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Laparoscopy Assisted versus Open Distal Gastrectomy with D2 Lymph Node Dissection for Advanced Gastric Cancer: Design and Rationale of a Phase II Randomized Controlled Multicenter Trial (COACT 1001)

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Purpose: Laparoscopy-assisted distal gastrectomy for early gastric cancer has gained acceptance and popularity worldwide. However, laparoscopy-assisted distal gastrectomy for advanced gastric cancer is still controversial. Therefore, we propose this prospective randomized controlled multi-center trial in order to evaluate the safety and feasibility of laparoscopy assisted D2-gastrectomy for advanced stage gastric cancer.

Materials and Methods: Patients undergoing distal gastrectomy for advanced gastric cancer staged cT2/3/4 cN0/1/2/3a cM0 by endoscopy and computed tomography are eligible for enrollment after giving their informed consent. Patients will be randomized either to laparoscopy-assisted distal gastrectomy or open distal gastrectomy. Sample size calculation revealed that 102 patients are to be included per treatment arm. The primary endpoint is the non-compliance rate of D2 dissection; relevant secondary endpoints are three-year disease free survival, surgical and postoperative complications, hospital stay and unanimity rate of D2 dissection evaluated by reviewing the intraoperative video documentation.

Discussion: Oncologic safety is the major concern regarding laparoscopy-assisted distal gastrectomy for advanced gastric cancer. Therefore, the non-compliance rate of clearing the N2 area was chosen as the most important parameter for the technical feasibility of the laparoscopic procedure. Furthermore, surgical quality will be carefully reviewed, that is, three independent experts will review the video records and score with a check list. For a long-term result, disease free survival is considered a secondary endpoint for this trial. This study will offer promising evidence of the feasibility and safety of Laparoscopy-assisted distal gastrectomy for advanced gastric cancer. Trial Registration: NCT01088204 (international), NCCCTS-09-448 (Korea)

Key Words: Gastrectomy; Stomach neoplasms; Lymph node excision

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Introduction

Minimally invasive surgery has become a treatment option for cancer. In Korea, laparoscopy-assisted distal gastrectomy (LADG) for early gastric cancer has gained acceptance and became a treat-

ment option.[1,2] Many randomized controlled studies reported that LADG had better short-term results such as a less pain, earlier mobilization, faster recovery of bowel function, shorter hospital stay, better cosmetic effect, and improved quality of life (QoL).[3-8] Moreover, some retrospective studies showed comparable long-term survival.[9-11] According to the study by An et al.,[11] the overall 5-year survival rate of patients at stage IB did not differ between LADG and open distal gastrectomy.

However, LADG for advanced gastric cancer (AGC) is still controversial. Only a few case-control trials were demonstrated postoperative outcomes in AGC patients treated with LADG and open distal gastrectomy.[12-18] In a meta-analysis by Qiu et al.,[19] the oncologic outcomes of LADG for AGC patients were comparable with open approach. LADG did not differ significantly from open surgery in terms of overall survival and tumor recurrence after surgery on the basis of long-term follow-up, and it has the several advantages of a rapid resumption, such as less bleeding, few analgesic requirements, and shorter hospital stay.

However, results from those studies appear not to yield sufficient data to apply laparoscopic surgery to AGC patients. So far no randomized controlled trials revealed the oncologic safety of laparoscopy assisted gastrectomy in advanced stage gastric cancer. Therefore, we propose this prospective multi-center randomized controlled trial to confirm the feasibility and safety of laparoscopic gastrectomy in AGC.

Materials and Methods

1. Study population, inclusion and exclusion criteria

All patients with clinically advanced stage non metastatic, histologically proven gastric cancer (cT2/cT3/cT4 cN0/cN1/cN2/cN3 cM0 according to the sixth Union for International Cancer Control edition) as assessed by esophagogastroduodenoscopy and computed tomographys are eligible for enrollment in this trial (Fig. 1). Because considerable discrepancy for clinical stage was expected, all computed tomography images were sent to one radiologist (J.S.L.) before enrollment and he reviewed them. When the clinical stage by the radiologist accorded with inclusion criteria, we enrolled the patient. All patients giving informed consent have to be aged between 20 to 80 years. Participation in another trial interfering with the outcome of this study, language problems, lack of compliance, mental inability, synchronous or previous malignant disease (except curatively treated in situ cervical cancer or curatively resected non-melanoma skin cancer), systemic administration of corticosteroids, unstable angina or myocadial infarction witin 6 months of the trial, severe respiratory disease, American Society of Anesthesiologists score >3, previous major abdominal surgery, previous chemo- or radiotherapy, inadequate liver-, kidney- and bone-marrow functions and Eastern Cooperative Oncology Group status >1 are considered exclusion criteria. The study protocol was approved by the Institutional Review Board of the National Cancer Center Korea on 21st of January 2010 (NCCCTS-09-448). All participating centers approved the trial by local Institutional Review Boards subsequently. Further the trial was registered in the clinical trials database (NCT01088204).

2. Randomization and surgical procedures

After consenting in participation of the trial, patients are preoperatively randomized to either of the two treatment groups (LADG or open distal gastrectomy, the procedures are displayed in detail in

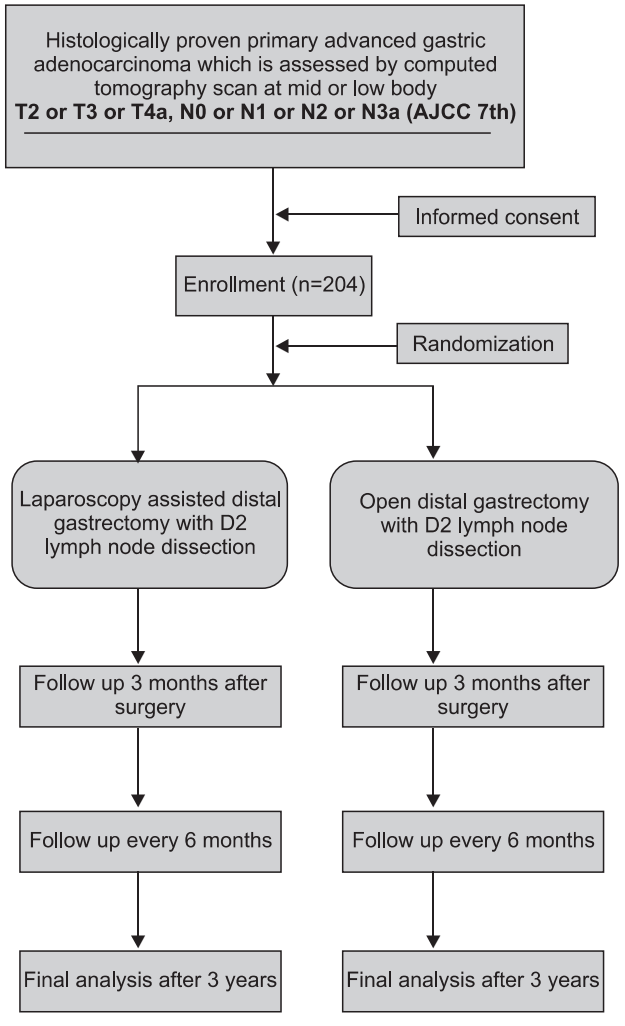

Fig. 1. Study scheme. AJCC = American Joint Committee on Cancer.

Appendix 1). Randomization is performed as block randomization in fixed block sizes in a 1 : 1 allocation ratio using a centralized web-based randomization system (eVelos [http://eresearch.ncc.re.kr/eres/jsp/ereslogin.jsp]). In order to achieve equal group sizes randomization is stratified for each respective center. The surgical procedures are performed according to the guidelines of the Japanese Research Society for Gastric Cancer.[20] Briefly, after laparotomy or placement of laparoscopic ports, the stomach is mobilized by dissection of the greater and lesser omenta, lymph node stations #1, #3, #4sb, #4d, #5, #6, #7, #8a, #9, #11p, #12a and the gastrosplenic ligaments. Extension of lymph node dissection may be applied according to surgeon's estimation in case of further suspicious involvement. The duodenum is dissected distal to the pyloric ring and the stomach should be dissected proximally with a margin of at least 3 cm. Distal margin should be at least 1 cm. The mode of dissection is left to the surgeon's discretion (ultrasonic shears, electrocautery, etc). Reconstruction is also left to the surgeon's discretion (Billroth I, Billroth II, Roux-en-Y). All laparoscopic procedures are recorded for further evaluations. Photo documentation of the N2 area (at least three photos) is mandatory for the open resection.

3. Study objectives

1) Primary endpoint

Primary efficacy endpoint is the evaluation of feasibility of D2 lymph node dissection by laparoscopic surgery compared to open distal gastrectomy by calculating the non-compliance rate between the two groups. The non-compliance rate is defined as the proportion of patients with more than one missing lymph node station. The compliance rate was first reported in the Dutch D2 trial.[21] Non-compliance is being determined in the pathologic report. After oncologic dissection the surgeons dissect each lymph node station from the removed specimens and send them separately for pathologic examination. If the pathologist does not find any lymph nodes in more than one lymph node station, the definition of non-compliance is met.

2) Secondary endpoints

Major secondary endpoints are surgical and oncologic outcomes. The following surgical outcomes are evaluated: Hospital stay, operating time, time to first flatus, surgical stress by measurement of serum C-reactive protein (CRP), and interleukin-6 (IL-6) levels. Postoperative complications are recorded according to the Accordion Severity System.[22] Medical complications (pulmonary, vascular, cardiac) are distinguished from surgical complications such as anastomotic leakage, intraabdominal abscess, hemorrhage, ileus and wound infection.

The following oncologic outcomes are investigated in this trial. Immediate postoperative oncologic outcomes to be determined are the total number of dissected lymph nodes, the number of lymph nodes at each station, and the distance from the primary tumor to the proximal and distal resection margins. Intraperitoneal spillage of tumor cells is determined by reverse transcriptase-polymerase chain reaction (RT-PCR) in anti-cytokine19 (CK19) and anti-carcinoembryonic antigen (CEA) antibody stained cells in the washing solution of the celiac axis before and after resection. It is further planned to determine the rate of patients with a lymph node count of less than 26 as surrogate number of completeness of dissected lymph nodes in D2 dissection. Further surgical quality is reviewed by three independent randomly assigned experts who examine the unedited video documentation of the laparoscopic procedure and the photo documentation of the open surgery. The raters are going to review the completeness of the surgical D2 dissection by using a scoring tool (Appendix 2). The rate of patients with disease free survival after three postoperative years is determined during regular follow up visits every six months to the outpatient clinic. Evaluation of surgical and oncologic outcomes is also analyzed according to center stratification (high/low volume center).

4. Methods against bias

1) Selection bias

Randomization into two treatment groups will be performed in order to omit selection bias from this trial. Comparable intervention groups are achieved by block randomization using a web based randomization tool (eVelos [http://eresearch.ncc.re.kr/eres/jsp/ereslogin.jsp]). Randomization is stratified according to center and clinical stage in fixed block sizes (1 : 1 allocation ratio) in order to achieve equal groups.

2) Information bias

Blinding procedures are not possible in this trial due to the nature of the intervention. Patient and observers for postoperative outcomes are blinded to guarantee an optimal study outcome.

3) Confounding

Potential confounding will be reduced by the randomization process. In order to reduce procedural outcomes all surgical proce-

dures are going to be defined in operating manuals. Further intraoperative photo documentation is mandatory to proof completeness of D2 dissection in open resections. Unedited video documentation is mandatory for the laparoscopic cases. Surgical quality will be reviewed by three independent and randomly assigned experts using an evaluation tool (Appendix 2). Postoperative care is standardized. Blinded assessment of the primary outcome will be provided by blinded observers. Patient blinding will not be possible due to the nature of the surgical procedure.

5. Sample size calculation

The present study aims to evaluate the surgical and oncological safety of LADG with D2 lymph node dissection, and the primary end point is non-compliance rate. The trial hypothesis is the non-compliance rate for LADG does not statistically differ from the one for open distal gastrectomy. We, first, evaluated the compliance rate for open approach in the institutional database of more than 5,000 cases and found it to be about 60%.[23] Therefore, we expected 60% of the compliance rate for LADG and the expected compliance rate will be estimated with the following precision: margin of error of 10% with 95% confidence level. The sample size needed based on the above mentioned considerations would be 92 patients per treatment group. Considering a 10% of follow-up loss, 102 patients per each arm have to be enrolled. Thus a total of 204 patients are to be enrolled in this study.

6. Documentation and data handling

All protocol required information collected during this trial is entered in the electronic case report form (eCRF) using the web based eVelos system (http://eresearch.ncc.re.kr/eres/jsp/ereslogin.jsp). The completed eCRFs are reviewed and signed by the investigator or subinvestigator and sent to the independent data management group in the eVelos team. Quality control is being enforced by site visits and CRF review. The data is going to be handled, managed and analyzed according to appropriate regional standard operating procedures.

Discussion

This will be the first randomized controlled study to evaluate the feasibility of LADG in patients with AGC. We compared the oncological outcome by non-compliance rate between LADG and open distal gastrectomy. Moreover, surgical outcomes such as operating time, hospital stay, postoperative complications and pathological outcomes such as the total number of dissected lymph node, and the number of lymph node at each station were also evaluated. Additionally, surgical stress by measurement of serum CRP and IL-6 levels and intraperitoneal spillage of tumor cells determined by RT-PCR in anti-CK19 and anti-CEA antibody stained cells in the washing solution were also identified.

Oncologic safety is supposed to be the major concern among many surgeons. In order to achieve the best possible oncologic result, D2 dissection is considered standard of care, especially in advanced stage gastric cancer.[24] The importance of D2 dissection for locally AGC has been demonstrated in several multicenter trials.[24-26] There is evidence that adequate D2 lymphadenectomy seems to be sufficient to control tumor recurrence. The trial by Sasako et al.[25] showed that five year survival rates for patients undergoing surgery only were between 70% and 80%. Another trial by Sakuramoto et al.[26] confirmed an overall five year survival rate of approximately 65%. Even European trials reported improved long-term outcomes for patients having undergone D2 dissection when postoperative morbidity and mortality can be kept at an acceptable level.[24]

However, it remains elusive whether adequate D2 dissection is possible in laparoscopic surgery for advanced stage gastric cancer. So far there is only low level evidence of laparoscopic surgery in advanced stage gastric cancer. Although previous case-control studies revealed the safety and feasibility of LADG compared with open approach, bias cannot be excluded in these cohorts.[12-18] There are several reasons: data for advanced stage patients were obtained only incidentally, when postoperative reports revealed an advanced cancer stage although patients underwent laparoscopic surgery under the assumption of early gastric cancer. Further selection and information bias may not be excluded in those studies. Therefore, we encourage this multicenter randomized controlled trial to shed light on the feasibility of minimally invasive surgery for advanced stage gastric cancer.

The primary endpoint of non-compliance rate of clearing the N2 area was chosen as the most important parameter for the technical feasibility of the laparoscopic procedure. Non-compliance in D2 dissection is defined as inability to retrieve lymph nodes from more than one lymph node station as they are defined by JRSGC guidelines.[20] In this trial, the lymph node stations are separated by the responsible surgeon and sent for pathologic examination. If the pathologist is unable to find any lymph nodes in more than one of the respective stations, non-compliance is confirmed. The compliance rate of D2 dissection is a widely accepted endpoint measure and was already applied in a prospective clinical trials.[21,22] It might

be debatable that in oncologic studies disease-free and overall survival should be chosen as primary outcome measures, but N2 area clearance can be considered as a surrogate parameter for long term oncologic outcome. Therefore disease free survival is considered a secondary endpoint for this trial. If feasibility cannot be proven in this randomized controlled phase II trial, further phase III trials evaluating overall and long term survival should not be encouraged.

Numerous surgical and oncologic outcomes are evaluated in this trial. Besides commonly used secondary endpoints this trial records postoperative complications according to the Expanded Accordion Severity Classification of Postoperative Complications which was proposed in 2009.[22] The Accordion Severity Classification System can be easily used for small and large studies and is independent on the surgical procedure investigated. We chose the Expanded Version for complication classification as we consider D2 gastrectomy a complex procedure bearing potential risks for the patients, especially in advanced stage gastric cancer. The profile of intra- and postoperative complications for possible complications in laparoscopic gastric cancer surgery was published by our institution before.[27]

It might be debatable why QoL will not be evaluated in this trial as a secondary endpoint. The principal investigator already conducted a trial with a focus on QoL evaluation and found out that short term improvements in postoperative QoL were observed in the laparoscopic group.[6] Therefore evaluation of QoL was not reconsidered in this trial, although it is conceivable that perception of QoL might be different (better) in advanced stage gastric cancer patients.

Further surgical quality will be carefully reviewed in this trial. Three independent experts are reviewing the video records of all laparoscopic procedures. Oncologic safety is of utmost importance in this trial, especially for advanced stage gastric cancer patients. Video and photo documentation are considered to ensure homogenous surgical quality over all participating centers, although surgical expertise for laparoscopic gastric cancer surgery is excellent among the (sub-)investigators. All participating surgeons are obliged to having performed over 50 cases of laparoscopy assisted distal gastrectomies before the study. As open D2 gastrectomy is a standard procedure in Korea, no specific training for the lymph node dissection itself is considered necessary.

Conclusively this randomized controlled trial is believed to confirm feasibility and safety of laparoscopy assisted distal gastrectomy with D2 lymph node dissection for advanced stage gastric cancer patients.

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Appendix 1. Description of surgical procedures

Laparoscop assisted distal gastrectomy

1. Open placement of umbilical 11 mm camera port.
2. Inspection of abdomen for adhesions, peritoneal seeding and check for resectability.
3. Placement of 12 mm trocar in the right clavicular midline under camera control.
4. Placement of 5 mm trocar at right subcostal area (1~2 cm below rib bow) under camera control.
5. Placement of 5 mm trocar at left subcostal area (1~2 cm below rib bow) under camera control.
6. Placement of 5 mm trocar in the left clavicular midline under camera control.
7. Liver lift (optional): Transcutaneous placement of straight needle thread and grasping with needle holder, intraabdominal turn and leading the needle back through the abdominal wall on the opposite site of the hepatic ligament. Liver lift with grasper and placement of hemolok clip and thread to the base of the ligamentous structure at the base of the left liver lobe.
8. Dissection of greater omentum near the transverse colon from the hepatic flexure to splenic lower pole using either the harmonic scalpel or electrocautery. Preparation and visualization of omental branch, saving of omental branch.
9. Preparation and visualization of left gastroepiploic artery clipping and separation. Dissection of #4sb lymph nodes.
10. Preparation of prepancreatic plane around the pancreatic head, dissection of embryologic plane, optional Kocher maneuver. Preparation and visualization of right gastroepiploic vein at the confluence with the anterior superior pancreatoduodenal vein, clipping and separation of right gastroepiploic vein and preserving the ASPDV. Preparation and visualization of right gastroepiploic artery, clipping and separation. Further dissection of #6 lymph nodes.
11. Dissection of lesser omentum near the hepatic insertion using either the harmonic scalpel or electrocautery.
12. Dissection of lymphatic tissue at the right side of the diaphragmatic crus to expose the esophagus using either the harmonic scalpel or electrocautery.
13. Dissection of suprapancreatic area: Preparation and visualization of coronary vein, clipping and separation. Dissection of LN #8a, #9 and #7 along the common hepatic artery and the celiac trunk using either the harmonic scalpel or electrocautery. Preparation and visualization of left gastric artery, clipping and separation.
14. Dissection of posterior attachment of the gastric fundus and right cardiac lymph nodes (#1).
15. Transverse or longitudinal 5 cm incision in the epigastric area, retraction of the specimen and clamping.
16. Proximal transsection using Allen/Kelly clamp and GIA.
17. Continuous reinforcement suture of the GIA staple line.
18. Upon surgeon's choice reconstruction according to Billroth I or Billroth II.
19. B-I reconstruction: Placement of anvil in duodenum after application of pursestring suture, stapled (CEEA) anastomosis between gastric remnant and anastomosis, closure of stapler introduction site by GIA and reinforcement suture.
20. B-II reconstruction: Antecolic pull-up of first jejunal limb, hand sewn double-layered anastomosis.
21. Bleeding control, placement of Surgicel in LN dissection areas, JP-drain placement upon surgeon's choice.
22. Continuous suture of the peritoneum (Vicryl 1).
23. Continuous fascia closure with Maxon sling.
24. Skin stapling, dressing.

Open distal gastrectomy

1. Midline incision, fascia separation and inspection of abdomen.
2. Optional peritoneal washing cytology after exclusion of metastatic disease and check for technical resectability.
3. Dissection of greater omentum near the transverse colon from the hepatic flexure to splenic lower pole using either the harmonic scalpel or electrocautery. Preparation and visualization of omental branch, saving of omental branch.
4. Preparation and visualization of left gastroepiploic artery clipping and separation. Dissection of #4sb lymph nodes.
5. Preparation of prepancreatic plane around the pancreatic head, dissection of embryologic plane, optional Kocher maneuver. Preparation and visualization of right gastroepiploic vein at the confluence with the anterior superior pancreatoduodenal vein, clipping and separation of right gastroepiploic vein and preserving the ASPDV. Preparation and visualization of right gastroepiploic artery, clipping and separation. Further dissection of #6 lymph nodes.
6. Dissection of lesser omentum near the hepatic insertion using either the harmonic scalpel or electrocautery.
7. Dissection of lymphatic tissue at the right side of the diaphragmatic crus to expose the esophagus using either the harmonic scalpel or electrocautery.
8. Dissection of suprapancreatic area: Preparation and visualization of coronary vein, clipping and separation. Dissection of LN #8a, #9 and #7 along the common hepatic artery and the celiac trunk using either the harmonic scalpel or electrocautery. Preparation and visualization of left gastric artery, clipping and separation.
9. Dissection of posterior attachment of the gastric fundus and right cardiac lymph nodes (#1).
10. Proximal transsection using Allen/Kelly clamp and GIA.
11. Continuous reinforcement suture of the GIA staple line.
12. Upon surgeon's choice reconstruction according to Billroth I or Billroth II.
13. B-I reconstruction: Placement of anvil in duodenum after application of pursestring suture, stapled (CEEA) anastomosis between gastric remnant and anastomosis, closure of stapler introduction site by GIA and reinforcement suture.
14. B-II reconstruction: Antecolic pull-up of first jejunal limb, hand sewn double-layered anastomosis.

15. Bleeding control, placement of Surgicel in LN dissection areas, JP-drain placement upon surgeon's choice.
16. Continuous suture of the peritoneum.
17. Continuous fascia closure with Maxon sling.
18. Skin stapling, dressing.

Appendix 2. Scoring method for D2 lymph node dissection

Procedure	3	2	1	0
1. Omentectomy is well done.	☐	☐	☐	☐
2. Left gastroepiploic artery is ligated at its origin.	☐	☐	☐	☐
3. Right gastroepiploic artery is ligated at its origin.	☐	☐	☐	☐
4. Common hepatic artery is completely exposed.	☐	☐	☐	☐
5. Right gastric artery is ligated at its origin.	☐	☐	☐	☐
6. Portal vein is exposed.	☐	☐	☐	☐
7. Splenic artery is completely exposed to posterior gastric artery branch point.	☐	☐	☐	☐
8. Splenic vein is confirmed.	☐	☐	☐	☐
9. Left gastric artery is ligated at its origin.	☐	☐	☐	☐
10. Gastroesophageal junction is exposed.	☐	☐	☐	☐

<Detailed question>

1. Omentum is completely incised.
   *Does omentectomy begin as close to the large intestine as possible?
   **Is Omentum dissected from right colic flexure to left colic flexure?
   ***Is the anterior layer of transverse mesocolon detached from peritoneum, which connects it to the anterior part of pancreas?
2. Is the left gastroepiploic artery ligated at its origin?
3. Is the right gastroepiploic artery ligated at its origin?
4. Is the common hepatic artery exposed?
   *Is more than half of the anterior part of the common hepatic artery exposed?
5. Is the right gastric artery ligated at its origin?
6. Is the portal vein exposed?
7. Is the splenic artery exposed all the way to the branch of the posterior gastric artery?
   *Is more than half of the front part of the splenic artery exposed?
   **Is the area from the celiac trunk to to the branch of the posterior gastric artery exposed?
8. Is the splenic vein confirmed?
   *Is the splenic vein confirmed at least partly?
9. Is the left gastric artery ligated at its origin?
10. Is the gastroesophageal junction exposed?
    *Are the anterior and the right lateral side of the ventral esophagus exposed from the esophageal junction?

<Rating definition>

3 : completely performed
2: incompletely performed (> 50%)
1: partially performed (< 50%)
0: not performed
All scores are added up, maximum score 30P/reviewer ⇒ 90P overall maximum score D2 Dissection successful, if at least 85P are achieved.