EUROPEAN STUDY GROUP FOR PANCREATIC CANCER - TRIAL 5F

Four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy.

SURGICAL HANDBOOK
OVERVIEW

This handbook has been written for the ESPAC-5F trial (Four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy). The ESPAC-5F surgical working party have reviewed and agreed on the content.

The handbook is intended as a guide to the surgical procedures involved in the trial and provides a reference for investigators to ensure that the surgical procedures are standardised as much as possible across sites.

It is acknowledged that local practice and surgeon preference will be accepted when necessary.

The surgical procedures are presented under relevant headings and are classified as:

- Mandatory (M) – considered an essential step and must be performed as described in all cases.
- Equivocal (E) – may be considered an essential step for the procedure but can be performed as per surgeon preference.
- Prohibited (P) – considered as not allowed as part of this trial.

The ESPAC-5F trial acceptable standard surgical procedures*# are:

(i) Pylorus preserving pancreatoduodenectomy (PPPD).
(ii) Classic pancreatoduodenectomy (PD).
(iii) Total pancreatectomy (TP).
(iv) Bypass (gastric+/-biliary) procedure (BP).
(v) Laparotomy (L).

*The surgical interventions in the ESPAC-5F trial are complex and it is understood that surgeons may need to perform procedures in addition to (i)-(v) above when clinically indicated. This is acceptable and should be carefully documented.

# Staging laparoscopy is regarded as a screening assessment tool and is allowed as per local practice, but is not considered as part of the surgical procedure for ESPAC-5F.

The stages of surgery are described below. The order of procedures is flexible. This allows the most appropriate assessment and dissection of the tumour as per each patient.
1. ANAESTHESIA (M).

The patient will require general anaesthetic for the surgical procedure. This will be as per local practice.

2. INCISION (M).

Rooftop or as per local practice.

3. INSPECTION (M).

The surgeon will perform a visual inspection of the abdomen to assess for unresectable and/or metastatic disease. This will include inspection of:
   a) Liver.
   b) Small and large bowel.
   c) Duodeno-jejunal flexure.
   d) Transverse mesocolon.
   e) Peritoneum.

If metastatic disease is suspected a biopsy and frozen section should be performed.

4. INITIAL MOBILISATION (M).

   a) Division of adhesions if required eg. previous surgery.
   b) Lesser sac dissection to adequately expose the pancreas as required.
   c) Mobilise the hepatic flexure and right colon as required to adequately expose the operating area, 2\textsuperscript{nd} and 3\textsuperscript{rd} part of duodenum.
   d) Full Kocherisation of the duodenum to the aorta and left renal vein, through to the left-hand side of the superior mesenteric vessels.

5. ASSESSMENT OF RESECTABILITY (M).

This may require repeated assessment throughout the operation if it is not clear at this stage. The decision to resect will be made by the operating surgeon at an appropriate stage of the operation. This will rely on palpation to determine whether the tumour is clear of the superior mesenteric artery (SMA) or if the surgeon can dissect the tumour off the SMA.

6. EXPOSURE OF THE SUPERIOR MESENTERIC VEIN (SMV) (M).

   a) The SMV should be dissected from the transverse mesocolon to the inferior border of the pancreas if possible.
   b) Henle’s trunk should be ligated +/-transfixed and divided if possible (see Figure 1 below).
   c) The inferior part of the tunnel for the SMV at the pancreatic neck should be dissected as much as possible at this stage.
Figure 1. This photograph demonstrates the dissection area at the time of ligation of Henle’s trunk. The Lahey forceps are behind Henle’s trunk which has been ligated and is about to be divided.

7. **EXPOSURE OF THE GASTRODUODENAL ARTERY (GDA) (M).**

a) Incise the lesser omentum and supraduodenal peritoneum.
b) Dissect and remove lymph node 8 (see Figure 2 below).

c) Sloop the GDA and test clamp to check arterial anatomy.

![Figure 2. Japanese Pancreas Society classification of regional lymph nodes of the pancreas][1].

- 8 = Lymph nodes around common hepatic artery;
- 9 = lymph node around coeliac trunk;
- 10 = lymph nodes at hilum of sleep;
- 11 = lymph nodes along splenic artery;
- 12 = lymph nodes in hepatoduodenal ligament;
- 13 = posterior pancreatoduodenal;
- 14 = lymph nodes around the superior mesenteric artery;
- 15 = lymph nodes along the middle colic artery;
- 16 = para-aortic lymph nodes;
- 17 = anterior pancreatoduodenal;
- 18 = inferior border of body and tail of pancreas.

Expose the hepatic artery and GDA.

8. **TRANSLATIONAL STUDY – TRANSDUODENAL TRU-CUT BIOPSY OF TUMOUR. (E)**

- If taking part in the translational study then six tru-cut biopsies to be taken at this point before division of any major vessels before resection.
- The biopsies should be taken transduodenally into the tumour with the tru-cut biopsy needle lying parallel to the SMV and portal vein.
- The cores should be placed in Allprotect and then frozen according to ESPAC-5F standard operating procedures (see main protocol). Ultimately all tissue samples will be stored at -150°C.

9. **CHOLECYSTECTOMY AND BILE DUCT (M).**

- Cholecystectomy performed as per local practice. The preferred option is that the gallbladder should be resected en-bloc with the specimen.
- Dissection of the bile duct from the hepatic artery and portal vein.
c) Sloop the bile duct.

10. GDA DIVISION AND FORMATION OF PANCREATIC TUNNEL (M).

a) Ligate +/- transfix and divide the GDA.
b) Dissection to expose the superior border of the pancreas and neck.
c) Dissection of the tunnel under the pancreatic neck as far as possible.
d) A sloop may be placed under the neck of the pancreas if the tunnel is completely dissected. If this is not possible then as much of the tunnel should be dissected as appropriate.

11. MOBILISATION OF STOMACH AND JEJUNUM (M).

a) For PPPD divide duodenum using stapler as per local practice.
b) For PD divide distal stomach using stapler as per local practice.
c) Divide the jejunum using a stapler at a suitable distance to allow reconstruction.
d) Divide the jejunal mesentery as per local practice until the resected jejunum can be passed under the mesenteric vessels.

12. UNCINATE DISSECTION AND BILE DUCT DIVISION (M).

a) Mobilise and resect the uncinate process from the SMA as per local practice.
b) Stapler must not be used to divide areas of tissue.
c) Divide the bile duct above the cystic duct.
d) Leave the proximal end open and oversew the distal end of the divided bile duct.
e) Resect the lymphatic tissue of the porta hepatis proximally (as near to the hilum as possible) down to the specimen.

13. PANCREATIC RESECTION (M).

a) Transect the pancreatic neck as per local practice.

If taking part in the translational study then pancreatic juice should be aspirated from the pancreatic duct (on the felt hand side) using a fine umbilical catheter and syringe. The pancreatic juice should be collected, centrifuged and stored according to ESPAC-5F standard operating procedures (ESPAC-5F protocol section 8.5) (E).

b) Resection of the pancreas along the SMV and SMA to include lymphatic tissue to the right of the vessels as per local practice.
c) Stapler must not be used to divide areas of tissue.
d) Venous resection will be allowed if thought necessary by the operating surgeon. The types of venous resection include (see Figure 3). The venous involvement must be recorded in the ESPAC-5F surgical CRF. (M).
Figure 3. Demonstrates the types of venous resection that may be necessary during surgery. A and B refer to the spleno-portal confluence, C refers to superior mesenteric vein alone, D refers to portal vein alone and E refers to part of the vessel wall [2].

e) Venous reconstruction may include primary closure, patch, end to end anastomosis or interposition graft. The type of reconstruction must be recorded in the ESPAC-5F surgical CRF and photographed (M).

f) Arterial resection and reconstruction is not allowed in the ESPAC-5F trial (P). If arterial resection and reconstruction is performed eg. as a life saving procedure then this must be recorded in detail (M).

g) Dissection and removal of lymph node station 16 as per local practice (E).

h) The resection area to be photographed to show the mesenteric vessels and transected pancreatic neck and bile duct (see Figure 4 below).

Figure 4. Photograph demonstrating the resection area. The transected pancreatic neck (P) is seen with two stay sutures. The superior mesenteric vein has undergone a primary closure (arrow).

Note on resection:
Posterior or artery first dissection [3] may be necessary due to the location and involvement of the tumour (please see Figures 5a-d). This is acceptable for ESPAC-5F (E).

Figure 5a. Posterior dissection approach. Following Kockerisation of the duodenum the origin of the SMA is dissected (slooped). IVC=inferior vena cava, LRV=left renal vein.

Figure 5b. Posterior dissection approach. Dissection of the posterior pancreas along the SMA. The right hepatic artery (RHA) originates from the SMA. P= pancreas, PV=portal vein.

Figure 5c. Further dissection of the pancreas off the SMV and portal vein. SMA=superior mesenteric artery; RHA=right hepatic artery; SMV=superior mesenteric vein; P=pancreas.
14. RECONSTRUCTION (M).

a) Reconstruction performed as per local practice see example in Figure 6a and b.
b) Pancreatic stent to be placed as part of the pancreatic anastomosis (E).
c) Reconstruction to be recorded in the ESPAC-5F CRF and photographed.
d) Washout using saline (E).

Figure 6a. Demonstrates Roux-en-\text{y} reconstruction for a classic pancreatoduodenectomy; pancreato-jejunostomy, gastro-jejunostomy and jejuno-jejunostomy. Figure 6b. Demonstrates reconstruction for a pylorus preserving pancreatoduodenectomy; pancreatojejunostomy and duodeno-jejunostomy.

15. CLOSURE (M).
a) Two drains to be placed, one at the site of the biliary anastomosis and one at the site of the pancreatic anastomosis. One drain may be used if that is standard practice in that centre (E).
b) Closure of abdominal wall and skin as per local practice (M).

16. POST OPERATIVE CARE (M).

a) Patient managed post-operatively as per local practice.
b) Octreotide 100 micrograms administered subcutaneously TDS for 7 days post-op (E).
c) Drains left in for 7 days post op may be shortened according to local policy (E).
d) Amylase measured in drain fluid on post-op days 3, 5 and 7 (E).

17. OPERATIVE DETAILS (M).

a) Operative details recorded on the ESPAC-5F surgical CRF.
b) Intra-operative photographs of:
   (i) Post resection area of SMA and SMV.
   (ii) Venous resection/reconstruction if performed.
   (iii) Post reconstruction area.

TOTAL PANCREATECTOMY.

Total pancreatectomy is acceptable for ESPAC-5F when clinically indicated. The operating surgeon should record the reasons why TP has been performed.

Steps to include:
a) Mobilisation of the splenic flexure. (M).
b) Mobilisation of the pancreatic body and tail. (M).
c) Dissection of the splenic artery and sloop placed around artery. Test clamp. (M).
d) Short gastric arteries ligated and divided. (M).
e) Spleen mobilised. (M).
f) Splenic vein dissected and sloop placed. (M).
g) Splenic artery ligated +/- transfix and divided. (M).
h) Splenic vein ligated +/- transfix and divided. (M).
i) Resection of pancreas en bloc or pancreatic neck divided and then right and left pancreas resected. (M).
j) The resection area to be photographed. (M).
k) Reconstruction of hepatico-jejunostomy and duo/gastrojejunostomy according to local practice. (M).
l) The reconstruction area to be photographed. (M).
m) Post operative care as per local practice. (M).

PATIENTS FOUND TO HAVE UNRESECTABLE TUMOURS AT LAPAROTOMY.
a) If during the inspection/dissection the tumour is thought to be inoperable due to metastatic disease or local invasion then the operating surgeon may perform gastric+/− biliary bypass (E).

b) If possible a photograph of the area responsible for unresectability should be taken (M).

c) The type of surgery should be recorded and the reasons why resection was not possible on the ESPAC-5F surgical CRF (M).

DEFINITIONS OF COMPLICATIONS

1. Post-operative pancreatic fistula.

‘Drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than 3 times the serum amylase activity’ [4]. The grading for pancreatic fistula is seen in Table 1.

Table 1. Main parameters for POPF grading.

<table>
<thead>
<tr>
<th>Grade</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical conditions</td>
<td>Well</td>
<td>Often well</td>
<td>Ill appearing/bad</td>
</tr>
<tr>
<td>Specific treatment:</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes</td>
</tr>
<tr>
<td>US/CT (if obtained)</td>
<td>Negative</td>
<td>Negative/positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Persistent drainage (after 3 weeks)</td>
<td>No</td>
<td>Usually yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Reoperation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Death related to POPF</td>
<td>No</td>
<td>No</td>
<td>Possibly yes</td>
</tr>
<tr>
<td>Signs of infections</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Sepsis</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Readmission</td>
<td>No</td>
<td>Yes/no</td>
<td>Yes/no</td>
</tr>
</tbody>
</table>

2. Post pancreatectomy haemorrhage.
Postpancreatectomy hemorrhage is defined by 3 parameters: onset, location, and severity. The onset is either early (≤24 hours after the end of the index operation) or late (>24 hours). The location is either intraluminal or extraluminal. The severity of bleeding may be either mild or severe. Three different grades of PPH (grades A, B, and C) are defined according to the time of onset, site of bleeding, severity, and clinical impact (see Table 2) [5].

<table>
<thead>
<tr>
<th>Grade</th>
<th>Time of onset, location, severity and clinical impact of bleeding</th>
<th>Clinical condition</th>
<th>Diagnostic consequence</th>
<th>Therapeutic consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Early, intra- or extraluminal, mild</td>
<td>Well</td>
<td>Observation, blood count, ultrasonography and, if necessary, computed tomography</td>
<td>No</td>
</tr>
<tr>
<td>B</td>
<td>Early, intra- or extraluminal, severe</td>
<td>Often well/intermediate, very rarely life-threatening</td>
<td>Observation, blood count, ultrasonography, computed tomography, angiography, embolisation, relaparotomy for early PPH</td>
<td>Transfusion of fluid/blood, intermediate care unit (or ICU), therapeutic endoscopy, embolisation, relaparotomy for early PPH</td>
</tr>
<tr>
<td>C</td>
<td>Late, intra- or extraluminal, severe</td>
<td>Severely impaired, life-threatening</td>
<td>Angiography, computed tomography,</td>
<td></td>
</tr>
</tbody>
</table>

3. Delayed gastric emptying.

Delayed gastric emptying represents the inability to return to a standard diet by the end of the first postoperative week and includes prolonged nasogastric intubation of the patient (see Table 3).

<table>
<thead>
<tr>
<th>DGE grade</th>
<th>NGT required</th>
<th>Unable to tolerate solid oral intake by POD</th>
<th>Vomiting/gastric distension</th>
<th>Use of prokinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4–7 days or reinsertion &gt; POD 3</td>
<td>7</td>
<td>±</td>
<td>±</td>
</tr>
</tbody>
</table>
Three different grades (A, B, and C) were defined based on the impact on the clinical course and on postoperative management (see Table 4) [6].

Table 4. Parameters for grading of DGE

<table>
<thead>
<tr>
<th>DGE</th>
<th>Grade A</th>
<th>Grade B</th>
<th>Grade C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical condition</td>
<td>Well</td>
<td>Often well/minor discomfort</td>
<td>Ill/bad/severe discomfort (increased overall risk owing to complications and procedures)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>No</td>
<td>Possibly yes (pancreatic leak or fistula, intraabdominal abscess)</td>
<td>Possibly yes (pancreatic leak or fistula, intraabdominal abscess)</td>
</tr>
<tr>
<td>Specific treatment</td>
<td>Possibly yes (prokinetic drugs)</td>
<td>Yes (prokinetic drugs, potential reinsertion of NGT)</td>
<td>Yes (prokinetic drugs, NGT)</td>
</tr>
<tr>
<td>Nutritional support (enteral or parenteral)</td>
<td>Possibly yes (slower return to solid food intake)</td>
<td>Yes (partial parenteral nutrition)</td>
<td>Yes (total parenteral or enteral nutrition via NGT, prolonged, i.e., &gt;3 weeks postoperatively)</td>
</tr>
<tr>
<td>Diagnostic evaluation</td>
<td>No</td>
<td>Possibly yes (endoscopy, upper GI contrast study, CT)</td>
<td>Yes (endoscopy, upper GI contrast study, CT)</td>
</tr>
<tr>
<td>Intervventional treatment</td>
<td>No</td>
<td>No</td>
<td>Possibly yes (e.g., abscess drainage, relaparotomy for complication, relaparotomy for DGE)</td>
</tr>
<tr>
<td>Prolongation of hospital stay</td>
<td>Possibly yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Delay of potential adjuvant therapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Definitions of wound infection [7]

Superficial Incisional Surgical Site Infection
Infection within 30 days after the operation and only involves skin and subcutaneous tissue of the incision and at least one of the following:

1. Purulent drainage with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI made by a surgeon or attending physician.

Deep Incisional Surgical Site Infection
Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissue (e.g. fascia, muscle) of the incision and at least one of the following:
1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.

2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localised pain or tenderness, unless incision is culture-negative.

3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

4. Diagnosis of deep incisional SSI made by a surgeon or attending physician.

**Organ/Space Surgical Site Infection**

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs and spaces) other than the incision which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.

2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.

3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

4. Diagnosis of organ/space SSI made by a surgeon or attending physician.
Clavien-Dindo classification of complications [8]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.</td>
</tr>
<tr>
<td>Grade II</td>
<td>Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.</td>
</tr>
<tr>
<td>Grade III</td>
<td>Requiring surgical, endoscopic or radiological intervention.</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Intervention not under general anesthesia.</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Intervention under general anesthesia.</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Life-threatening complication (including CNS complications)* requiring IC/ICU management.</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Single organ dysfunction (including dialysis).</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Multiorgan dysfunction.</td>
</tr>
<tr>
<td>Grade V</td>
<td>Death of a patient.</td>
</tr>
<tr>
<td>Suffix “d”</td>
<td>If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.</td>
</tr>
</tbody>
</table>

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks. CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.
# Clinical Examples of Complication Grades

<table>
<thead>
<tr>
<th>Grades</th>
<th>Organ System</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Cardiac</td>
<td>Atrial fibrillation converting after correction of K⁺-level</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Atelectasis requiring physiotherapy</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Transient confusion not requiring therapy</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Noninfectious diarrhea</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Transient elevation of serum creatinine</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Wound infection treated by opening of the wound at the bedside</td>
</tr>
<tr>
<td>Grade II</td>
<td>Cardiac</td>
<td>Tachyarrhythmia requiring β-receptor antagonists for heart rate control</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Pneumonia treated with antibiotics on the ward</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>TIA requiring treatment with anticoagulants</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Infectious diarrhea requiring antibiotics</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Urinary tract infection requiring antibiotics</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Same as for I but followed by treatment with antibiotics because of additional phlegmonous infection</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>Cardiac</td>
<td>Brudyrhythmia requiring pacemaker implantation in local anesthesia</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>See grade IV</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Biloma after liver resection requiring percutaneous drainage</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Stenosis of the ureter after kidney transplantation treated by stenting</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Closure of dehiscent noninfected wound in the OR under local anesthesia</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>Cardiac</td>
<td>Cardiac tamponade after thoracic surgery requiring fenestration</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Bronchopleural fistula after thoracic surgery requiring surgical closure</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>See grade IV</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Anastomotic leakage after descendorectostomy requiring relaparotomy</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Stenosis of the ureter after kidney transplantation treated by surgery</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Wound infection leading to evertedation of small bowel</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>Cardiac</td>
<td>Heart failure leading to low-output syndrome</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Lung failure requiring intubation</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Ischemic stroke/brain hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Necrotizing pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Renal insufficiency requiring dialysis</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>Cardiac</td>
<td>Same as for IVa but in combination with renal failure</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Same as for IVa but in combination with renal failure</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Same as for IVa but in combination with hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Neurological</td>
<td>Ischemic stroke/brain hemorrhage with respiratory failure</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>Same as for IVa but in combination with hemodynamic instability</td>
</tr>
<tr>
<td>Suffix “d”</td>
<td>Cardiac</td>
<td>Cardiac insufficiency after myocardial infarction (IVa-d)</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>Dyspnea after pneumonectomy for severe bleeding after chest tube placement (IIIB-d)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Residual fecal incontinence after abscess following descendorectostomy with surgical evacuation (IIIB-d)</td>
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<td>Neurological</td>
<td>Stroke with sensorimotor hemiparesis (IVa-d)</td>
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<td></td>
<td>Renal</td>
<td>Residual renal insufficiency after sepsis with multiorgan dysfunction (IVb-d)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>Hoarseness after thyroid surgery (I-d)</td>
</tr>
</tbody>
</table>

TIA, transient ischemic attack. OR, operating room.
References

Acknowledgements

We would like to acknowledge the members of the ESPAC-5F Surgical Working Party who have contributed to this handbook:

Christopher Halloran   Liverpool
Michael Raraty         Liverpool
Colin Johnson          Southampton
Ross Carter            Glasgow
Mark Duxbury           Glasgow
Euan Dickson           Glasgow
Richard Charnley       Newcastle
Jeremy French          Newcastle
Keith Roberts          Birmingham
Derek O’Reilly         Manchester
Andrew Smith           Leeds
Amer Al-Douri          Leeds
Ambereen Kausar        Blackburn
James Gardner Thorpe   Sheffield