

Introduction

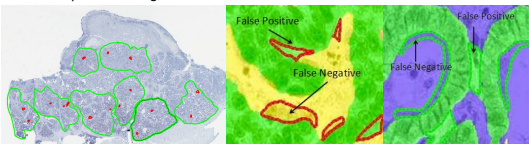
Despite recent improvements in surgical techniques and chemotherapy treatments, locally advanced/metastatic gastroesophageal junction (GEJ) and gastric cancers (GC) are still associated with poor clinical outcome. Results from the Trastuzumab for Gastric Cancer (ToGA) trial demonstrated that trastuzumab, a monoclonal antibody directed against the extracellular domain of HER2 can enhance the efficacy of cytotoxic chemotherapy in patients with advanced gastric and gastroesophageal cancers. Pathology analysis for HER2 is currently done with either manual scoring or the use of FDA cleared HER2 algorithms designed for breast cancer.

Tumor heterogeneity presents a difficult problem in breast cancer HER2 scoring and likely an even greater problem in gastric cancer. Our previous work in breast cancer has shown that effective algorithms for quantification of heterogeneity in breast cancer cannot depend on pathologists manually selecting regions of interest. Thus the ability to develop a heterogeneity algorithm is dependent on effective sampling techniques that include automated pattern recognition of tumor target tissue.

In this presentation, we discuss results from a custom pattern recognition training algorithm designed to detect target tumor tissue in GI and GEJ slides on HER2 stained immunohistochemistry slides.

Method

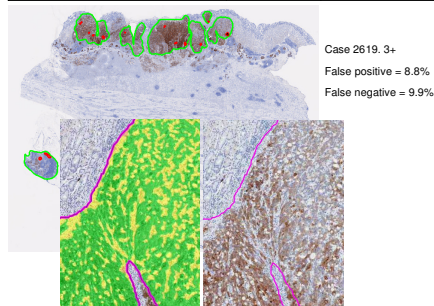
Eleven GC/GEJ cases with high levels of either tumor or cell level HER2 heterogeneity were selected from a larger archive and scanned at 20x on an Aperio ScanScope CS. A histology pattern recognition solution based on Genie (Aperio) was then developed to identify tumor versus non-tumor tissue. Initially, one training set was utilized for multiple slides, but the results were not satisfactory on high heterogeneity slides. Instead, a single training set was developed for each tumor section, and was not applied to other sections. The solution was then applied across the entire tumor. To evaluate performance, a digital grid was placed across each tumor section, and ten randomly sampled fields of view were selected. Across each of these sections, false positive (non-tumor tissue identified as tumor) and false negative (tumor tissue identified as non-tumor) rates were recorded. The results were then reviewed by a pathologist to discuss where there were problematic areas and where heterogeneity played a role in the pattern recognition results.



On ten random samples across each slide, percentage of false positive and false negative rates were identified. Random sampling was conducted with a grid-based sampling approach

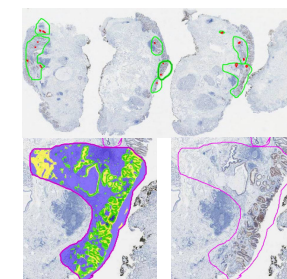
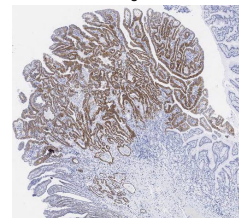
Results

Case ID	Specimen type	IHC Score (pathologist)	Phenotype	False Positive	False Negative	Case comments
106634	Resection	1+	Intestinal	8.0	1.1	
3334	Resection	1+	Intestinal	8.9	3.4	
3123	Resection	3+	Intestinal	5.6	2.0	
3122	Resection	1+	Intestinal	10.5	1.7	Intestinal phenotype, some infiltration, some cytoplasm staining
3119	Resection	1+	Intestinal	8.4	6.5	Well circumscribed nodule of tumor, fairly well differentiated, intestinal phenotype, highly homogeneous
2620	LN met	3+		5.5	20.9	Lymph node
2620	Resection	3+	diffuse	8.8	9.9	Diffuse pattern, deeply invasive
2618	Resection	2+	Intestinal	25.0	7.6	Endoscopic mucosal resection in an elderly patient. Invasive in submucosa. Has heterogeneity. Superficially invasive, HER2 expression is patchy, GEJ present. High tumor and cell heterogeneity. Positive glands next to negative glands.
2617	Resection	1+	Intestinal	10.9	14.8	High level of HER2 staining heterogeneity from gland to gland and cell level heterogeneity
2617	Resection	3+	Intestinal	7.2	9.2	Not deeply invasive, intestinal phenotype, fairly well differentiated. Areas of very strong positivity, and other areas very weak or not present.
2615	Resection	1+	Intestinal	11.7	7.2	Intestinal phenotype, moderate heterogeneity
TOTALS:						
median				8.8	7.2	
mean				10.0	7.7	

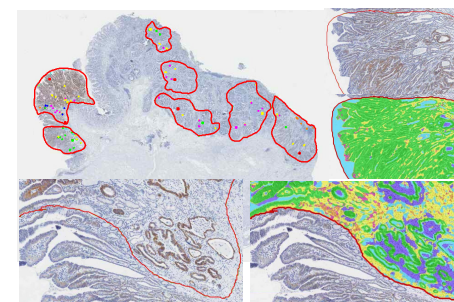


Case 2619. 3+
False positive = 8.8%
False negative = 9.9%

Slides with high tumor-level heterogeneity like the slide below performed well in pattern recognition provided that both positive and negative target tissue are included in the training set



Slide 2618. 2+
Endoscopic mucosal resection in an elderly patient. GEJ present
False positive = 25%
False negative = 7.6%



Case 2617. 3+
High degree of tumor-level heterogeneity
False positive = 7.2%
False negative = 9.2%

Conclusions

- Pattern recognition will work effectively in high heterogeneity cases of GI HER2 provided that the training set is developed for each slide.
- Areas with higher levels of cell-level heterogeneity present more problems for pattern recognition than slides with higher levels of tumor level heterogeneity
- Gastroesophageal junction adenocarcinomas will present strong obstacles to pattern recognition programs