Update in Gastric Cancer

Sirisha Karri, MD

University of Texas Southwestern Medical Center

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[Internal medicine Grand Rounds]

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Sirisha Karri, MD
Assistant Professor
Division of Hematology Oncology

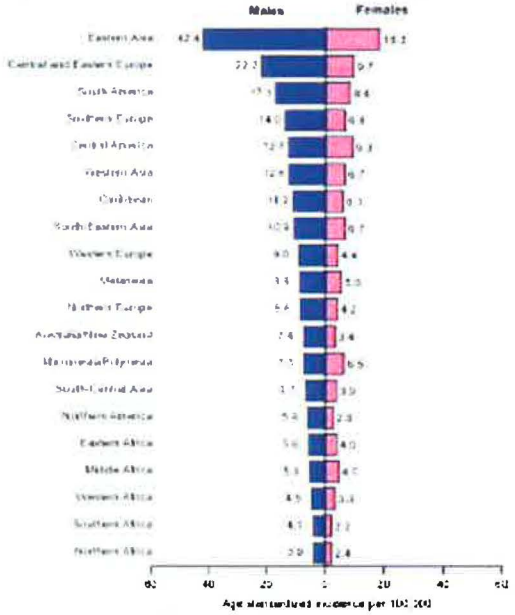
Dr. Karri sees patients at the Simmons Cancer Center and Parkland Hospital. She has special interest in GI malignancies and sarcomas.

Objectives:

1. Review the epidemiology of gastric cancer.
2. Review current standard in surgical management of gastric cancer
3. Review role of systemic therapy in gastric cancer and advances in systemic therapy.

INTRODUCTION

Gastric cancer shows wide variation in geographic incidence. Estimated new cases in US in 2012 are 21,320 and estimated deaths 13,020.[1]Worldwide 989,600 new cases and 738,000 deaths are estimated to have occurred in 2008. Stomach cancer accounts for 8% of total cases and 10% of total cancer deaths worldwide[2,3]. Highest incidence rates (>20/100,000 population) are in Eastern Europe, East Asia and South America. Lowest incidence rates are in North America and most parts of Africa (<10/100,000).70% of new cases and deaths occur in developing countries. Stomach cancer is twice as common in males as compared to females. Within the US, nonwhites and males show higher incidence and mortality.



Gastric cancer is the 4th most common cancer worldwide and 2nd leading cause of cancer mortality, whereas a century ago it was the leading cause of death.

Most frequent histology in gastric cancer is adenocarcinoma. Other histologies account for less than 10 % cases- malt lymphoma, squamous carcinoma, undifferentiated carcinoma, hepatoid, carcinoid and gastrointestinal stromal tumor.

Majority of gastric adenocarcinomas arise in the antrum or distal stomach (40%); about 25% occur in body of the stomach and 35% in fundus and gastroesophageal junction. In the US, although the overall incidence of

gastric cancer is decreasing, the incidence of gastroesophageal junction tumors has been increasing[4].

RISK FACTORS

Acquired factors: High salt consumption, high nitrate consumption, smoked and salted food, lack of refrigeration, Cigarette smoking, H.pylori infection rubber and coal workers, prior gastric surgery for benign gastric ulcer disease

N nitroso compounds are potent carcinogens . They come from food and water. High stomach ph as seen in achlorhydria promotes nitrosation. Although vegetables have high nitrite content theoretically should be higher risk of gastric cancer. However epidemiological studies have shown they are inversely related to gastric cancer, the more intake of vegetables lesser is risk of cancer. Unlike meats especially that are salted or cured. This is thought to be due to ascorbic acid and other micronutrients that act as scavengers of nitrates.

H.pylori is an important risk factor for gastric cancer[5,6]. 77% of noncardia gastric cancers are thought to be from H. pylori. However, gastric cancer incidence rates are not necessarily high in areas of high prevalence such as Africa, South Asia. Cag A positive strains are in particular associated with virulence. Cag A strains are more prevalent in high risk populations. Cag PAI is a cluster of genes and is a major determinant of H.pylori virulence. Cag A is a gene from this complex which encodes protein cag A and others encode a type IV secretion apparatus that translocates cag A into gastric epithelial cells. This is thought to start the chain of events leading to gastric adenocarcinoma. Another factor is vac A which is a multifunction cytotoxin that forms membrane channels in epithelial cells. Noncardia gastric cancers are more strongly associated with H.pylori infection. The causal relationship with cardia gastric cancer is less clear.

Genetic risk factors :Pernicious anemia, Hereditary diffuse gastric cancer, HNPCC, FAP, Li fraumeni,BRCA1 and BRCA2 mutations.

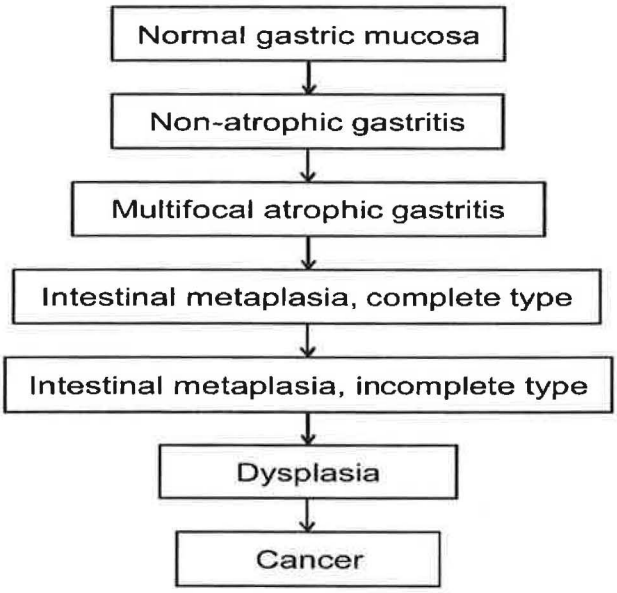
Familial clustering seen in 10-20% of gastric cancers; only 1-3% are associated with hereditary syndromes. HNPCC is associated with abnormality of mismatch repair genes. Gastric cancers that occur in the setting of HNPCC are usually of the the intestinal type. Germline truncating mutations in E cadherin gene (CDH1) are found in several families with

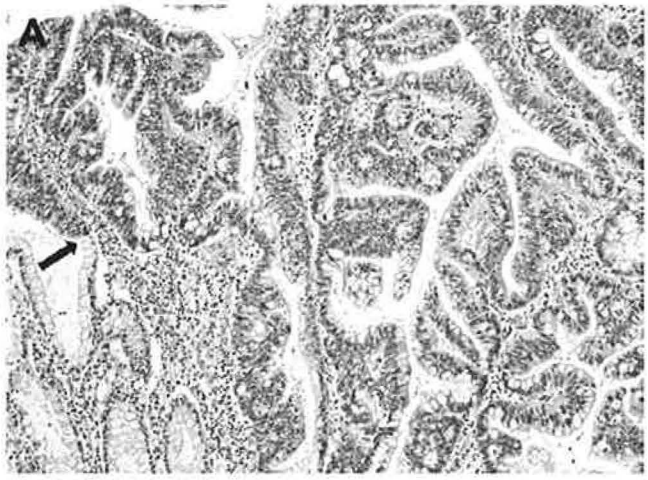
hereditary diffuse gastric cancer. Methylation in CDH1 promoter is the second genetic hit in hereditary diffuse gastric cancer. Less frequently gastric cancer also seen in polyposis syndromes such as FAP (familial adenomatosis polyposis) and in Li Fraumeni syndrome.

HISTOPATHOLOGY

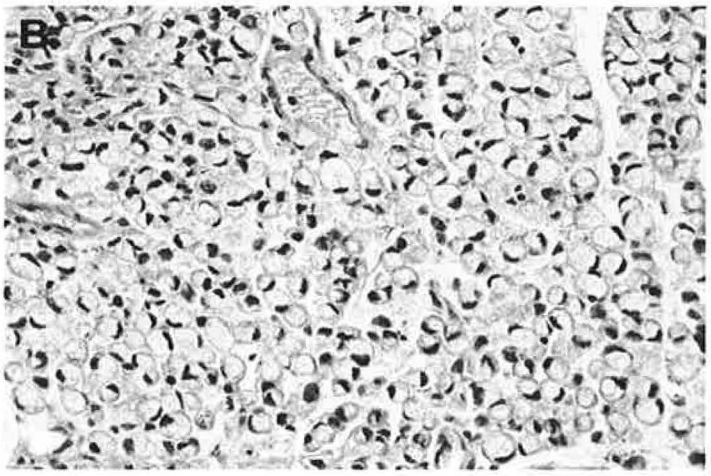
Histologically, there are several different classifications of gastric adenocarcinoma. Most commonly used is the Lauren classification. There are 2 main types- intestinal and diffuse. Intestinal type is predominant in areas with high incidence of gastric cancer whereas the diffuse type is more uniformly distributed.

Intestinal type is thought to be multistep process





Diffuse type does not arise from any recognizable precancerous lesions. It occurs more frequent in younger and female pts. Higher occurrence in familial cases. Somatic mutations in E cadherin gene and promoter hypermethylation of CDH1 gene are seen in sporadic diffuse gastric cancers.



Geographical and clinical differences in gastric cancer are also reflected at the molecular level. Tan et al studied RNA expression profiling of gastric cancer cell lines and identified 2 subtypes[7]. These subtypes G-INT and G-DIFF were associated with distinctive gene expression profiles and prognoses. These were significantly associated with Lauren intestinal and diffuse subtypes but concordance was 64% .Shah et al identified 3 distinct subtypes consistent with diffuse, proximal and distal intestinal type clinical and pathological classifications[8].

SYMPTOMS:

Symptoms are usually indicative of advanced disease. Patients have one or more of the following - early satiety, nausea, vomiting, weight loss, hematemesis, melena, abdominal pain, anemia.

Initial diagnostic test is usually upper endoscopy. Ct scans, endoscopic ultrasound, PET scan, diagnostic laparoscopy are used for staging.

STAGING:

Gastric cancer staging helps define prognostic groups and dictates treatment. Stage at diagnosis is the single most important prognostic factor for gastric cancer.

Early gastric cancer is confined to mucosa and submucosa irrespective of lymph node spread and clinical presentation. In advanced cancer, tumor cells invade muscularis propria and beyond. The American Joint Committee on Cancer uses the T(tumor) N(node)M (metastases) system for clinical and pathologic staging of cancer. Currently it is in the seventh edition.

Key changes that were made to the seventh edition:
Tumors arising at the esophagogastric junction, or arising in the stomach 5 cm or less for the esophagogastric junction and crossing the esophagogastric junction are now grouped under esophageal carcinoma. Tumors arising in the more distal stomach and tumors in proximal 5 cm but not involving esophagogastric junction are called gastric carcinomas.
T categories are harmonized with esophageal, small and large intestine cancers.
T1 subclassified as T1a (invasion of lamina propria and muscularis mucosa) and T1b (invasion of submucosa) to facilitate data collection efforts.
N categories modified based on number of involved lymph nodes.
Positive peritoneal cytology classified as metastatic disease (M1)
Anatomic staging/prognostic groupings changed.

	PRIMARY TUMOR (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ:* intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures*,**,***
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures**,***
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures

	REGIONAL LYMPH NODES (N)
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis*
N1	Metastasis in 1 to 2 regional lymph nodes
N2	Metastasis in 3 to 6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
N3a	Metastasis in 7 to15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
	* A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

GROUP	T	N	M
❑ 0	Tis	N0	M0
❑ IA	T1	N0	M0
❑ IB	T2	N0	M0
	T1	N1	M0
❑ IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
❑ IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
❑ IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
❑ IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
❑ IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
❑ IV	Any T	Any N	M1
❑ Stage unknown			

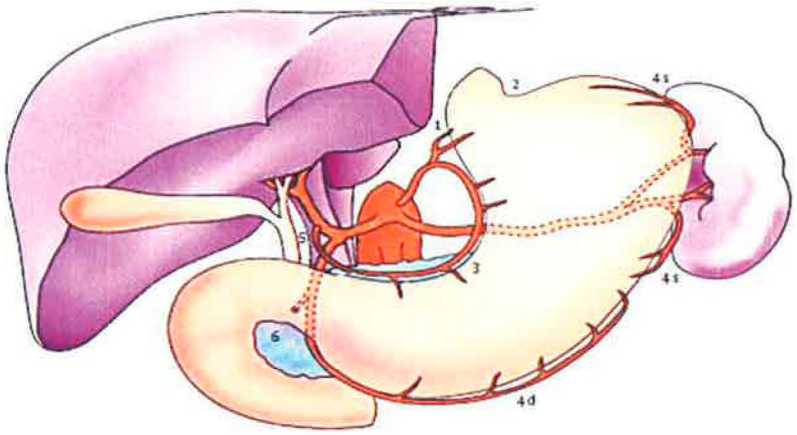
SURGERY

Early gastric cancer

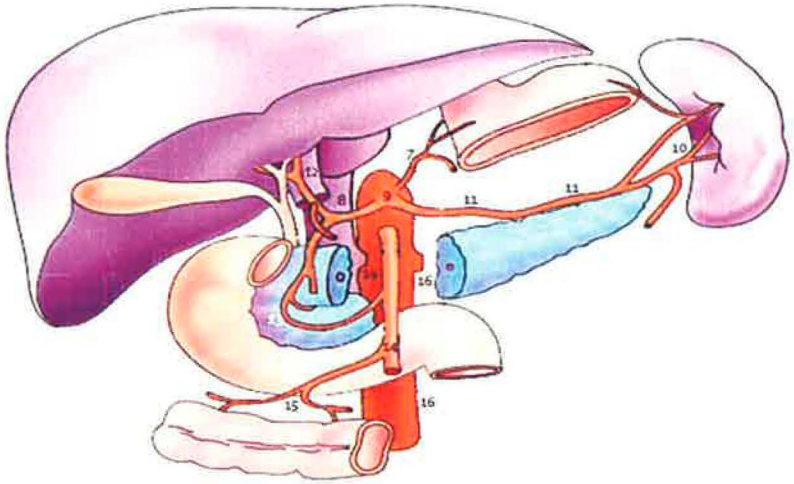
Endoscopic mucosal resection (EMR) and Endoscopic Submucosal dissection(ESD) can be used for very early tumors[9]. Small lesions upto 2 cm can generally be removed by EMR. Larger lesiosn can be removed using ESD. Tumors have to be intramusosal, moderately to well differentiated intestinal type as these have low risk of lymph node metastases. Intestinal type lesions with slight submucosal invasion can also be treated this way. Flat or scarred lesions are difficult to remove and may require full thickness resection. In Japanese series, risks are low in experienced handS and include- bleeding(2%), perforation(2%) both of which can be managed endoscopically. Delayed perforation occurred in 0.45% and needs emergent surgery.

Lymph node dissections have been defined by the Japanese Gastric Cancer Group and the American Joint Committee on Cancer (AJCC).

Nodes along lesser (station 1,3,5) and greater curvature (station 2,4,6) were grouped as N1. D 1 dissection includes removal of affected part of stomach along with nodes along lesser and greater curvature and lesser and greater omentum.



N2 nodes are those along left gastric (station 7), common hepatic (station 8), celiac(station 9) and splenic arteries(stations 10 and 11). D 2 dissection involves removal of nodes along left gastric, common hepatic, celiac and splenic arteries.



1=right cardial nodes. 2=left cardial nodes. 3=nodes along lesser curvature. 4 s and 4 d=nodes along greater curvature. 5=suprapyloric nodes. 6=infrapyloric nodes. 7=nodes along left gastric artery. 8=nodes along common hepatic artery. 9=nodes around celiac axis. 10=nodes at splenic hilus. 11=nodes along splenic artery. 12=nodes in hepatoduodenal ligament. 13=nodes at posterior aspect of pancreas head. 14=nodes at root of mesenterium. 15=nodes in mesocolon of transverse colon. 16=para-aortic nodes.

Many surgeons have little experience with gastric cancer resections. Inadequate margins of normal stomach and failure to perform adequate lymph note dissections cause local and lymph node recurrences in more than half of surgical failures.

In 1980s series of multi instituutional studies in Japan, Korea showed that extended lymphadenectomy could be performed safely in high volume centers. Subsequent reports from the United States and Western countries confirmed that thorough lymphadenectomy could be performed with low morbidity and mortality. The key was to show that extended lymphadenectomy was beneficial in the setting of randomized controlled trials.

In 1999, 2 studies were published simultaneously. Cuschiere et al published results of the MRC trial[10]. 400 pts with gastric adenocarcinoma were randomized to D1 or D2 resection. The 5 yr survival rates were 35% for D 1 resection and 33 % for D 2 resection.

Bonenkamp et al published a study for the Dutch Gastric Cancer group.711 patients were randomized[11]. Pts in D2 group had higher rate of complications than the D1 group(43 % vs 25% p <0.001), more postoperative deaths(10% vs 4% p0.004), longer hospital stays (median 16 vs 14 days p <0.001). Five year survival rates were similar for both groups 45% for D1 group and 47% for D2 group. In 2004, update of the Dutch study was published. There was no difference in overall survival (30% vs 35% p 0.53). Of all subgroups analyzed only N2 patients may benefit from D2 dissection. In 2010 15 yrs follow up of the Dutch study showed overall survival of 21% for D1 group and 29 % for D 2 group (p0.34)[12].Gastric cancer related death rate was higher in D1 group 48% compared to D2 group 37%. Local recurrence was 22% in D 1 group vs 12% in D2 group; regional recurrence was 19% in D1 vs 13% in D2.

Technique of D2 lymphadenectomy was improving, routine splenectomy and pancreatectomy was no longer being performed[13,14]. A meta analysis published in 2011 looked at 5 randomized studies and showed overall hospital mortality and reoperation rates were higher in D2 group[15]. Subgroup

analysis showed improved survival trends in patients with T3/T4 tumors and those with spleen/pancreas preservation.

Japanese trials studying adjuvant chemotherapy have reported survival rates upto 70% in the groups having surgery (D2 lymphadenectomy) alone[16,17].
Wu et al reported a single institution study of 221 pts assigned to D1 vs D3 resection. All 3 surgeons had 25 case experience. Overall survival at 5yrs was higher in D3 group than D1 group 59.5% vs 53.6% (p0.041).This D3 surgery would now be considered modified D2 surgery. In 215 pts with R0 resection, recurrence rate at 5yrs was 50.6% in D1 group and 40.3%in D3 group (p 0.192).

There did not seem any additional benefit to extending the lymph node dissection beyond D2. Study by Sasako et al from Japan randomized 523 patients with T2b,T3,T4 lesions to D2 lymphadenectomy vs D2 with para aortic lymph node dissection(PAND). No difference was found in complication rate or overall survival- 5 yr survival 69.2% in D2 alone group and 70.1% in D2 with PAND group[18].
D2 lymphadenectomy with spleen and pancreas preservation is considered standard surgery for gastric cancer. No survival benefit for extended lymphadenectomy beyond D2.

RADIATION AND CHEMOTHERAPY
Even after potentially curative resection, 5 yr survival for gastric cancer patients remains 20-30%. [19]Additional therapy with chemotherapy or radiation could improve survival in these patients.

Neoadjuvant radiation offers theoretical advantage of target delineation and intact vascular supply in tumor bed before disruption by surgery.
A prospective study from China involving 307 pts showed improved 5 yr survival (30% vs 19.8% p 0.009), local recurrence (39% vs 52% p 0.025) and increased resectability (90% vs 79% p 0.01) with preop radiation.
In a European study of 102 pts, there was no benefit to preop radiation after 20 yrs of follow up.

A phase 2 study from MD Anderson and the RTOG 9904 studied induction chemotherapy and concurrent chemoradiation prior to surgery and showed tumor downstaging, even pathologic complete responses. However large

randomized trials of neoadjuvant therapy are lacking and this may be done in carefully selected patients.

Several early clinical trials have have shown variable, usually negative survival benefit for chemotherapy in resectable gastric cancer. Some of the well conducted studies in 2000s have shown survival benefit with adjuvant therapy. MacDonald et al published results of the Intergroup study INT 0116 in 2001. This is a North American study of 556 pts who were randomized to surgery alone or surgery followed by chemotherapy with 5FUwith leucovorin and radiation. Radiation given was 4500cGy. 64 % of pts in chemoradiotherapy arm completed planned therapy. 3 yr survival rates were 50% in chemoradiotherapy group vs 41% in surgery alone group. Median overall survival at 5 yrs was 36 months in patients who received post surgery chemoradiation and 27 months in those who had surgery alone. 10% of patients in the study had D2 lymph node dissection, 36% had D1 dissection and 54% had less than D1 dissection[20,21].

MAGIC trial conducted Europe involved 500 pts[22]. Patients were assigned to either surgery or chemotherapy and surgery. Chemotherapy was ECF regimen(epirubicin,cisplatin, 5FU), 3 cycles given preoperatively and 3 cycles given postoperatively. 5 yr survival was 36% in chemotherapy arm, 23% in surgery alone arm (p 0.009.) Of patients assigned to chemotherapy 86% completed preop chemotherapy, 41.6% completed all post op chemotherapy. Rate of curative surgery 66 % in surgery group, 70% in surgery with chemotherapy group.~20% of pts had D1 resection.

The FNCLLC study involved 224 pts, of whom 25% had gastric cancer. Patients given chemotherapy 5FU and cisplatin 2-3 cycles preoperatively and 3-4 cycles post operatively. 5 yr survival rates 38% in surgery and chemotherapy arm and 24% in surgery alone arm (p 0.02)[23].

S 1 is an orally active drug and is a combination of tegafur (a prodrug that is converted to 5FU), gimeracil (inhibitor of dihropyrimidine dehyrogenase, which degrades fluorouracil) and oteracil (which inhibits the phopshorylation of flurouracil in gastrointestinal tract and thereby reducing gastrointestinal side effects of flurouracil).

ACTS study from East Asia involved 1060 pts[17]. Patients either had surgery alone or surgery followed by one year of adjuvant therapy with oral drug, S1. Overall survival at 3 yrs was80% in surgery followed by chemotherapy arm

compared to 70% in surgery alone arm(p0.003). All patients had D2 dissection.

Classic study was conducted in South Korea, China and Taiwan[16]. Study of 1035 pts, all had D2 resection. Patients either had surgery or surgery followed by adjuvant therapy with capecitabine and oxaliplatin. 3 yr disease free survival was 74% in chemotherapy arm vs 59% in surgery alone arm.
Adjuvant therapy improves survival in resectable gastric cancer patients; choice of therapy depends on geographical location and institutional practice.

SYSTEMIC THERAPY FOR ADVANCED DISEASE

Early chemotherapy agents included 5FU, cisplatin, doxorubicin,etoposide, methotrexate, mitomycin. Newer agents are capecitabine, S1, irinotecan, docetaxel, paclitaxel.
A metaanalysis published in 1997 included 3 studies comparing 5FU /LV with etoposide to best supportive care. 45% of patients receiving chemotherapy had improved quality of life compared to 20% on best supportive care. Median overall survival was better at 8 months compared to 5 months for pts on best supportive care[24].

Weber in 1997 published study comparing ECF regimen to FAMTX and showed better response rate (45% vs 21%), median survival (8.9 vs 5.7 months)[25]. Ross et al published in 2002 compared ECF to 5FU/cisplatin/mitomycin showed similar response rates(44 and 42%) , slightly better median survival at 9.4 vs 8.7 months, 40% of pts were alive at 1 yr in ECF arm vs 32% in 5fu/cisplatin/mitomycin arm[25]. V-325 study compared 3 drug combination of DCF (docetxel,cisplatin,5fu) to 2 drug combination of cispaltin,5fu and showed longer time to tumor progression (5.6 months vs 3.6 months) and better response rates(37 vs 25%)[26].

Wagner et al showed that chemotherapy was better than best supportive care in improving survival (HR 0.39), combination chemotherapy was better than single agent (HR 0.83) and 3 drug combination including anthracycline was better than 2 drug combinations(HR 0.77)[27].
However, toxicity from these combination regimens can be substantial. DCF caused neutropenia in 82% cases, complicated neutropenia in 29% compared to 57% and 12% respectively with CF; diarrhea in 18% of patients, 50% were taken off study either due to toxicities or withdrawal of consent[28].

Japanese studied S vs S1 and cisplatin in 305 pts with advanced gastric cancer as first line therapy[29]. Median overall survival was 13 months in S1 and cisplatin arm and 11 months in S1 arm. Response rate 54% with cisplatin, S1.Efficacy of S1 in western population needs to established and this agent remains investigational in the US.
Irinotecan has been studied in second line setting. Second Line treatment with FOLFIRI was active and well tolerated in pts with metastatic gastric cancer not previously treated with fluoropyrimidine[30].

TARGETED THERAPY
HER2 growth factor receptor is a member of the ERBB/HER growth receptor family. Trastuzumab is a humanized monoclonal antibody that binds to the extracellular ligand binding domain of the HER 2 receptor.
TOGA study which is a phase 3 international study for patients with gastric and gastroesopahegal junction tumors[31]. 594 patients were randomized to chemotherapy 5FU or capecitabine with cisplatin and chemotherapy with trastuzumab. Median overall survival was 13.8 months in trastuzumab plus chemotherapy arm versus 11.1 months in those assigned to chemotherapy alone. Post hoc analysis looked at pts with high (IHC 2+ and FISH positive; IHC 3+) and low (IHC 0 or 1+ and FISH positive) levels of HER 2 protein in their tumors. Median overall survival was 16 months in high expression group that received trastuzumab.

EGFR is growth factor receptor that is overexpressed on 37-64% of gastric cancers. Cetuximab is a monoclonal antibody that binds to the EGFR receptor and is the most studied. Several phase 2 trials have studied cetuximab in combination with chemotherapy with response rates ranging from 41- 63% and overall survival 9- 16.6 months[32]. Results from randomized phase 3 trials are awaited.

Success of antiangiogenic therapy in other cancers led to studies in gastric cancer as well. The AVAGAST study showed that adding bevacizumab to chemotherapy in patients with advanced gastric cancer improves progression-free survival and tumor response rate but not overall survival[32,33]. The study included a prospective, mandatory biomarker program. Patients with previously untreated, locally advanced or metastatic gastric cancer were randomly assigned to bevacizumab (n = 387) or placebo (n = 387) in combination with chemotherapy. Blood and tumor tissue samples were

collected at baseline. Prespecified biomarkers included plasma vascular endothelial growth factor-A (VEGF-A), protein expression of neuropilin-1, and VEGF receptors-1 and -2 (VEGFR-1 and VEGFR-2). Patients with high baseline plasma VEGF-A levels showed a trend toward improved overall survival (hazard ratio 0.57) versus patients with low VEGF-A levels (HR, 1.01, p = .07). Patients with low baseline expression of neuropilin-1 also showed a trend toward improved overall survival (HR 0.75) versus patients with high neuropilin-1 expression (HR 1.07,p = .06). For both biomarkers, subgroup analyses demonstrated significance only in patients from non-Asian regions.

CONCLUSIONS:

Gastric cancer is a global health problem with high mortality. Surgery is the only curative therapy. Systemic therapy improves survival in both adjuvant setting and advanced disease. Understanding the molecular biology of the disease is important in advancing therapy of this disease.

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