenocortical lesions with high specificity but is unable to differentiate benign from malignant lesions. In addition, retention of [^{123}I]IMTO in metastatic lesions can identify patients suitable for specific, targeted radioactive treatment[31–33]. When available, [^{123}I]IMTO imaging might help to detect distant metastasis before surgery as well as recurrences, as it is an adrenocortical specific tracer.

Recommendation 4

The panel recommends ^{18}FDG-PET within a maximum of 6 weeks before adrenalectomy for suspected ACC.

Agreement: *Strong*
Recommendation grade: *Weak*
Evidence level: *Low*

Definition of an adrenal mass at increased risk of malignancy

Adrenal incidentalomas are the most common adrenal disorder[34–36]. They encompass a wide spectrum of lesions, the vast majority of which are benign[36–38]. Based on various recommendations[37,39–41], surgical resection is required only for secreting tumours, symptomatic lesions and atypical large lesions with significant risk of malignancy.

The suspicion of malignancy is driven mainly by tumour size, intratumoral radiological signs of malignancy, signs of local invasion or distant metastasis, and type of hormonal secretion.

The risk of malignancy increases with tumour size and becomes significant for lesions larger than 4 cm. Intratumoral radiological signs of malignancy include the following: spontaneous density above 10 HU; signal loss on chemical-shift imaging below 20 per cent on MRI; high ^{18}FDG-PET uptake, low central enhancement due to areas of haemorrhage and necrosis, and slow wash-out after intravenous injection of contrast material.

Tumours secreting androgen, oestrogen, steroid precursors or multiple hormones are more likely to be malignant.

An adrenal biopsy is of very limited value for the evaluation of adrenal neoplasms, except for very rare primary adrenal lymphoma or when trying to demonstrate metastatic disease. Furthermore, biopsy can be dangerous in phaeochromocytomas and ACCs[42]; therefore, adrenal biopsy should be avoided.

Recommendation 5

The panel recommends considering the adrenal mass at increased risk of malignancy when it presents with:

1 *Multiple hormonal, steroid precursor or sex hormone oversecretion, and/or*
2 *Intratumoral radiological signs of malignancy and/or a diameter greater than 6 cm, and/or*
3 *Evidence of local invasion, suspected metastatic lymph nodes, distant metastasis and/or high ^{18}FDG-PET uptake*

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Strong*

Recommendation 6

The panel recommends against preoperative biopsy of suspected ACC if surgical radical excision is feasible.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Optimal surgical approach to non-metastatic primary ACC

Recommendations for the surgical approach to non-metastatic primary adrenocortical carcinoma are summarized in *Fig. 1*. It is important to note that in many patients

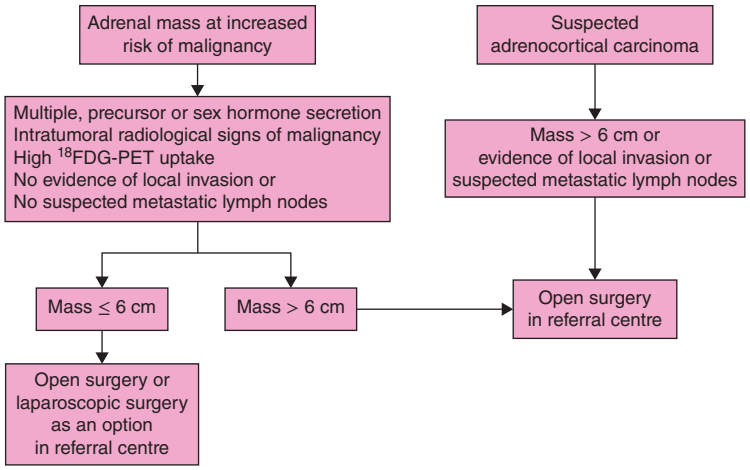

Fig. 1 Recommended surgical approach for non-metastatic primary adrenocortical carcinoma. ^{18}FDG, [^{18}F]fluorodeoxyglucose

the ACC diagnosis is confirmed only after surgery; hence the surgical strategy is based on a supposed diagnostic procedure.

Management in referral centres

Surgeons and their training, as well as the volume of the hospital, have a positive effect on postoperative morbidity/mortality and long-term survival for various types of cancer[43–45], including those for pancreatic cancer[46], rectal cancer[47,48], liver cancer[46] and oesophageal cancer[49]. For adrenal surgery, surgeons with a higher caseload have a higher rate of R0 resection[50], and studies have highlighted the value of hospital or surgeon volume and the need for centralization irrespective of specialty practice[51–53]. This is especially important because the widespread use of laparoscopic adrenalectomy has made surgical indications more liberal[54,55]. For ACC surgery[56,57], the expertise of dedicated centres appears to have a positive impact on outcome, at least attributable to a multidisciplinary approach[58], even though a recent large series[59] from the USA failed to demonstrate improved overall survival in patients treated more aggressively in high-volume centres.

Various cut-offs have been proposed to define expert centres, from four to ten adrenalectomies for ACC[56,59], or ten laparoscopic adrenalectomies[60] to 20 adrenalectomies per year[61], but no strong conclusion can be drawn from the available evidence, and the definition of a high-volume centre is often controversial and culturally oriented.

The minimum consensus reached was that referral centres can be defined as those with surgeons who perform at least 15 adrenal procedures a year. A referral centre should at least have surgeons with expertise in both open and laparoscopic adrenal surgery, and with expertise (or available help if required) in vascular, hepatic or pancreatic resection. Within the referral centre, all patients should be discussed before surgery by a multidisciplinary team including surgeons, endocrinologists, oncologists, radiologists, pathologists, nuclear medicine physicians, biologists and geneticists.

Recommendation 7

The panel recommends that care of patients with ACC should be limited to referral centres – those with established multidisciplinary teams consisting of surgeons, endocrinologists, oncologists, radiologists, pathologists, nuclear medicine physicians, biologists and geneticists. The surgery should be performed by surgeons with expertise in adrenal surgery (open and laparoscopic) and with a volume of more than 15 adrenalectomies per year (benign and malignant).

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Low*

Oncological standards of adrenocortical cancer resection

Taking into account the aggressive behavior of ACC, the only chance for cure in patients without metastatic disease is complete primary tumour resection, avoiding violation of the tumour capsule or spillage of tumour cells, and achieving microscopically margin-free resection (R0)[62–65]. Intraoperative tumour rupture or spillage and R2 resection are associated with very high recurrence rates and poor overall survival[66–68], and even R1 resection significantly diminishes the prognosis[67]. Because the ACC capsule can be thin

or fibrotic, and the tumour itself often harbours softer and tighter parts, the resection of ACC should be performed with the utmost caution to avoid tumour spillage.

The anatomy of the upper retroperitoneum[69] supports the concept of *en bloc* removal of the tumour and the periadrenal/peritumoral retroperitoneal fat. This could help decrease the risk of local recurrence from tumour cells invading the retroperitoneal fat. This is also in the line with the new ENSAT classification, as patients with stage III tumours (ACCs extending beyond the adrenal gland, T3 and T4 tumours without distant metastasis) have only a 30–40 per cent 5-year survival rate after complete resection[70].

To increase the number of patients amenable to R0 resection, some benefit of neoadjuvant chemotherapy (mitotane and etoposide or cisplatin-based chemotherapy) has been suggested recently for the treatment of patients with 'borderline' resectable adrenal tumours[71]. Nevertheless, in view of the low response rate to available chemotherapy[72] and the rapid growth of ACC, surgery first remains recommended if the lesion is amenable to R0 resection. This should be re-evaluated regularly according to the new therapeutic regimens.

Recommendation 8

The panel recommends complete en bloc *resection of the ACC with the peritumoral/periadrenal retroperitoneal fat. Enucleation and partial adrenal resection are contraindicated for suspected ACC. Intraoperative tumour capsule rupture or spillage must be avoided for ACC and the suspected malignant adrenal mass.*

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Recommendation 9

The panel does not recommend neoadjuvant chemotherapy in patients with resectable ACC.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Low*

Optimal surgical route: open *versus* laparoscopic approach

The standard surgical procedure for ACC is open surgery using a subcostal, midline or thoracoabdominal incision. It is widely accepted that open adrenalectomy is necessary for large malignant tumours invading the surrounding tissues (ENSAT stage III). Laparoscopic adrenalectomy can be considered for small tumours, and in experienced centres some advocate it as acceptable for tumours with diameter of 5–8 cm without invasion of adjacent organs (adrenal mass at increased risk of malignancy).

Owing to the low incidence of ACC, there are no randomized trials comparing laparoscopic and open approaches[73], and current knowledge is based on retrospective studies and expert opinion[74]. In addition, most laparoscopic series published to date did not report long-term follow-up and included low numbers of patients[19,75–83].

After the first report of a laparoscopic adrenalectomy by Gagner and colleagues in 1992[84], several studies[19,75–83] have reported favourable oncological outcomes for laparoscopic surgery in ACC compared with the open approach, with conflicting results regarding the risk of tumour rupture, peritoneal carcinomatosis, local and distant recurrence, and disease-free survival.

The choice of the best surgical approach for ACC or suspected malignant adrenal mass should be based on both the size and evidence of local invasion. If a laparoscopic approach is considered for an adrenal tumour at increased risk of malignancy (a mass with radiological intratumoral signs of suspicion and without clear locoregional involvement), the procedure should be performed only for small lesions (reasonable cut-off of 6 cm) by highly experienced surgeons. The transperitoneal approach with the patient in the flank position might be preferred: first, because reported experience with the retroperitoneoscopic approach for ACC is very limited; second, because it might allow intraoperative assessment of the presence of distant metastasis; and, finally, because it might allow larger *en bloc* resection of the tumour. It is important to note that there is no evidence for the superiority of the transperitoneal approach in the literature.

If the adrenalectomy is performed laparoscopically, the principles of oncological surgery should be respected. As in the open approach, the laparoscopic procedure should include lymphadenectomy of the renal hilum. Because 30 per cent of preoperative stage II ACCs are upstaged to stage III after pathological examination, primarily due to microscopic invasion of the surrounding tissues[76], the periadrenal fat has to be removed *en bloc* with the adrenal tumour[19].

Considering the technical feasibility of laparoscopic adrenalectomy, tumour size is of major importance, and the risk of spillage or capsule rupture, even for benign tumours, appears to be higher if they are larger than 6 cm. This remains controversial, however, and some

consider that for stage I/II ACCs smaller than 10 cm, the laparoscopic approach did not compromise the long-term oncological outcome as disease-specific and disease-free survival rates were comparable in the two groups[19].

In the present authors' opinion, a size of less than 6 cm represents a reasonable cut-off for considering the laparoscopic approach for a suspected malignant adrenal mass, provided there is no invasion of adjacent organs and the procedure is performed by a highly experienced surgeon. When the likelihood of malignancy is high, the open approach is preferred. When involvement of the surrounding tissues is discovered, or there is a risk of spillage, capsule injury or incomplete resection, immediate conversion to an open approach must be done. Furthermore, any adverse intraoperative events should be reported in the operation notes, as this might lead to the discussion of an adjuvant therapy.

Recommendation 10

The panel recommends the open approach as the standard of surgical care for confirmed or highly suspected ACC.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Recommendation 11

The panel does not recommend the laparoscopic approach for an adrenal mass with evidence of local invasion or suspected metastatic lymph nodes (ENSAT stage III).

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Recommendation 12

The panel suggests the laparoscopic approach for a suspected malignant adrenal mass with a diameter of less than 6 cm (ENSAT stage I or II) without evidence of local invasion or suspected metastatic lymph nodes, as an option, should be restricted to high-volume centres. If a laparoscopic approach is used, the transperitoneal approach in the flank position might be preferable.

Agreement: *Low*
Recommendation grade: *Weak*
Evidence level: *Very low*

Recommendation 13

The panel recommends, if the adrenalectomy is performed laparoscopically, that the principles of oncological surgery be respected, with immediate conversion to open operation if there is an increased risk of spillage or capsular disruption. In that setting, the specimen should be retrieved in a plastic bag and care taken to avoid crushing the specimen within the bag.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Role of regional lymphadenectomy

Retrospective data suggest that regional lymph node involvement in ACC has a negative impact on overall survival[67] and is frequently the cause of locoregional recurrence[85–87]. As reported recently by Fassnacht *et al.*[70], and independently validated in North America in the Surveillance, Epidemiology, and End Results (SEER) registries[88], patients with stage III tumours and positive lymph nodes can have a 10-year overall survival rate of up to 40 per cent after resection, although this finding has been challenged recently[89–91]. It is not yet decided whether a modified ENSAT classification should consider node-positive ACC as stage IV disease[89].

Discrepant reports regarding lymph node involvement ranging from 4 to 73 per cent[65–67,70,92,93] suggest that formal regional lymphadenectomy is neither formally performed by surgeons nor accurately assessed or reported by pathologists. According to large American and French series, approximately one-third of patients with ACC had formal lymphadenectomy as part of the tumour resection, reflecting the heterogeneity of operative management[65,93]. However, pathological post-mortem studies of patients with ACC showed involvement of lymph nodes in approximately 70 per cent of patients[92]. Data from the German ACC Registry suggest a reduced risk of local recurrence and disease-related death if more than five lymph nodes are removed[94]. In addition, lymph node dissection contributes to more accurate tumour staging, but its influence on overall and disease-free survival is uncertain[91]. The precise determination of which lymphatic fields and how many nodes should be dissected remains to be elucidated.

The lymph nodes involved most frequently are those located in the renal hilum and the para-aortic/paracaval lymph nodes[95]. Periadrenal nodes[96–103], even if they are rarely found and involved, and nodes at the origin of the renal vessels[104–106] should at least be sampled because they can be considered to be the first node stations of drainage[100]. If suspicious lymph nodes are observed on

preoperative imaging, they should be removed to reduce the risk of local recurrence. More extended lymphadenectomy is an option because several pathways may be involved owing to tumour size or lymph node involvement.

Recommendation 14

The panel suggests that routine locoregional lymphadenectomy should be performed with adrenalectomy for highly suspected or proven ACC. It should include (as a minimum) the periadrenal and renal hilum nodes. All suspicious or enlarged lymph nodes identified on preoperative imaging should be removed.

Agreement: *Strong*
Recommendation grade: *Weak*
Evidence level: *Low*

Recommendation 15

The panel suggests that removal of the coeliac axis, superior mesenteric artery, para-aortic node and/or paracaval lymphadenectomy ipsilateral to the tumour be additionally considered in ACC.

Agreement: *Low*
Recommendation grade: *Weak*
Evidence level: *Very low*

Need for adjacent organ resection or extended resection

The upper limit of the perirenal space is not covered by Gerota's fascia, explaining the clinical finding that right-sided ACCs may invade the liver and/or diaphragm, and left-sided ACCs may invade the spleen, pancreas and/or diaphragm[69,107]. Although published data offer sparse details about such intraoperative findings, it is generally agreed that adjacent organs should be resected *en bloc* if they are suspected to be invaded. This includes the spleen, distal pancreas, stomach, kidney, right liver, colon, diaphragm, and the wall of the IVC or left renal vein. The threshold for *en bloc* resection of adjacent organs, if they are suspected to be invaded, should be low.

To avoid the risk of capsular damage when dissecting the tumour from the kidney, some surgeons advocate performing *en bloc* resection of the retroperitoneal space including the kidney[65], although a survival benefit of this radical approach has not been proven[64,108]. A retrospective study[109] compared the oncological results of patients with stage II ACC treated by radical adrenalectomy alone or by nephroadrenalectomy. The results did not support the hypothesis that nephrectomy improved the oncological outcome. Combined nephrectomy, however, offers a lower risk of capsular rupture and can include complete lymphadenectomy of the renal hilum. In a multicentre European study[65] on surgery for ACC, pathological invasion of the kidney was observed in only 30 per cent of the patients with combined nephrectomy.

Extension of ACC to the adrenal, renal vein or IVC occurs in approximately 25 per cent of the patients[110,111]. Venous involvement consists mostly of intravenous tumour thrombus, but can be associated with direct vascular invasion. Thrombectomy may require IVC cross-clamping above or below the hepatic vein confluence or cardiopulmonary bypass, depending on the upper level of the thrombus[111]. The resection should include complete thrombectomy, a flush manoeuvre and, occasionally, vascular cuff or prosthetic IVC replacement. A 3-year overall survival rate of 25–29 per cent in a large series encourages the performance of a venous resection in the presence of IVC or renal vein invasion[110,112].

Recommendation 16

The panel recommends extended en bloc *multivisceral resection of the invaded adjacent organ(s) to avoid tumour rupture or spillage for stage III ACC.*

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Moderate*

Recommendation 17

The panel cannot recommend routine resection of the ipsilateral kidney in the absence of direct renal invasion.

Agreement: *Strong*
Recommendation grade: *Weak*
Evidence level: *Low*

Quality criteria for operation notes and pathological reports for ACC

Operation note

In the future, outcome analysis will have to be based on more accurate records of the extent and type of operation performed for each patient with a suspected or confirmed diagnosis of ACC. It can be anticipated that use of a standardized operating note could summarize perioperative information considered to be significant for future clinical studies. It is expected that a standardized operation note

Table 2 Minimum information required in the operation note for adrenocortical carcinoma

Patient identity					
Age (date of birth)		Operation date		Sex	
Preoperative assessment					
Initial diagnosis based on: Hormone excess Compressive symptoms Incidentaloma		Length of symptoms (weeks)	Biochemical assessment: Non-secreting Cortisol Aldosterone Sex steroids Precursor Other	Past medical history of cancer (if yes, give detail)	Genetic context (if yes, give detail)
Side	CT	MRI	PET SUVmax Tumour/liver SUV	Other imaging (if yes, give detail)	Maximum diameter (cm)
Local invasion (if yes, give detail)		IVC invasion (if yes, give detail)	Metastases (if yes, give detail)	Preoperative ENSAT stage	Other
Surgical approach and resection					
Laparoscopic: No Transperitoneal Retroperitoneal Robotic		Open: Subcostal Midline Thoracoabdominal Other	Gerota's fascia: Not opened Opened	Adjacent organ resection (if yes, give detail)	Lymph node dissection (if yes, give detail)
Operating time (min)		Intraoperative blood loss (ml)	Tumour rupture (if yes, give detail)	Transfusion (if yes, give detail)	Other
Macroscopic appearance					
Complete resection through normal anatomical planes (expected R0)		Possible positive margins (expected R1)	Definite positive margins (R2)	Tumour intact, with covering capsule	Minimal capsular destruction or tumour fracture

SUVmax, maximum standardized uptake value; IVC, inferior vena cava; ENSAT, European Network for the Study of Adrenal Tumours.

could be developed further to a point where the data fields could be incorporated into multicentre databases (such as Eurocrine or ENSAT). The minimum information to be filed is summarized in *Table 2* (an example of a standardized operation note is included in *Fig. S1*, supporting information).

Recommendation 18

*The panel recommends that an operation note should be standardized with detailed preoperative and surgical information (*Table 2*), and should ideally be included in a prospective collaborative database.*

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Very low*

Pathology report

The standards for reporting ACCs, as developed for example by the Royal College of Pathologists (available for download at https://www.rcpath.org/resourceLibrary/g109_adrenaldataset_jan12-pdf.html) or the French practice guidelines issued by the COMETE group (http://sfendocrino.org/article/599/recommandations) were used to make these comments and recommendations[113].

The request form that accompanies the specimen should include: clinical details (clinical syndrome and any history of familial disease (for example, multiple endocrine neoplasia type 1 or Li–Fraumeni syndrome); any significant intraoperative events (such as tumour rupture and sutures marking the adrenal vein or areas of the tumour where margins might have been compromised); if the operation was performed laparoscopically, a statement should be made about intraoperative fragmentation of the tumour, which is very difficult to assess retrospectively by the pathologist. Indeed, removal of the specimen in a laparoscopic bag may lead to tumour disruption that compromises the assessment of tumour size, integrity of the tumour capsule and completeness of the excision.

The histological diagnosis of adrenal tumours remains challenging. If adrenocortical origin of the tumour remains debatable, expression of SF1 is the most valid marker[114,115]. From a surgical perspective, the minimum information needed in the pathological report includes: the integrity of the tumour capsule, and the presence or absence of invasion into periadrenal soft tissues and adjacent organs

(to be noted separately). If the normal adrenal gland can be identified, its relationship to the tumour and its appearance must be noted. The adrenal vein should be sampled to determine whether tumour thrombus is present (this is especially important in specimens with an attached kidney). The number of lymph nodes submitted or identified in the main specimen must be recorded. A clear statement must be made as to whether the resection status is R0, R1 or R2, because this parameter has a strong influence on predicted 5-year survival (50, 20 or 15 per cent respectively)[67].

The modified staging system introduced by ENSAT[70] must be used, including the modified definition for stage III (a tumour with any one of the following: positive lymph nodes, extra-adrenal tissue infiltration, or venous tumour thrombus in renal vein/IVC) and stage IV (any tumour with distant metastasis) tumours. The prognostic value of the ENSAT classification (*Table S2*, supporting information) was demonstrated recently in a large SEER cohort[88]. Weiss score[116] (*Table S3*, supporting information) and Ki-67 proliferation index must be recorded.

Recommendation 19

The panel recommends the use of a standardized pathology report including several macroscopic and microscopic features (Weiss score, ENSAT stage and Ki-67 proliferation index), ideally included in a prospective collaborative database.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Very low*

Follow-up after surgery for ACC

The risk of recurrence after surgery is influenced mainly by ENSAT stage, R resection status and Ki-67 findings[117], and could be stratified as shown in *Table 3*.

No randomized or prospective studies have compared different follow-up protocols after surgery for ACC. The following recommendations are based on selected retrospective series from specialized centres and expert opinion. Follow-up evaluation should include clinical and hormonal evaluation, thoracoabdominal CT and ^{18}FDG-PET. If available, [^{123}I]IMTO imaging could be used as an alternative to ^{18}FDG-PET. The first postoperative follow-up should be done within 3 months of surgery. Follow-up should then be conducted every 3 months for the next 2 years, every 4 months for patients at intermediate or high risk of recurrence, or every 6 months for patients with a low recurrence risk. After 5 years, follow-up should be every 6–12 months for up to 10 years. In case of doubt, hepatic MRI (with diffusion-weighted MRI) could be used to characterize small liver lesions more accurately.

Table 3 Risk stratification of recurrence after surgery for adrenocortical carcinoma

Moderate risk	Intermediate risk	High risk
Stage 1–2 *and* R0 resection *and* Ki-67 < 10%	Stage 3 *and* R0 resection *and* N0 category *and* Ki-67 < 10%	Stage 3 *and/or* R1/2 resection *and/or* N1 category *and/or* Ki-67 > 10% *and/or* tumour spillage

Adjuvant mitotane treatment has become the standard treatment for many patients with ACC[118–120] and is currently being addressed in an ongoing randomized trial.

Recommendation 20

The panel recommends that follow-up should include clinical evaluation, hormonal evaluation, thoracoabdominal CT and ^{18}FDG-PET every 3 months for the first 2 years and, thereafter, every 4–6 months based on the risk of recurrence.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Very low*

Surgical management of metastatic and/or recurrent ACC

Local and/or metastatic recurrence occurs in up to 74 per cent of patients after surgery, even following R0 resection[121]. Local and/or metastatic recurrences usually occur within the first 2 postoperative years[68,86,122], with a median interval between resection and first recurrence of approximately 1 year[86,122]. Only a few studies have reported the results of surgical management of recurrent ACC[62–64,86,108,123–128].

Local recurrence

Approximately 20–60 per cent of reported recurrences are locoregional. The recurrence is isolated in one-quarter of cases[64,85]. Whether adjuvant radiotherapy of the tumour bed can reduce the risk of local recurrence remains to be proven formally[85,129,130]. Patients with local recurrence are sometimes symptomatic because of mass symptoms and/or hormonal oversecretion. Less than half of the patients with local recurrence are amenable to radical R0 resection of the recurrent disease[86]. Only R0 resection of the locally recurrent disease provides a survival benefit. Laparoscopic resection should be contraindicated in the management of recurrent ACC. After reoperation, median

progression-free survival is between 6 and 32 months[122,124], and survival is more favourable in patients with an initially long disease-free interval. Reoperation is also associated with improvement of symptoms in most patients[122]. The decision to offer reoperation should be balanced with the risk of morbidity (12–55 per cent) and mortality (0–4 per cent) associated with reoperation[108,122,126,127,131]. A third resection can be offered to patients with local recurrence after initial resection of local recurrence, especially if R0 resection is possible. Mitotane adjuvant treatment after resection of local recurrence could help reduce second recurrence, even though this remains controversial[122,128]. If R0 resection of the locoregional recurrence is unlikely, neoadjuvant treatment should be discussed. Patients with early recurrence (within less than 6 months) are usually poor candidates for surgery because of their overall dismal prognosis.

Recommendation 21

The panel recommends, when feasible, complete resection of locally recurrent ACC. The best results after surgery for recurrent ACC are found in patients with delayed recurrence (more than 12 months), low Ki-67 status and R0 complete resection. The panel recommends that laparoscopic resection be contraindicated in the management of recurrent ACC.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Low*

Synchronous and metachronous metastatic ACC

Metastatic disease is a common feature in patients with ACC, with about one-third of patients having synchronous metastasis at diagnosis[70,132]. More than half of the patients will develop distant metastases despite complete initial resection of the primary tumour[67,133]. The overall 5-year survival rate in patients with metastatic disease is less than 20 per cent, with median survival between 6 and 20 months[65,134]. The number of metastatic organs at the time of the first metastasis and a high mitotic rate (more than 20 per 50 high-power fields) are independent prognostic factors for patients with stage IV disease[134]. Nevertheless, metastatic ACC is a heterogeneous disease, and long survival has been reported following resection and repeated surgery[63,64]. The number of patients with metastatic ACC referred for surgery in each centre remains low[124].

Resection of metastatic ACC is rarely curative, but can be associated with prolonged survival. Surgery should be considered only if R0 resection is achievable at both the primary and metastatic sites, with low morbidity and mortality rates. The decision to operate on metastatic ACC should also include tumour criteria: disease-free interval of more than 1 year for metachronous metastasis[108,125]; low Ki-67 proliferation index of the primary lesion or metastasis, if available; young age at the time of the first metastasectomy[127]; and favourable response to neoadjuvant chemotherapy[135]. Time to first recurrence after adrenalectomy and ENSAT T category of the primary tumour were associated with increased overall survival after pulmonary metastasectomy[126]. In selected patients, median survival and the 5-year survival rate from the time of first metastasectomy were 1.9–4.1 years and 29–41 per cent respectively[99,125]. The recurrence of pulmonary or liver metastases should not exclude repeated surgical resection, if repeat R0 resection is achievable. Ablation techniques such as microwave or radiofrequency ablation can be combined with surgery to achieve R0 resection[136]. It is also important to note that patients with synchronous metastases are usually poor candidates for surgery because of their overall dismal prognosis.

Recommendation 22

The panel suggests that surgical resection of liver and/or pulmonary metastases be considered for metastatic ACC if R0 resection is achievable, and can be performed with low morbidity and mortality rates.

The best results are observed in highly selected patients with favourable biological behaviour (low Ki-67 index and long disease-free interval).

Agreement: *Strong*
Recommendation grade: *Weak*
Evidence level: *Low*

Palliative surgery for ACC

The benefit of R2 resection of the primary ACC in patients with unresectable metastatic or locally recurrent disease has not been well studied. Studies of other cancers, such as renal carcinoma[137], cannot be extrapolated to ACC. In this setting, resection of primary ACC in the case of unresectable metastatic disease or palliative (R2) resection cannot be recommended. Patients with incomplete resection (R2 or debulking surgery) and patients not undergoing any surgery have similar progression-free survival[86], even though anecdotal series have reported favourable outcome after surgery[122]. However, debulking surgery may be considered for large, symptomatic and/or oversecreting ACC resistant to medical treatment when at least 80 per cent of the tumour is removable with minimal/acceptable morbidity.

Recommendation 23

The panel cannot recommend the routine resection of asymptomatic primary ACC in the presence of unresectable metastasis.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Low*

Recommendation 24

The panel cannot recommend routine debulking or R2 resection for primary, recurrent or metastatic ACC.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Low*

Need for inclusion in a collaborative and/or prospective database

Recent collaborative studies[72,118,138] have led to important clinical and scientific advances in the understanding of ACC. Because of the rarity of the disease, even in referral centres, the inclusion of patients and tumours in collaborative and/or prospective databases and biobanks such as ENSAT (http://www.ensat.org) or Eurocrine (http://www.eurocrine.eu) is strongly encouraged.

Recommendation 25

The panel recommends the inclusion of patients and tumours in collaborative prospective databases and biobanks.

Agreement: *Strong*
Recommendation grade: *Strong*
Evidence level: *Low*

Collaborators

All members of the working group contributed to the work and are to be considered co-authors.

The following are also members of the ESES/ENSAT working group on surgical management of adrenocortical carcinoma: B. Carnaille (Department of Endocrine Surgery, Centre Hospitalier Universitaire (CHU) and Université de Lille, Lille, France), B. Dousset (Department of Digestive and Endocrine Surgery, Cochin Hospital, APHP, Faculté de Médecine, Université Paris Descartes, and INSERM Unité 1016, Centre National de la Recherche Scientifique Unité Mixte de Recherche 8104, Institut Cochin, Paris, France), C. Fiori and F. Porpiglia (Division of Urology, Department of Oncology, University of Turin –'San Luigi Gonzaga' Hospital, Orbassano (Turin), Italy), P. Hellman (Department of Surgery, University Hospital, Uppsala, Sweden), M. Iacobone (Endocrine Surgery Unit, Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy) J.-L. Kraimps and G. Donatini (Department of Endocrine Surgery, Jean Bernard Hospital, Poitiers, France), J. Langenhuijsen (Department of Urology, Radboud University Medical Centre, Nijmegen, The Netherlands), K. Lorenz (Department of General, Visceral and Vascular Surgery, University of Halle-Wittenberg, Halle, Germany), M. Mathonnet (Department of Digestive and Endocrine Surgery, CHU Dupuytren, Limoges, France), E. Mirallié and C. Blanchard (Clinique de Chirurgie Digestive et Endocrine, Hôtel Dieu, CHU, Nantes, France), E. Nieveen van Dijkum (Department of Surgery, Academic Medical Centre, Amsterdam, The Netherlands), M. Raffaelli (Unità Operativa di Chirurgia Endocrina e Metabolica, Policlinico 'A. Gemelli', Università Cattolica del Sacro Cuore, Rome, Italy), N. Rayes (Department of General, Visceral and Transplant Surgery, Charité, Berlin, Germany), F. Sébag (Department of Endocrine and Metabolic Surgery, Hôpital de la Conception, Marseilles, France), F. Triponez (Thoracic and Endocrine Surgery, University Hospitals of Geneva, Geneva, Switzerland), A. Valeri (SOD 1 Chirurgia Generale, d'Urgenza e Mini-invasiva, Florence, Italy), J. Waldmann (General Surgery, Centre for Endocrine Surgery, University Hospital Giessen and Marburg, Marburg, Germany) and F. Zinzindohoue (Department of Digestive and Endocrine Surgery, Georges Pompidou European Hospital, APHP, Paris, France).

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Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Minimum biological investigation before surgery for adrenocortical carcinoma (Word document)

Table S2 Classification of the European Network for the Study of Adrenal Tumours (Word document)

Table S3 Weiss score: histopathological criteria (Word document)

Fig. S1 Example of preformatted operation note (Word document)