Prevention and Early Detection: New Tools and Research Opportunities

Andrew T. Chan, MD, MPH
Massachusetts General Hospital
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Shifting the curve

Overall Survival

Time after surgery (months)

Stage I
Stage II
Stage III
Stage IV
How can we detect GC early?

1. Normal Gastric Mucosa
2. Chronic Gastritis
3. Atrophic Gastritis
4. Intestinal Metaplasia
5. Adenoma/Dysplasia
6. Intestinal-Type GC

Factors:
- H. pylori
- Diet/smoking
How can we detect GC early?

Normal Gastric Mucosa → Chronic Gastritis → Atrophic Gastritis → Intestinal Metaplasia → Adenoma/Dysplasia → Intestinal-Type GC
How can we detect GC early?

Normal Gastric Mucosa → Chronic Gastritis → Atrophic Gastritis → Intestinal Metaplasia → Adenoma/Dysplasia → Intestinal-Type GC

Hereditary (CDH1) → Non-Hereditary

Diffuse-Type GC
How can we detect GC early?

Early detection and improved interception in clinical practice

**Blood Biomarkers:**
- Circulating Tumor Cells
- Cell-free DNA
- Exosomes

**Advanced Imaging Approaches:**
- Near Infrared Molecular Imaging
- Minimally-invasive Capsule Imaging

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Early / 'at-risk'

- Normal Gastric Mucosa
- Chronic Gastritis
- Atrophic Gastritis
- Intestinal Metaplasia
- Intestinal Type GC

Precancer

- Adenoma/Dysplasia
- Diffuse-Type GC

Cancer

- Intestinal-Type GC
- Non-Hereditary
- Hereditary (CDH1)
Gastric neoplasia
1. Cell free DNA (cfDNA/ctDNA)
2. Circulating Tumor/Epithelial Cells (CTC/CEC)
3. Exosomes
1. Cell free DNA (cfDNA/ctDNA)

Blood-based biomarkers

- Mutations
- Copy-number alterations
- Gene fusions
- DNA methylation

Corcoran and Chabner *NEJM* 2018
Novel advanced imaging

LUM015 for NIR Imaging in Human GI Cancers

(DF/HCC IRB: 13-415; clinicaltrials.gov NCT02584244)

Drew et al. DDW, 2018
Novel preclinical models of diffuse and intestinal GC

Project 1: Models of Intestinal and Diffuse Gastric Cancer

Preclinical

Discover novel interception biomarkers

Early / ‘at-risk’

Normal Gastric Mucosa → Chronic Gastritis → Atrophic Gastritis → Intestinal Metaplasia → Adenoma/ Dysplasia → Intestinal-Type GC

Precancer

Hereditary (CDH1)

Non-Hereditary

CTC/cfDNA/Exosomes

NIR/Capsule Imaging

Precancer expression profiling

Cancer

Diffuse-Type GC
Translating preclinical findings to patient populations

Project 2: Profile the spectrum of gastric malignancies in diverse screening and surveillance populations

Translation

Refine biomarkers

Early / ‘at-risk’
- Normal Gastric Mucosa
- Chronic Gastritis
- Atrophic Gastritis
- Intestinal Metaplasia
- Adenoma/Dysplasia
- Intestinal-Type GC
- Diffuse-Type GC

Precancer

Cancer

Hereditary (CDH1)

Non-Hereditary
• Existing GC and CDH1 cohorts*
• Centralized biorepository
• Standardized blood processing
• Open data sharing

Friedman M et al. *Clin Gastroenterol Hepatol*, 2019
Leveraging the combined power of existing annotated clinical biorepositories across the US

- CDH1 cohort
- Paired tissue/blood
- Enriched for Asian and Hispanic

- High volume GC surgery
  - Paired tissue/blood
  - Enriched for African American

- High volume CDH1 prophylactic gastrectomy
  - Prospective tissue and plasma bank

Data coordinating center / central biorepository
Learning from the world’s largest gastric screening program

Korea clinical practice – population-based screening

- Normal Gastric Mucosa
  - Chronic Gastritis
  - Atrophic Gastritis
  - Intestinal Metaplasia
  - Adenoma/Dysplasia
  - Intestinal-Type GC

- Early / ‘at-risk’

- Precancer

- Cancer
  - Diffuse-Type GC

- US Clinical Practice

- Non-Hereditary
  - Hereditary (CDH1)
Prospective validation in a GC trial for rapid clinical translation

Project 3: Proof-of-principle for biomarkers/imaging modalities in GC patients

Validate biomarkers

Early / ‘at-risk’
- Normal Gastric Mucosa
- Chronic Gastritis
- Atrophic Gastritis

Precancer
- Intestinal Metaplasia
- Adenoma/Dysplasia

Cancer
- Intestinal-Type GC
- Diffuse-Type GC

Hereditary (CDH1)

Non-Hereditary
Clinically-actionable Biomarkers for Early Detection/Interception

1. PRECLINICAL MODELS
   Models of gastric cancer TCGA subtypes mimicking human biology
   - Translation of putative markers to humans
   - Refine, Validate, and Extend Human Findings in GC Models

2. SCREENING/SURVEILLANCE COHORTS
   - Multi-center early gastric cancer/precancer patient population
   - Fresh / Fixed Tissue Blood
   - N=100s

3. VALIDATION IN A GC TRIAL
   - Standardized sample collection
   - Gastric cancer patients
   - N=25-50

Directly translatable GC Findings
An international, interdisciplinary team of experts in gastric cancer, advanced imaging, & molecular biomarkers

Massachusetts General Hospital
Boston, MA
- Andrew Chan
- Gary Tearney
- David Ting
- Theodore Hong
- Samuel Klemperner
- Daniel Chung
- Ryan Corcoran
- Ralph Weissleder
- Project Manager: David Drew
- Managing Director: Marina Magicheva-Gupta
- LEADER: Daniel Chung
- CO-LEADER: Andrew Chan

University of Pennsylvania
Philadelphia, PA
- Sandra Ryeom
- Bang-Jim Kim
- Aki Smith
- Jason Diaz
- Principal: Jeeyun Lee
- Principal: Hyuk Lee
- Project Manager: Marina Magicheva-Gupta

City of Hope Comprehensive Cancer Ctr.
Duarte, CA
- Yanghee Woo
- Joseph Chao

Memorial Sloan Kettering Cancer Center
New York, NY
- Sam Yoon
- Scott Lowe
- Josef Leibold
- Principal: Daniel Catenacci

University of Chicago
Chicago, IL
- Principal: Daniel Catenacci

Stomach Cancer Awareness Network (StoCAN)
- Aki Smith
- Jason Diaz

NIH
NCI
Rockland, MD
- Jeremy Davis

Samsung Medical Center
Seoul, Korea
- Principal: Jeeyun Lee
- Principal: Hyuk Lee
- Project Manager: Marina Magicheva-Gupta
- Principal: Daniel Catenacci