# Other HALT-C Tests and Procedures: Endoscopy and Ultrasound

## Endoscopy Protocol

I. Introduction:
All randomized patients will have a baseline endoscopy performed within 4 weeks of randomization (W24 visit or R00), unless one has been performed within the previous 12 months. They will be repeated at proscribed intervals as stated below.

II. Objectives of the endoscopy:
To document the presence or absence of esophageal varices, gastric varices, and portal gastropathy.

III. Procedure:
Panendoscopy will be performed using conscious sedation in most cases. Appropriate safety guidelines, as defined by the American Society of Gastrointestinal Endoscopy, will be used during the procedure

IV. Assessments:

A. **Esophageal varices** will be assessed in the distal 5 cm of the esophagus with air-insufflation of the esophagus. The following parameters will be noted:
   1. Number of columns of varices
   2. Extent of varices
   3. Size of varices: small, medium and large corresponding to F1-F3 of the NIEC classification.
      a. Grade 0 (none): No varices present
      b. Grade 1 (small): Small, straight varices
      c. Grade 2 (medium): Enlarged, tortuous varices which occupy less than 33% of the lumen of the esophagus
      d. Grade 3 (large): Enlarged, tortuous varices which occupy more than 33% of the lumen of the esophagus

   4. **Red signs:** red wale marks, cherry red (hematocystic) spots, varix on varix defined as follows:
      a. Red wale marks: Red streaks along the long axis of the varices
      b. Cherry red (hematocystic): A blood blister along the axis of the varices
      c. Varix on varix: A superficial vein overlying a varix

B. **Gastric varices** will be identified and classified according to Sarins classification as:
   1. Isolated gastric varices (IGV) type I: An isolated cluster of varices in the fundus of the stomach
   2. Isolated gastric varices (IGV) type II: Isolated varices in regions of the stomach other than in the fundus.
   3. Gastro-esophageal varices (GOV) type I: Gastric varices in continuity with esophageal varices along the lesser curve of the stomach.
   4. Gastro-esophageal varices (GOV) type II: Gastric varices in continuity with esophageal varices along the greater curve of the stomach.

V. Portal Gastropathy Score:

A. **Endoscopic assessment** will be defined as follows for the purposes of calculating the portal gastropathy score:

1. **Mucosal mosaic pattern** will be defined as small polygonal areas demarcated by a distinct white-to-yellow border and with a slight central bulge that have a mosaic, fish scale-like appearance upon endoscopy. They will be scored as follows:
   a. Mild: the color of the mucosa is pink
   b. Severe: there is diffuse erythema (redness).

2. **Red Marks** will be defined as flat or slightly bulging red lesions seen in the gastric mucosa. Red marks fall into 3 categories:
   a. Localized: Isolated discrete spots.
   b. Diffuse: Confluent areas of submucosal hemorrhage.
   c. Black-brown spots, which represent old submucosal hemorrhage, and will not be scored.

3. **Gastric antral vascular ectasia (GAVE)** will be diagnosed by the presence of flat or slightly raised red stripe-like lesions radiating from the pylorus to the antrum and body of the stomach for a variable distance

B. Assigning scores to calculate portal gastropathy:
   1. The severity of the portal gastropathy will be scored as proposed by Sarin (points to be given as indicated below (See Table1):
      a. **Mosaic Pattern**
         1 = Mild mosaic pattern
         2 = Severe mosaic pattern
      b. **Red Marks**
         1 = Isolated red marks
         2 = Confluent red marks.
      c. **GAVE**
         0 = Absence of GAVE
         2 = Presence of GAVE will be scored as 2.

C. Calculation of Portal Gastropathy Score:
   The portal gastropathy score is calculated by adding the assigned scores from above (or see Table 1). This will be calculated centrally. Severity will be determined as follows:
   1. Mild portal gastropathy is a score less than or equal to 3
   2. Severe portal gastropathy is a score of 4 or greater.

VI. Weeks of Assessment:
   A. Randomization (W24 or R00): within 4 weeks, unless performed in the previous 12 months
   B. Month 24 (M 24): (if varices present at randomization)
   C. Month 48 (M 48): (all patients)

VII. Data Collection:
   A. Form # 23, Endoscopy should be completed by the person performing the endoscopy and data entered at the clinical center
   B. Form # 110, Central Endoscopy Review, will be completed at the central review.

VIII. Source Documentation:
   A. Appropriate source documentation
      The following documents must be obtained for and attached to Form 23 each endoscopy:
      1. A written report
      2. Photo-documentation: Endoscopy will be documented by photograph at the following sites:
         a. Esophagus 5 cm above GE junction

b. Retroflex view in the cardia of the stomach looking at the fundus
c. In the mid-body of the stomach looking towards the antrum

B. Proper procedure for identifying source documentation:
The written endoscopy report and one copy of the photographs should be kept with the data entry form. The second copy of photographs will be sent to the DCC for central review as described below. Identifying information, such as patient name and medical record number should be blacked out and replaced with the patient ID number (labels provided by the DCC may be used).

IX. Blinded Central Review:
The photographs will be reviewed in a blinded manner by a panel of endoscopists at a central location and scored separately by each member of the panel. The photographs will be assessed for the presence or absence of esophageal and gastric varices and their grades.

X. Shipping of photo documentation:
1. Preparation: Label all photographs with patient ID and visit # on the back of each photo. If the patient's name is on the photograph please black it out with a marker.
2. Packaging: Put the photos inside an envelope and FedEx them to NERI at the address below.
3. Shipping: One copy of the photographs should be sent to:

NERI
HALT-C Trial – Linda Massey
9 Galen Street
Watertown, MA 02472

XI. Patient Information:
1. Patient should be fasting (NPO after midnight except for meds)
2. Patient should be given Endoscopy Patient Information Sheet (see Appendix F) or institutional information sheet

**Table 1**

**PORTAL HYPERTENSIVE GASTROPATHY SCORING SYSTEM**

**as proposed at the Baveno consensus conference**

| Parameter | | Score |
|---|---|---|
| 1. Mucosal mosaic pattern: | | |
| | Mild: | 1 |
| | Severe: | 2 |
| 2. Red marking: | Isolated: | 1 |
| | Confluent: | 2 |
| 3. Gastric antral vascular ectasia: | | 0 |
| | Absent: | 2 |
| | Present: | |

Mild gastropathy = score $\leq$ 3
Severe gastropathy = score > 4

**Ultrasound, MRI, CT Protocol**

I. Introduction:
All patients will have an ultrasound prior to enrollment in the HALT-C Trial and at prescribed intervals throughout the study. The preference is to use an ultrasound test, but if an MRI or CT has been recently performed, either of these tests may be used in place of an ultrasound.

II. Objectives of Ultrasound, MRI, CT:
The major goal of the ultrasound is to detect Hepatocellular Carcinoma (HCC) and ascites, although other parameters will be assessed. A new, discrete and enlarging defect(s) is most likely to represent HCC.

III. Procedure:
A. Equipment: The equipment should be modern, real-time ultrasound, MRI, CT.
B. No special settings are required.
C. Routine hard copy images should be obtained.
D. Representative hard copy images should be taken of all abnormalities.

IV. Assessments:
The following should be evaluable from the ultrasound, MRI and/or CT report. This information is documented on Form # 22, Ultrasound, MRI, CT:

A. **Hepatic Mass** will be assessed and classified as follows (representative images should be obtained:
1. Size
a. Best estimate of maximum diameter of liver mass expressed in centimeters

2. Defect Characteristics
a. **Margins**
i. **Well-defined, discrete:** Relatively sharp margins indicating a clear-cut abnormality
ii. Ill-defined: Poorly defined margins or equivocal abnormality (i.e., geographic)

3. Change Over Time (compared to prior film or report)
a. Seen and stable: Present on prior exam and unchanged in size or character of defect
b. Seen and increased in size: Present on prior exam and increased in size
c. Seen and decreased in size; Present on prior exam and decreased in size
d. Other: Specify any other comparison not outlined above.

4. Liver Mass requiring follow-up
If there is evidence of a liver mass on the present Ultrasound, MRI, or CT, and further testing is necessary, the follow-up test should be performed and the report made available. Specify on Form # 22 whether the follow-up test confirms evidence of HCC.

B. **Spleen Size** will be assessed and classified as follow:
1. Size should be recorded as greatest length in any dimension
2. Splenomegaly will be defined as a span >13 cm

C. **Ascites** will be assessed and classified as follows:
1. Amount
a. Absent: No clear-cut evidence of abnormal peritoneal fluid
b. Minimal: Isolated thin sliver of fluid around the liver, or small pelvic pocket, or small amount of fluid in lesser sac

c. Mild: Multiple small collections as a thin sliver around liver, pelvic pockets, small abdominal pockets
d. Moderate: Fluid collection in multiple areas of the abdomen and around the intestines
e. Large: Bowel loops separated by fluid and large pools around liver, pelvis and peritoneal gutters

D. **Other findings**
1. Assess and document other abnormal findings (i.e., portal vein thrombosis, gall stones, pancreatic lesions).

V. Weeks of Assessment

Ultrasounds (MRI, CT) will be obtained at the following intervals:

A. All patients: Screening visit 2 (or within last 6 months) and W20.
B. Randomized Phase patients: M12, M24, M36, and M48.
C. Responders Phase patients: W48, W72, and W36 or W60 for those who have virologic breakthrough or relapse and wish to be randomized.
D. According to HCC Guidelines
See Section C.2. HCC Screening of the HALT-C Protocol for guidelines for performing ultrasound, MRI, CT with a rising AFP and other possible concerns for possible HCC.

VI. Data Collection

A. Form # 22, Ultrasound, MRI, CT should be completed.
B. Form # 63, Clinical Outcomes, should be completed if HCC is diagnosed. A diagnosis of HCC requires the following:
1. Histology (one of the following):
- Liver biopsy report
- Pathology report
- Autopsy report OR

2. AFP result plus one of the following showing a new defect:
- Liver ultrasound report or
- Liver CT report or
- Liver MRI report

C. Form # 63, Clinical Outcomes, should be completed if ascites is diagnosed, when combined with a finding of ascites on physical exam. A diagnosis of ascites requires the following:
1. Physical exam note plus one of the following:
- Paracentesis lab report
- Liver ultrasound report
- Liver CT report
- MRI report

VII. Source Documentation

A. Appropriate source documentation: A written report must be obtained for each ultrasound, MRI, CT and made available.

VIII. Patient Information

A. Patient should be fasting (NPO for 8 hours except for meds).
B. Patient should be given clinical center specific information sheet.