Examining the WHO and HOW to investigate for upper GI cancers: Diagnostic work up for Esophageal, Gastric and Pancreatic cancer

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Relationships with commercial interests:
- Investigator: Cook Medical/Endoscopy
Mitigating Potential Bias

Not applicable
Epidemiology

Esophageal cancer: Decreasing squamous cell (less smoking): 3/100,000. NOTE: 3x more common in men, and 6x more common in blacks. Increasing adenocarcinoma (obesity, GERD, other factors?): 3-5/100,000. NOTE: 7-10x more common in men.

Gastric cancer: Stable or decreasing rates in North America. Increasing and very high rates in Asia. Canada: 4-9/100,000/year, less in women (down from >20/100,000 in the 1970's/80's).

Better treatment of H.pylori, and decreased reliance on salt preservation of food? Better hygiene? Refrigeration?

Pancreatic cancer: Slow steady increase in rates over time (aging population?). ~ 10/100,000/year or 4-5000 new cases in Canada/year.

All 3 cancers are relatively rare, but have very high mortality rates, and are...
Who should we investigate for esophageal cancer?

- Abdominal pain?
- GERD? Non-responsive GERD, long-standing GERD, atypical GERD?
- Family history of cancers?
- Alcohol and smoking use/abusers?
- Dysphagia? ★★
- Unexplained Weight loss? ★
- Iron deficiency anemia?
The GERD question

Hypothesis: Longstanding or severe GERD -> Barrett’s esophagus -> Dysplastic Barrett’s -> Esophageal adenocarcinoma

Old guidelines recommended screening pts. with GERD >10 years, for Barrett’s. No study has ever shown this is effective at reducing cancer or mortality. It is expensive, it is stressful for patients and all it does is increase the # of patients with Barrett's that need further testing. With NO benefit.

New guidelines from AGA, ACG, and European GI consortium all explicitly recommend against the routine screening for Barrett's.

Instead patients with a combo of GERD >10 years plus other risk factors (smoking, severe obesity, ETOH abuse, family history, etc) or a concerning symptom (dysphagia, weight loss, anemia etc) should be screened.
<table>
<thead>
<tr>
<th>Barrett prevalence</th>
<th>Cancer incidence/100,000</th>
<th>Cancer distribution Adenocarcinoma</th>
<th>Annual cancer risk with this type</th>
<th>NNT for screening in Barrett’s esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>4.6</td>
<td>56%</td>
<td>0.32%</td>
<td>316</td>
</tr>
<tr>
<td>5%</td>
<td>1.9</td>
<td>24%</td>
<td>0.04%</td>
<td>2421</td>
</tr>
<tr>
<td>15%</td>
<td>1.7</td>
<td>20%</td>
<td>0.01%</td>
<td>9008</td>
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</table>
When should we screen patients with Barrett’s?

Currently, guidelines in America: short segment Barrett’s (<3cm) is recommended for a gastroscopy every 3-5 years (if risk factors?), and long segment every 2 years (or longer if stable for 2 scopes).

Patients with documented LGD: repeat within 1 year and or refer for ablation strategies.

Patients with HGD: need either ablation with RFA, endoscopic resection of HGD areas OR surgery.

The main problem is that AGAIN, no study in the Barrett’s surveillance population has shown mortality benefit, survival benefit or cost benefit… but new data is coming, this year that may show some benefit in targeted screening.
So who should we investigate for esophageal cancer?

Patients with new or progressive dysphagia.

Patients with known Barrett’s esophagus AND risk factors (smoking, ETOH use, family history, prior toxic ingestion etc), or Barrett’s with dysplasia.

Patients with unexplained weight loss, anorexia and anemia (as part of pan endoscopy).
How to diagnose Barium Swallow:

Can identify location and length of strictures, but is non-diagnostic for cancer vs. benign lesions. Length of stricture is an independent predictor of survival in EsoCa. May be able to get done faster than a scope, so occasionally still used, but should not delay referral for this test.

CT scan:

Can show thickening, strictures, extension, lymph nodes, mets, but again is not diagnostic. It is helpful and gives lots of info but DO NOT delay referral to get a CT scan.

Gastroscopy:

Gold standard test to visually diagnose and to biopsy. Multiple biopsies are needed. Gold standard is >6 biopsies to increase yield >95%.
Biopsies confirm either SSCa or AdenoCa:

usually takes 4-7 days even if sent rush.

CT scan of the chest/abdomen for staging is standard of care:
Assess local and distant nodes, and metastasis.

NOTE: Endoscopic ultrasound has good evidence for staging local lymph nodes
(95% accuracy vs. 45% CT for celiac nodes), and is far superior for determining
T2-T4 lesions, except post radiation therapy.

PET/CT often required, to differentiate malignant liver cysts and/or lung nodules.
Very high sensitivity and accuracy for distant metastases.

PET activity ALSO can be used to predict response to chemo and radiation
AND has been shown to predict survival overall survival.
Gastric cancer

Significant decrease in the last 60 years, due to less H.pylori, better food preservation, and smoking?

Paradoxical increase in younger patients in the last 15 years?
Gastic cancer

Two types:

- **Intestinal type:** Follows a similar route to colon cancers, intestinal metaplasia/polyp-dysplasia-carcinoma. Usually mass forming or ulcerative. Much easier to diagnose.

- **Infiltrative type ("linitus plastica"):** Unclear pathophysiology, more common in women and younger patients. Can be missed/misdiagnosed even with appropriate testing at early stages.
### Gastric Cancer

**What symptoms/signs predict gastric cancer?**

- Abdominal pain?
- Early satiety?
- Weight loss?
- Vomiting?
- Dysphagia?
- Abdominal mass?
- Iron def. anemia?
- Lymph node abnormalities?
- Gastric ulcers?
Symptoms experienced by patients newly diagnosed with Gastric CA of any type:

- Abdominal pain: 30-67%
- Early satiety: 45%
- Weight loss: 60-75%
- Vomiting: 7-17%
- Dysphagia: 5-25%
- Iron def. anemia: 20-39%
- Gastric ulcers: <15%
- Abdominal mass: 7% (always advanced disease)
- Lymph node abnormalities: <5% (always advanced disease)

Best pretest probability: Anemia + weight loss + early satiety: PPV = 72%
<table>
<thead>
<tr>
<th>Screening</th>
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<tr>
<td>50% of cases, are diagnosed with advanced disease, and are incurable. Screening is beneficial in HIGH risk populations.</td>
</tr>
<tr>
<td>Data from Japan/Korea/China, shows decrease in advanced cancer and mortality by 30% with biannual gastroscopy</td>
</tr>
<tr>
<td>Costs of $28,000/life year saved</td>
</tr>
<tr>
<td>Screening is not beneficial and is extremely costly in low risk groups (such as North Americans)</td>
</tr>
<tr>
<td>Costs of &gt;$240,000/life year saved (best case scenario from data!)</td>
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<tr>
<td>Tailored approach to screen at risk individuals and those with concerning symptoms is recommended in North America</td>
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Obesity: OR 1.22
Smoking: OR 1.55
Other more rare signs of Gastric Ca:

Other more rare signs of Gastric Ca:
a) DVT/thrombophelbitis (Trousseau sign)
b) Eruptive seborheic keratosis on the back (Sign of lesion trelat)
c) Membranous nephropathy
What test to order?

1. Lab work: Baseline CBC, ferritin/iron stores. No specific tumor markers are available for gastric cancer, although CA19-9, CA125, and CEA can all be positive.

2. Barium Swallow: Sensitivity 50%, specificity 85%, (even worse for early cancers). Not an adequate test. Occasionally can diagnose linitus plastica or infiltrative gastric cancer—ويربسطية of the stomach.

3. CT scan: Not routinely used for diagnosis. Sensitivity 40-80%, Specificity 60-90%, very useful for staging lymph nodes and mets.

4. Gastroscopy: Gold standard as biopsy is confirmatory. Addition of EUS = most sensitive test (>95%), and allows most accurate pre-surgical T staging (>90%).
Work up for established gastric cancer

1. CT scan (chest/abd/pelvis) with IV contrast: Looks for local, and widespread metastasis.

2. EUS: most effective staging for depth of invasion, and can sample possible nodal spread with FNA.

   T stage Accuracy compared to CT scanning 95% vs. 73% p<0.0001.

   N stage accuracy compared to CT: 80% vs. 65% p<0.05

3. PET/CT: Most sensitive for distant mets, in one study post EUS and CT, PET/CT upstaged disease state in 10% of cases… used very frequently to complete the staging, pre chemotherapy and surgery.

4. Staging laparoscopy: still the gold standard for N staging…
Pancreatic cancer
### Pancreatic Cancer: signs and symptoms

#### Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Weight loss</td>
<td>85</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>79</td>
</tr>
<tr>
<td>Anorexia</td>
<td>76</td>
</tr>
<tr>
<td>Cholestasis (dark urine/pale stool)</td>
<td>50-59</td>
</tr>
<tr>
<td>Back pain</td>
<td>49</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33</td>
</tr>
<tr>
<td>Steatorrhea</td>
<td>25</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>3</td>
</tr>
</tbody>
</table>

#### Signs

<table>
<thead>
<tr>
<th>Sign</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice</td>
<td>55</td>
</tr>
<tr>
<td>Hepatomegally</td>
<td>39</td>
</tr>
<tr>
<td>RUQ mass</td>
<td>15</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>13</td>
</tr>
<tr>
<td>Courvusier’s sign</td>
<td>13</td>
</tr>
<tr>
<td>Ascites</td>
<td>5</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>5</td>
</tr>
</tbody>
</table>

No individual symptom or sign if can effectively screen for Panc Ca.

* PPV of jaundice $\geq$ 50 yo is 20-33%
Other symptoms/signs

Idiopathic pancreatitis in those > 50 yo: follow up CT is warranted. New pancreatic lesions found in ~10-12% of individuals.

New onset diabetes >50 years old: Association has been shown in several cohort studies.

Not cost effective to screen all diabetics, but if they are lean, losing weight, have no family history, or have symptoms of steatorrhea -> consider a CT scan.
Initial testing for pancreatic Ca

1. Lab work: Liver enzymes, bilirubin, INR, albumin

2. Tumor markers: CA19-9, CEA

US abdomen: first test if jaundice is present. Sensitivity: 85%, spec: 93% (if tumors >2.5cm)

CT abdomen + IV contrast: The most clinically useful test for pancreatic CA. High sensitivity (+90%), high specificity (>85%). Allows assessment of mets, and of resectability (based on SMA, celiac, hepatic artery involvement or metastasis)

Sensitivity for "pancreas protocol CT" is 100% for tumors >2cm
Initial testing for pancreatic Ca

5. MRI/MRCP: no better than CT, EXCEPT for small liver metastasis…so it can be used for staging. But not necessary for diagnosis


In many centers this is standard of care 1st test.

7. ERCP: Allows direct evaluation of the duct, very sensitive (reported 95% sens, 85% spec), and allows cytology and/or biopsy. Most importantly for patients, it allows decompression of jaundice at the same time.

Cytology at ERCP is poor. Sensitivity 40-60%, specificity of 100%.
Initial testing for pancreatic Ca

Cholangioscopy/Pancreatoscopy: miniaturized endoscope that passes through an ERCP scope and into the bile duct or pancreas

Paradigm shift similar to switch from barium X-rays to actual Now we can directly visualize the contents of the bile duct and pancreas, rather than inferring their contents best on negative imaging (fluoroscopy)

Improves sensitivity 80-90% via visual diagnosis + targeted biopsies, and maintains >98% specificity
Tumor markers

The optimal serologic marker doesn’t exist.

CA19-9 is the best option, but still has limited sensitivity (70-90%) and specificity (68-80%).

Limited by needing + Lewis blood group antigen (90% of the population).

Limited by tumor size (levels increase with tumor size).

False positive in any kind of biliary obstruction, or biliary infection.

The magnitude of elevation is associated with long term survival, chance of respectability, and CAN be followed for signs of recurrence post surgery… so useful to have a baseline value.
Work up for established pancreatic cancer

1) CT chest, abdomen/pelvis: for staging
2) MRI liver: to accurately assess for mets and help with respectability staging
3) PET/CT: useful in some cases, but not routinely ordered
Targeted biopsy

Positive cytology

Pancreatoscopy/cholangioscopy and indeterminate cytology and stent placement

ERCP and cytology, if jaundiced

CT scan with contrast (US 1st if jaundiced)

Likely pancreatic cancer (mass)

Not resectable CT scan with contrast (US 1st if jaundiced)

PET, PET, PET, and permanent biliary stent

Chemotherapy assessment, and resection

Fully assess respectability: MRI, appears resectable

Positive biopsy

Assess respectability: MRI, PET, CT chest/abd/pelvis+

Not resectable

Laparoscopy +/- EUS with FNA
**Summary**

**Esophageal cancer:** Investigate patients with new/progressive dysphagia, or longstanding GERD with risk factors (smoking, ETOH, family history). Gastroscopy is the test of choice. No serologic markers.

**Gastric cancer:** Difficult disease to screen for in North America. Patients with early satiety, anemia and weight loss OR one symptom AND a family history of gastric CA OR H.pylori infection. Gastroscopy is the test of choice. No reliable tumor markers. Barium and CT can be supportive but not definitive.

**Pancreatic cancer:** Investigate for painless jaundice, or weight loss + steatorrhea. Note idiopathic pancreatitis in >50yo and late onset diabetes. First test US, but CT of the pancreas is superior for diagnosis and staging. EUS is best for diagnosis and biopsy. ERCP can biopsy but is best for palliation of obstructive symptoms. Serologic markers with CA19-9 +/- CEA can be supportive.