# Mide Kanserinde Tedavi Yaklaşımları

**Dr. Deniz Tural**
**Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi**
Tıbbi Onkoloji

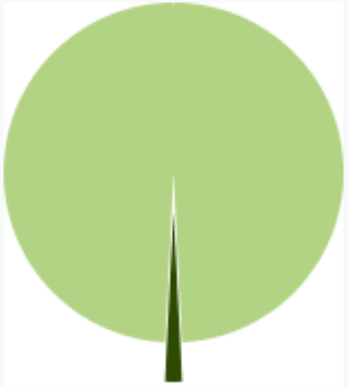
# Ders Planı

- Mide kanseri insidans ve mortalite
- Mide kanserinde evreleme
- Mide kanserinde  neoadjuvan-adjuvan tedavi
- Metastatik mide kanserinde yeni tedavi seçenekleri

# Mide Kanseri İnsidans ve Mortalite

| | Common Types of Cancer | Estimated New Cases 2016 | Estimated Deaths 2016 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 246,660 | 40,450 |
| 2. | Lung and Bronchus Cancer | 224,390 | 158,080 |
| 3. | Prostate Cancer | 180,890 | 26,120 |
| 4. | Colon and Rectum Cancer | 134,490 | 49,190 |
| 5. | Bladder Cancer | 76,960 | 16,390 |
| 6. | Melanoma of the Skin | 76,380 | 10,130 |
| 7. | Non-Hodgkin Lymphoma | 72,580 | 20,150 |
| 8. | Thyroid Cancer | 64,300 | 1,980 |
| 9. | Kidney and Renal Pelvis Cancer | 62,700 | 14,240 |
| 10. | Leukemia | 60,140 | 24,400 |
| | - | - | - |
| **15.** | **Stomach Cancer** | **26,370** | **10,730** |

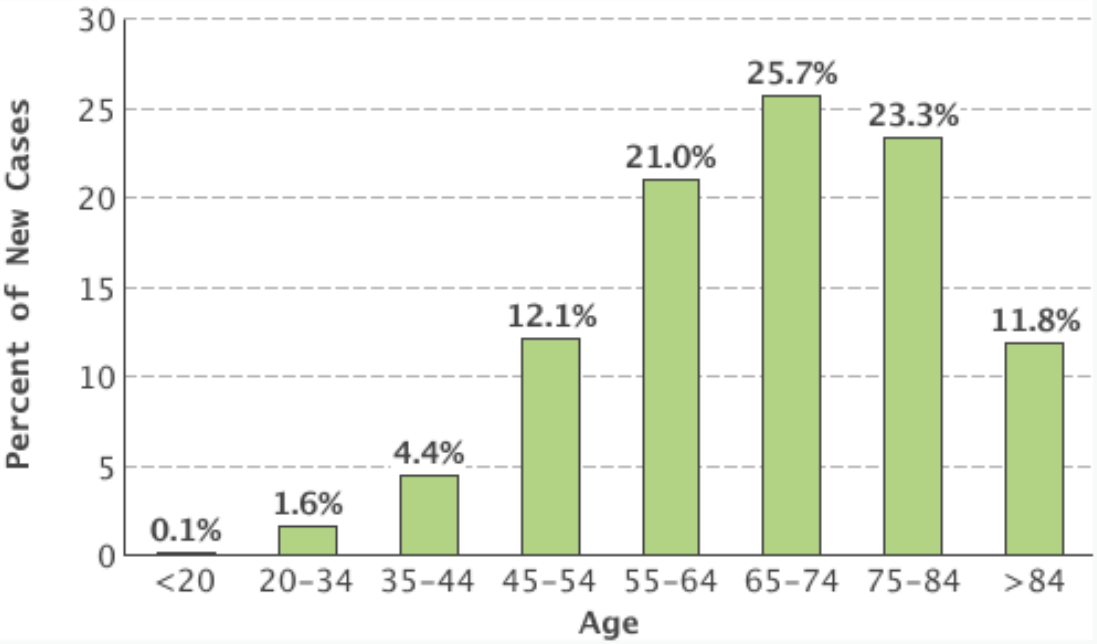
Stomach cancer represents 1.6% of all new cancer cases in the U.S.




In 2016, it is estimated that there will be 26,370 new cases of stomach cancer and an estimated 10,730 people will die of this disease.

# Mide Kanseri İnsidans ve Mortalite

## Percent of New Cases by Age Group: Stomach Cancer




Stomach cancer is most frequently diagnosed among people aged 65 -74.

**Median Age At Diagnosis**

**69**

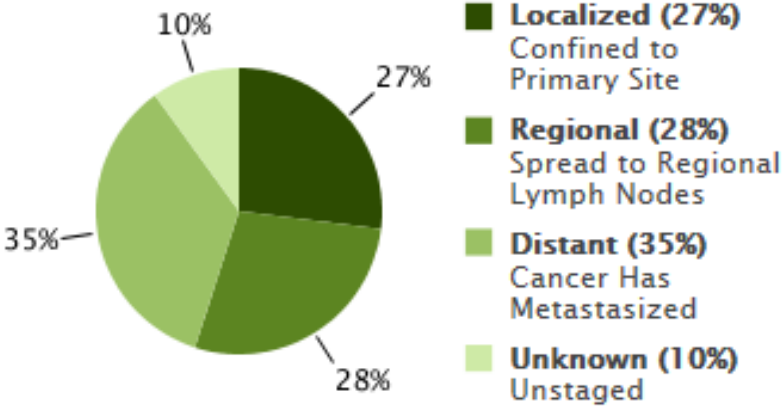
SEER 18 2009-2013, All Races, Both Sexes

## Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Stomach Cancer

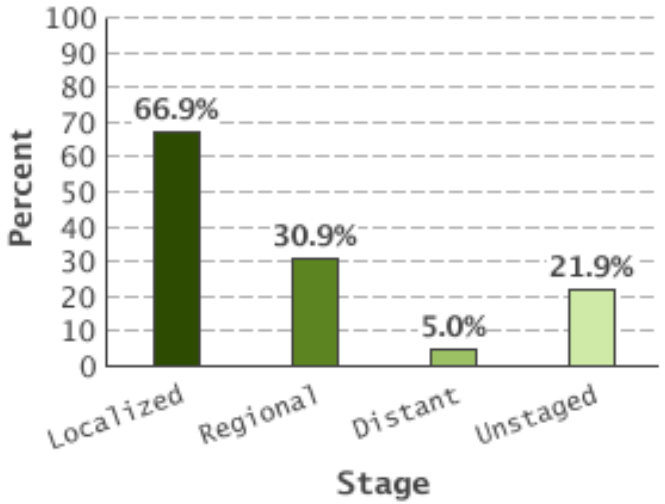
# Mide Kanseri İnsidans ve Mortalite

## Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Stomach Cancer

### Percent of Cases by Stage




### 5-Year Relative Survival

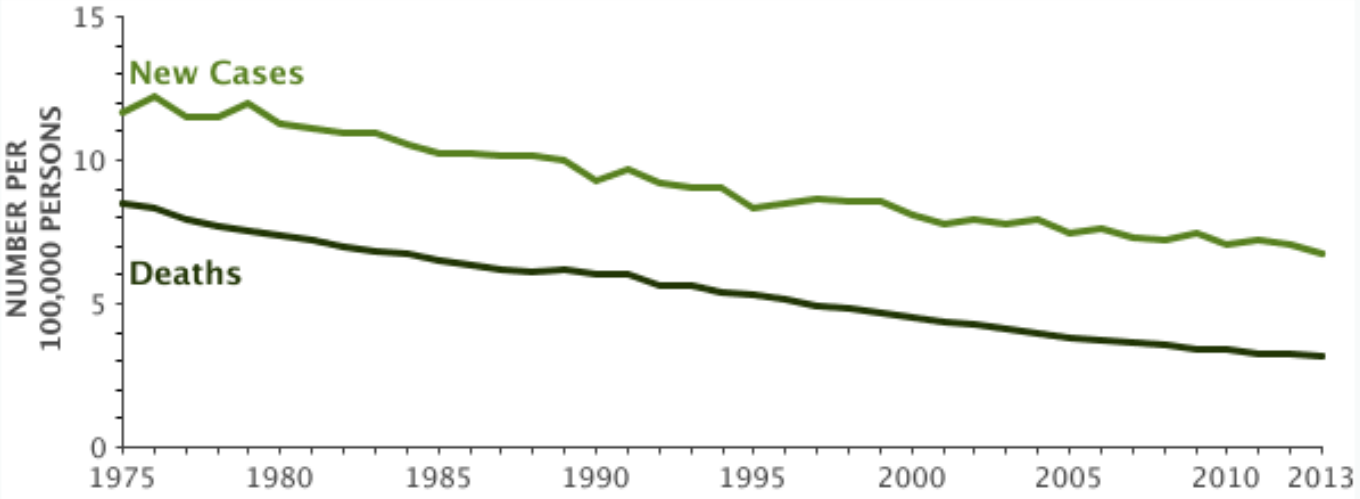



SEER 18 2006-2012, All Races, Both Sexes by SEER Summary Stage 2000

# Mide Kanseri İnsidans ve Mortalite

## New Cases, Deaths and 5-Year Relative Survival

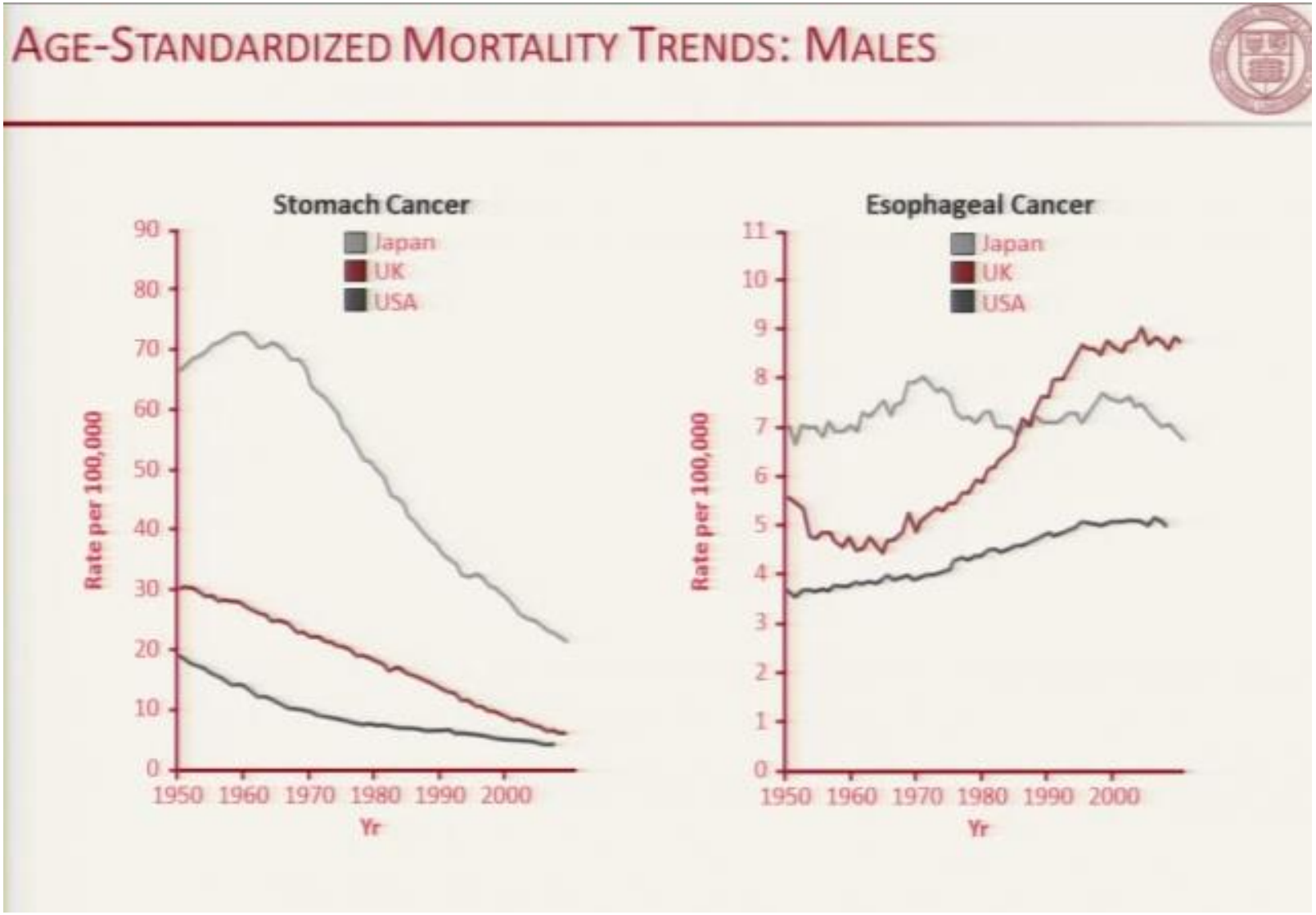
View Data Table




| Year | 1975 | 1980 | 1985 | 1990 | 1995 | 2000 | 2004 | 2008 |
|---|---|---|---|---|---|---|---|---|
| 5-Year Relative Survival | 14.3% | 15.7% | 17.6% | 20.0% | 21.9% | 22.9% | 28.2% | 31.6% |

SEER 9 Incidence & U.S. Mortality 1975-2013, All Races, Both Sexes. Rates are Age-Adjusted.

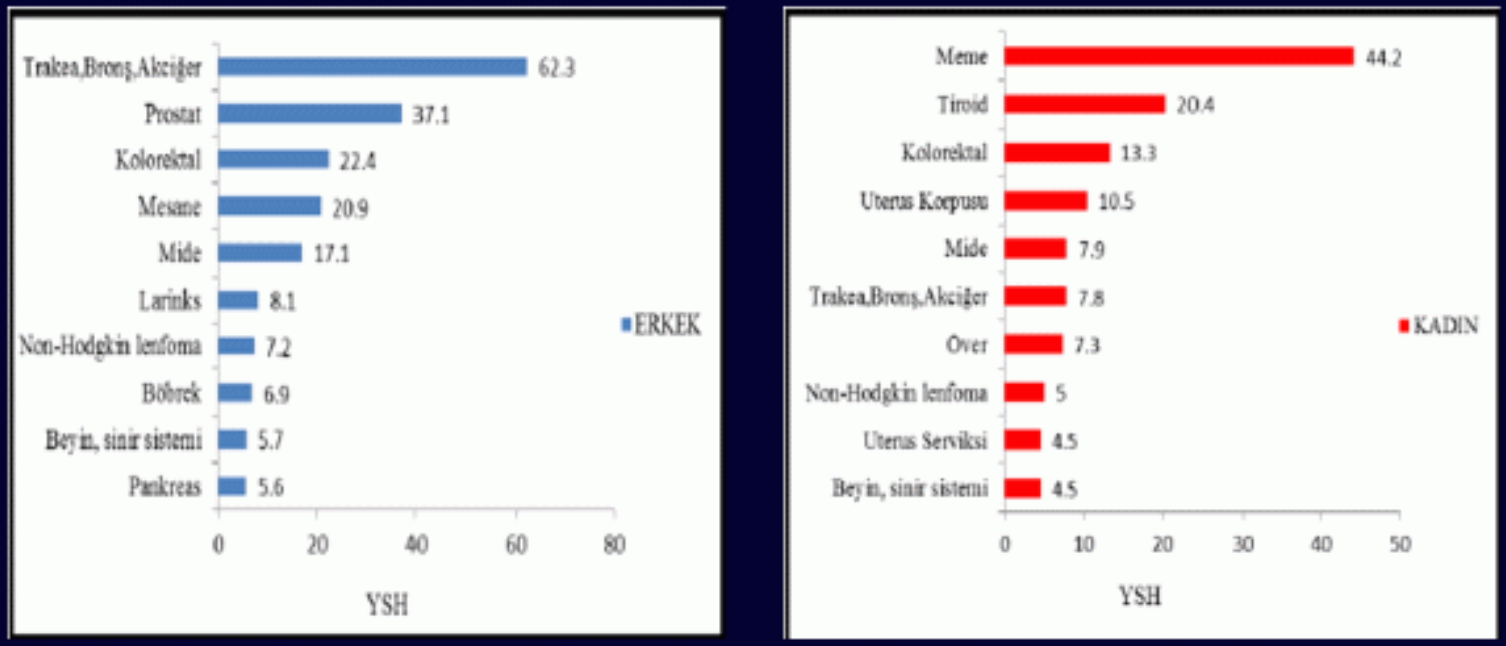
# Mide Kanseri İnsidans ve Mortalite



# Mide Kanseri İnsidans ve Mortalite

**Epidemiyoloji** Türkiye 2011

verileri

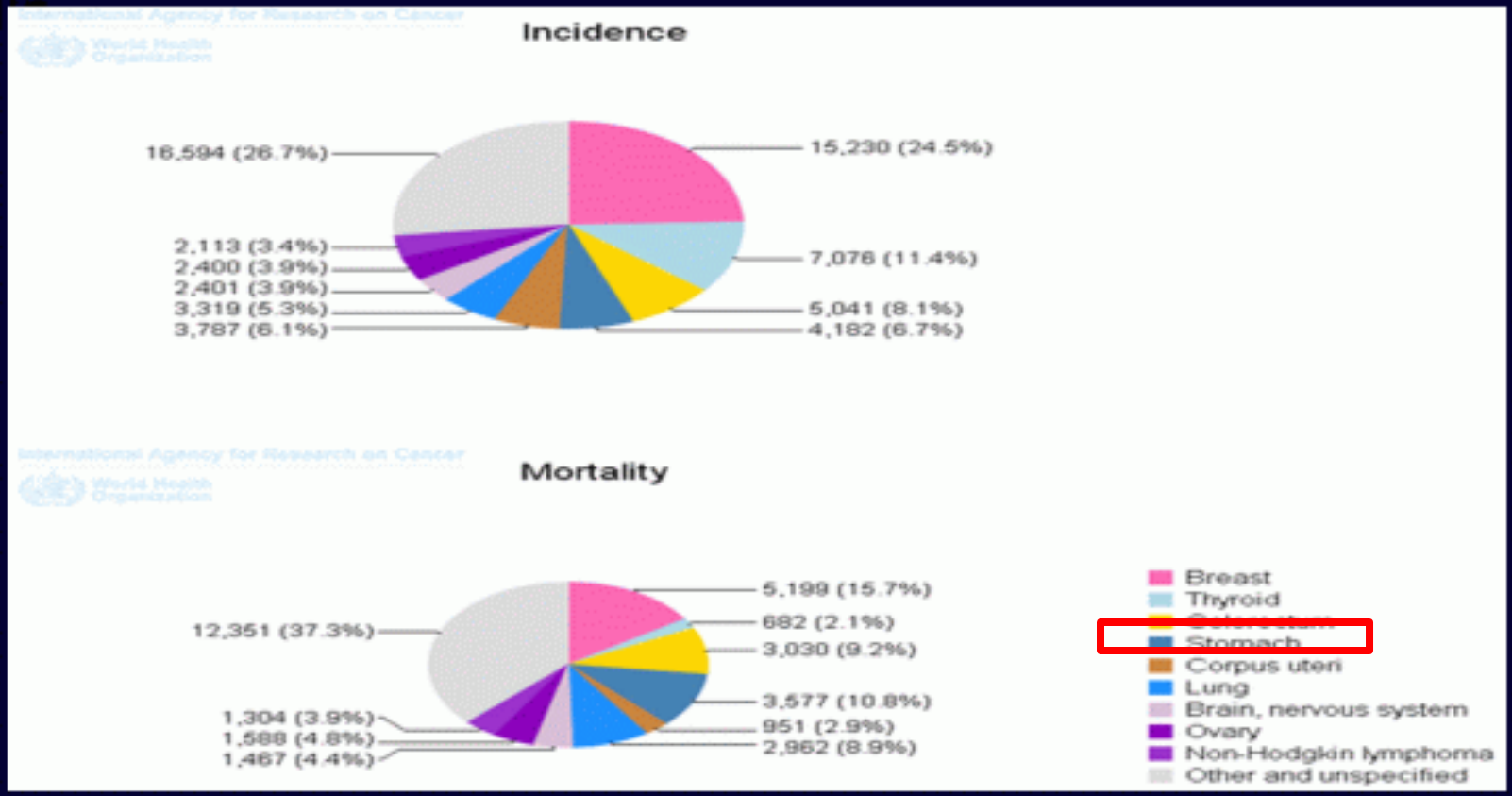



En sık 10 tümörün yaşa göre standardize edilmiş hızları (100.000 kişide)

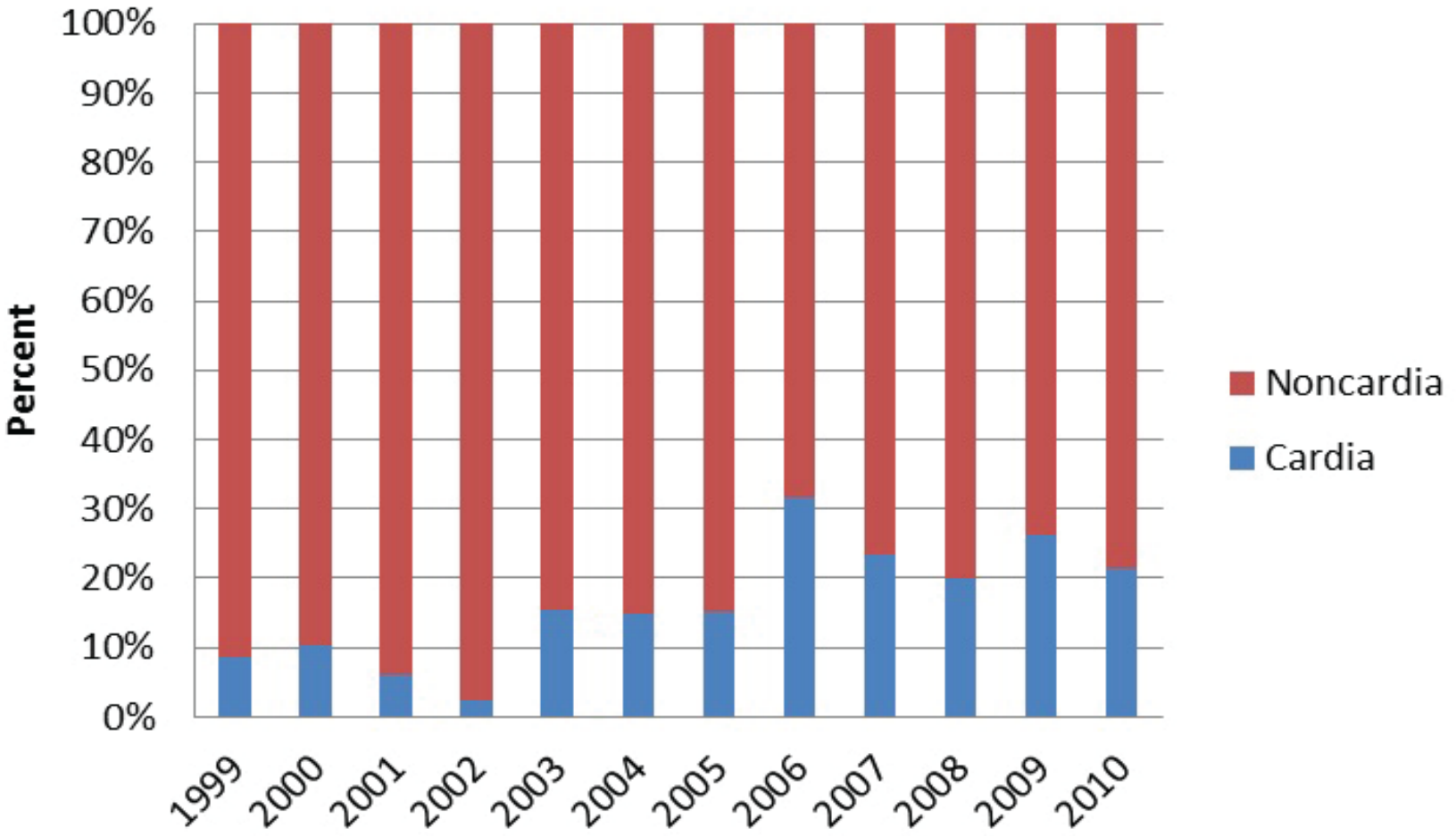
# Mide Kanseri İnsidans ve Mortalite

**Epidemiyoloji** GLOBOCAN 2012-Türkiye-

Kadın

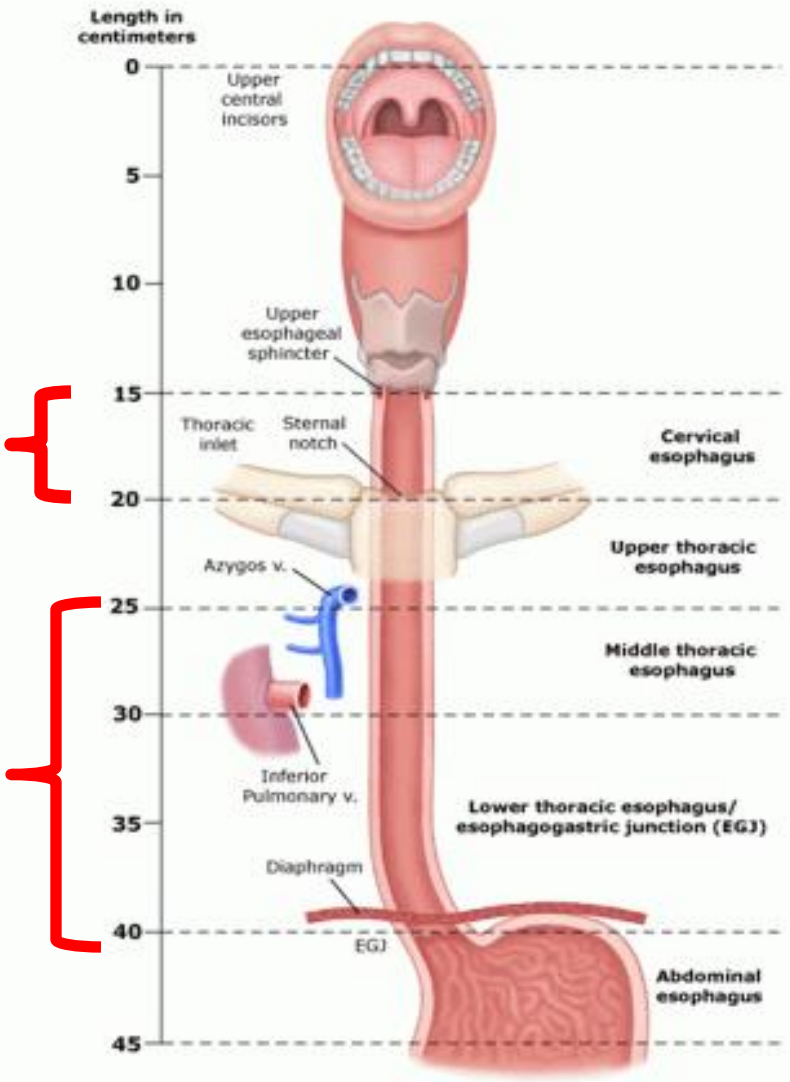


# Mide Kanseri İnsidans ve Mortalite




Tural D, et al. Gastric cancer: a case study in Turkey. J Cancer Res Ther. 2013

# Özofagus Kanserinde Evreleme




**Primary site of esophageal cancer based on proximal edge of tumor**

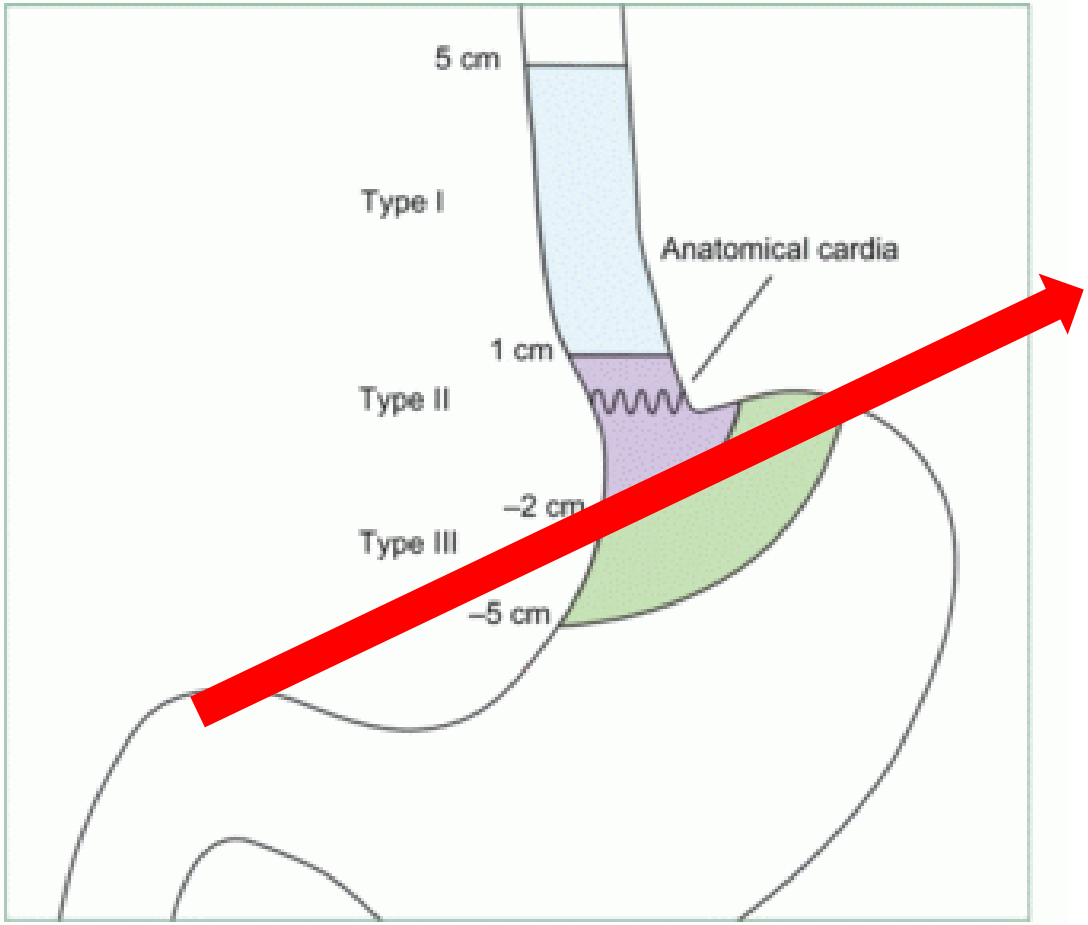
| Anatomic name | Esophageal location | Anatomic boundaries | Endoscopic distance from incisors |
|---|---|---|---|
| Cervical | Upper | Hypopharynx to sternal notch | 15 to <20 cm |
| Thoracic | Upper | Sternal notch to azygos vein | 20 to <25 cm |
| | Middle | Lower border of azygos vein to inferior pulmonary vein | 25 to <30 cm |
| | Lower | Lower border of inferior pulmonary vein to esophagogastric junction | 30 to <40 cm |
| Abdominal | Lower | Esophagogastric junction to 5 cm below esophagogastric junction | 40-45 cm |
| | Esophagogastric junction/cardia | Esophagogastric junction to 5 cm below esophagogastric junction | 40-45 cm |

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.*

UpToDate®

# Özofagus Kanserinde Evreleme

## Siewert Sınıflaması



# Özofagus Kanserinde Tedavi Yaklaşımları

## PREOP CHEMO VS CHEMO RT: META ANALYSIS

| | Trials | Pts | Mort. Reduc | HR | P value | 2 yr OS |
|---|---|---|---|---|---|---|
| Chemo | 8 | 1724 | 10% | 0.90 | 0.05 | 7% |
| Adeno | | | 22% | 0.78 | 0.024 | |
| Squam | | | 12% | 0.88 | 0.12 | |
| Chemo RT | 10 | 1209 | 19% | 0.81 | 0.002 | 13% |
| Adeno | | | 25% | 0.75 | 0.02 | |
| Squam | | | 16% | 0.84 | 0.04 | |

Gebski et al, Lancet Oncol 8: 226-234; 2007

# Özofagus Kanserinde Tedavi Yaklaşımları
# Cerrahi Öncesi KRT-Cerrahi

**Table 1.** CALGB 9781: Patient Characteristics

| Characteristic | Treatment Arm: Trimodality Therapy No. | Trimodality Therapy % | Surgery Alone No. | Surgery Alone % | Total No. | Total % | P* |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Male | 28 | 93 | 23 | 88 | 51 | 91 | .65 |
| Female | 2 | 7 | 3 | 12 | 5 | 9 | |
| Race/ethnicity | | | | | | | |
| White | 25 | 83 | 23 | 88 | 48 | 86 | .71 |
| Other | 5 | 17 | 3 | 12 | 8 | 14 | |
| Performance status | | | | | | | |
| 0 | 19 | 63 | 18 | 69 | 37 | 66 | .32 |
| 1 | 8 | 27 | 8 | 31 | 16 | 29 | |
| 2 | 3 | 10 | 0 | 0 | 3 | 5 | |
| Age, years | | | | | | | |
| Mean | 60.9 | | 61.9 | | 61.4 | | .69 |
| Median | 59.9 | | 62.2 | | 60.7 | | |
| Range | 38-77 | | 44-76 | | 38-77 | | |
| Tumor type | | | | | | | |
| Adenocarcinoma | 23 | 77 | 19 | 73 | 42 | 75 | 1.0 |
| Squamous | 7 | 23 | 7 | 27 | 14 | 25 | |
| Clinical N stage | | | | | | | |
| N0 | 20 | 67 | 22 | 85 | 42 | 75 | .22 |
| N+ | 10 | 33 | 4 | 15 | 14 | 25 | |
| Staging method | | | | | | | |
| Noninvasive | 16 | 53 | 15 | 58 | 31 | 55 | .79 |
| Invasive | 14 | 44 | 11 | 42 | 25 | 45 | |
| Albumin | | | | | | | |
| Mean | 3.8 | | 3.9 | | 3.9 | | .50 |
| Median | 3.9 | | 4.0 | | 3.9 | | |
| Range | 1.0-4.6 | | 2.5-4.5 | | 1.0-4.6 | | |

Abbreviation: CALGB, Cancer and Leukemia Group B.
*P values are associated with the exact $\chi^2$ test for categorical variables and the Van der Waerden (normal) scores for continuous variables.

**Patients with histologically documented untreated squamous cell carcinoma or adenocarcinoma of the thoracic esophagus (below 20 cm) or gastroesophageal junction and with less than 2cm distal spread into the gastric cardia were eligible**

# Özofagus Kanserinde Tedavi Yaklaşımları
# Cerrahi Öncesi KRT-Cerrahi

## CROSS Trial – pre-operative Chemo/RT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

- Purpose: To test the value of pre-operative chemoradiation in locally advanced esophageal carcinoma
- Eligibility: T1N1 – T2-3Nx (stage 1-3)
- Treatment: Radiation 4140 cGy + weekly taxol (50 mg/m2) and Carboplatin (AUC 2)

# Özofagus Kanserinde Tedavi Yaklaşımları
# Cerrahi Öncesi KRT-Cerrahi

- Potentially curable squamous-cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma of the esophagus or esophagogastric junction

- The upper border of the tumor had to be at least 3 cm below the upper esophageal sphincter. Patients who had proximal gastric tumors with minimal invasion of the esophagus were excluded.

- Only patients with tumors of clinical stage T1N1 or T2-3N0-1

- The length and width of the tumor could not exceed 8 cm and 5 cm, respectively.

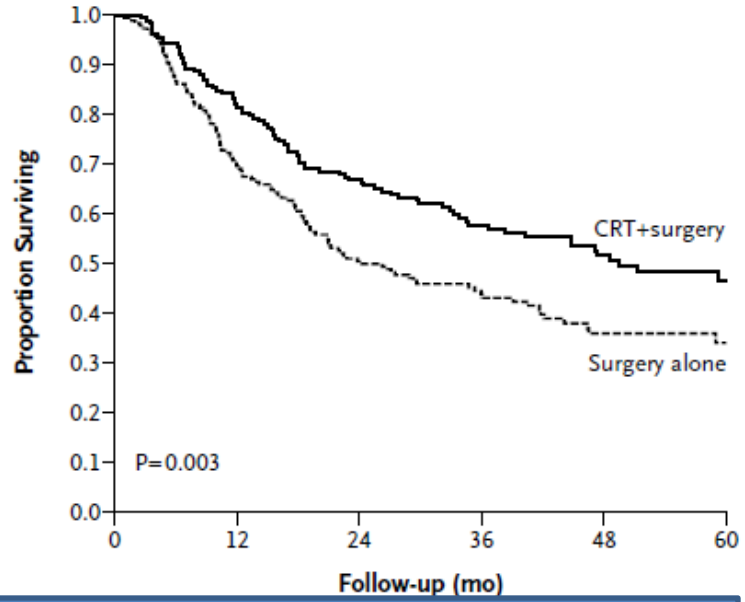
# Özofagus Kanserinde Tedavi Yaklaşımları
# Cerrahi Öncesi KRT-Cerrahi

**Table 1. Characteristics of Patients with Resectable Esophageal or Esophagogastric-Junction Cancer, According to Treatment Group.***

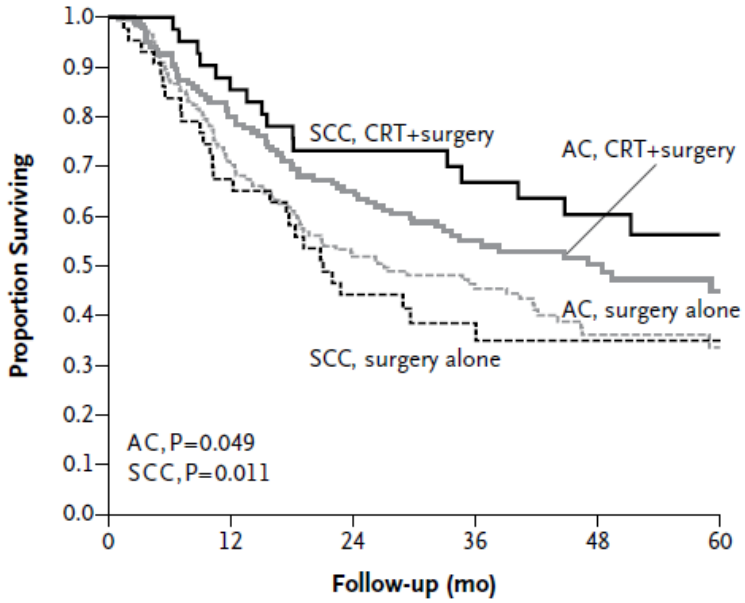
| Characteristic | Chemoradiotherapy and Surgery (N= 178) | Surgery Alone (N= 188) |
|---|---|---|
| Age — yr | | |
| Median | 60 | 60 |
| Range | 36–79 | 36–73 |
| Male sex — no. (%) | 134 (75) | 152 (81) |
| Tumor type — no. (%) | | |
| Adenocarcinoma | 134 (75) | 141 (75) |
| Squamous-cell carcinoma | 41 (23) | 43 (23) |
| Other | 3 (2) | 4 (2) |
| Tumor length — cm† | | |
| Median | 4 | 4 |
| Interquartile range | 3–6 | 3–6 |
| Tumor location — no. (%)† | | |
| Esophagus | | |
| Proximal third | 4 (2) | 4 (2) |
| Middle third | 25 (14) | 24 (13) |
| Distal third | 104 (58) | 107 (57) |
| Esophagogastric junction | 39 (22) | 49 (26) |
| Missing data | 6 (3) | 4 (2) |
| Clinical T stage — no. (%)‡ | | |
| cT1 | 1 (1) | 1 (1) |
| cT2 | 26 (15) | 35 (19) |
| cT3 | 150 (84) | 147 (78) |
| cT4 | 0 | 1 (1) |
| Could not be determined§ | 1 (1) | 4 (2) |
| Clinical N stage — no. (%)¶ | | |
| N0 | 59 (33) | 58 (31) |
| N1 | 116 (65) | 120 (64) |
| Could not be determined§ | 3 (2) | 10 (5) |
| WHO performance status score — no. (%)‖ | | |
| 0 | 144 (81) | 163 (87) |
| 1 | 34 (19) | 25 (13) |

# Özofagus Kanserinde Tedavi Yaklaşımları
# Cerrahi Öncesi KRT-Cerrahi

**A** Survival According to Treatment Group




**B** Survival According to Tumor Type and Treatment Group




**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| AC, CRT+surgery | 134 | 107 | 87 | 53 | 34 | 18 |
| AC, surgery alone | 141 | 99 | 73 | 50 | 25 | 10 |
| SCC, CRT+surgery | 41 | 35 | 30 | 21 | 15 | 8 |
| SCC, surgery alone | 43 | 29 | 19 | 11 | 8 | 4 |
| Total | 359 | 270 | 209 | 135 | 82 | 40 |

**Median overall survival of 49.4 months in the chemoradiotherapy–surgery group versus 24.0 months in the surgery group**

# Özofagus Kanserinde Tedavi Yaklaşımları
# Cerrahi Öncesi KRT-Cerrahi

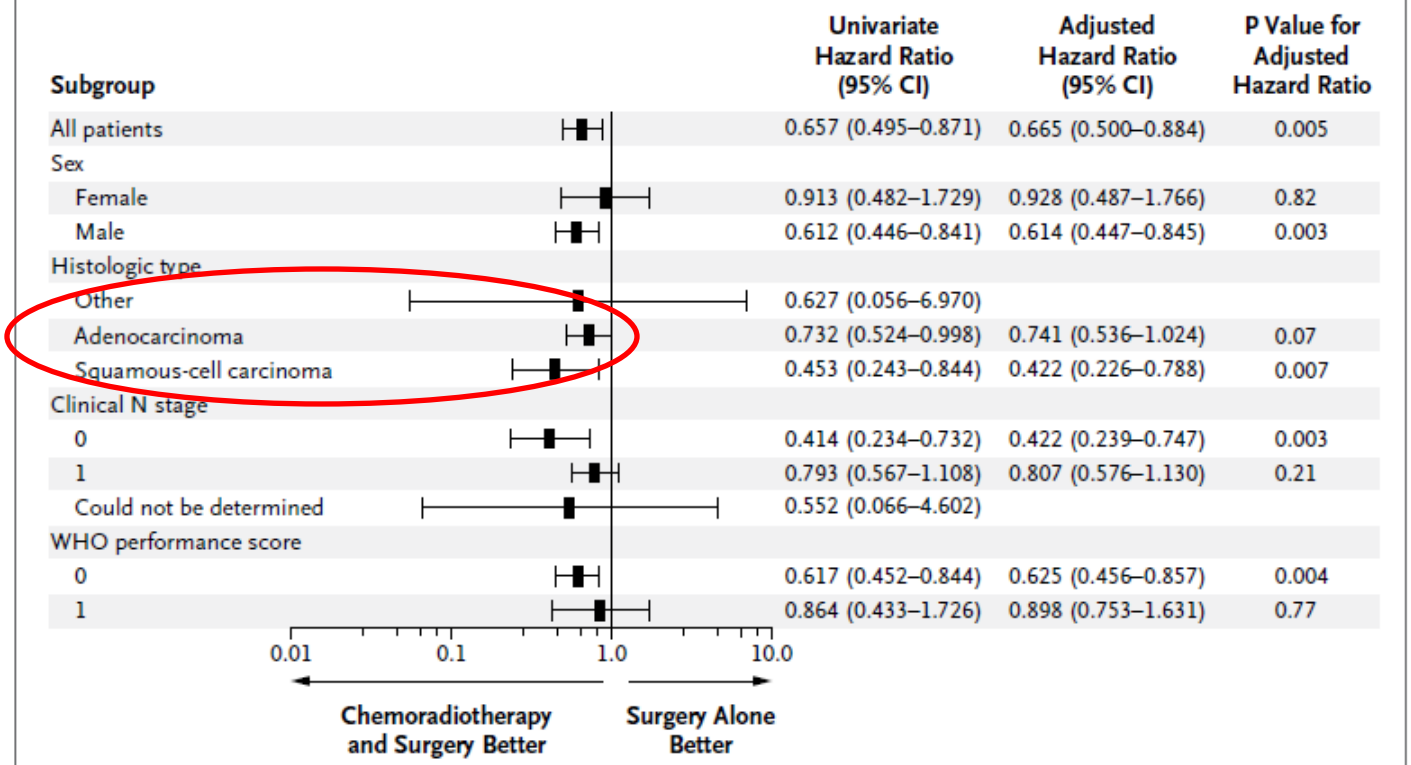
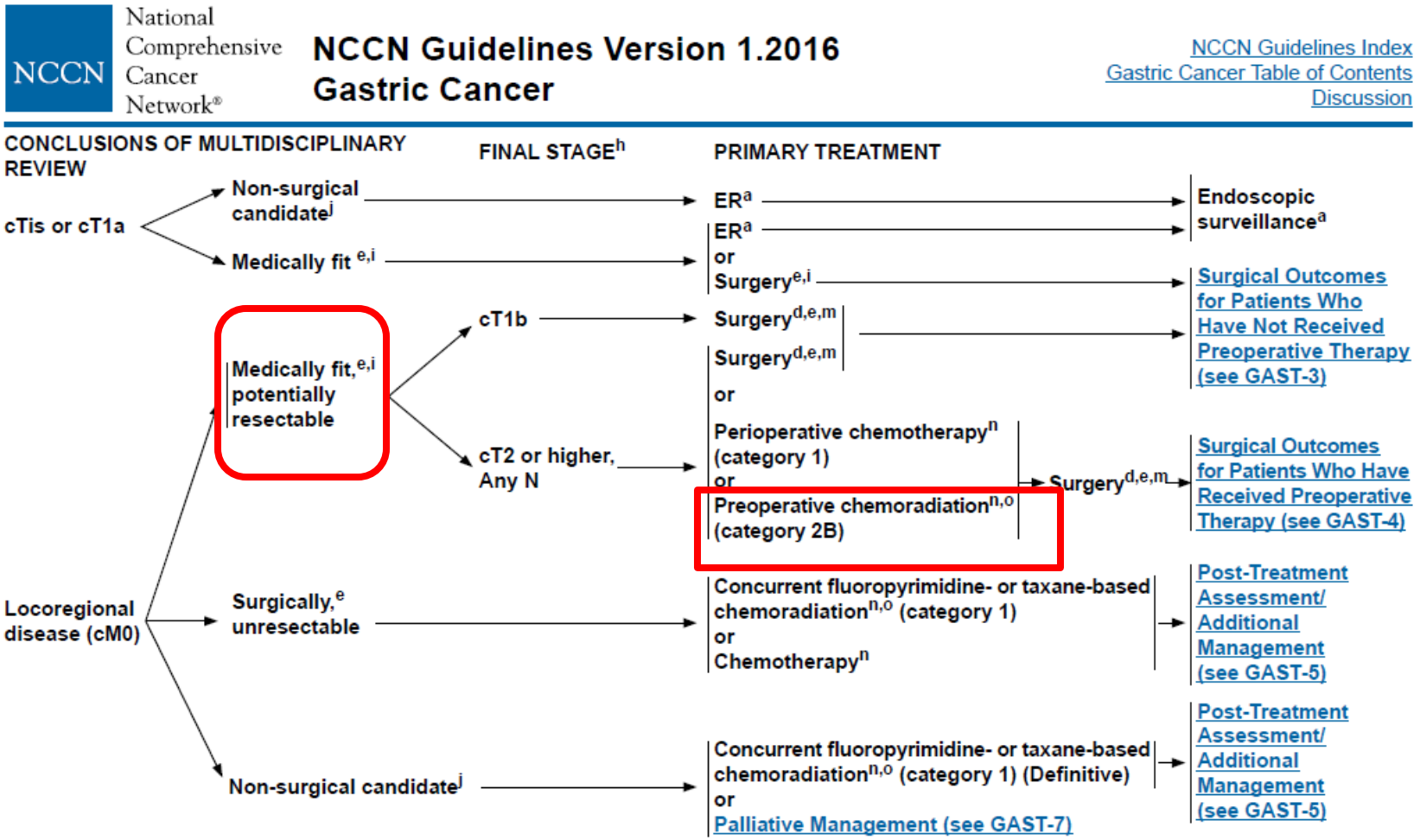



**Figure 3. Hazard Ratios for Death.**

This forest plot shows hazard ratios for death (oblongs) and 95% confidence intervals (I bars) for 366 patients with esophageal or esophagogastric-junction cancer, according to baseline characteristics. Univariate hazard ratios are shown, as well as hazard ratios adjusted for baseline covariates. Clinical lymph-node (N) stage was assessed by means of endoscopic ultrasonography, computed tomography, or $^{18}$F-fluorodeoxyglucose positron-emission tomography and classified according to the International Union against Cancer (UICC) tumor–node–metastasis (TNM) classification.[9]

# Mide Kanserinde Tedavi



# Mide Kanserinde Genetik Faktörler

## CRITERIA FOR TESTING FOR E-CADHERIN GENE MUTATION

UPDATED RECOMMENDATIONS FROM THE INTERNATIONAL GASTRIC CANCER LINKAGE CONSORTIUM (IGCLC)*

1. Two or more documented cases of gastric cancer in first degree relatives, with at least one documented case of diffuse gastric cancer diagnosed before the age of 50 years

2. Three or more cases of documented diffuse gastric cancer in first- or second-degree relatives, independent of age of onset

3. Diffuse gastric cancer before the age of 40 years without a family history

4. Families with diagnoses of both diffuse gastric cancer and lobular breast cancer, with one case before the age of 50 years

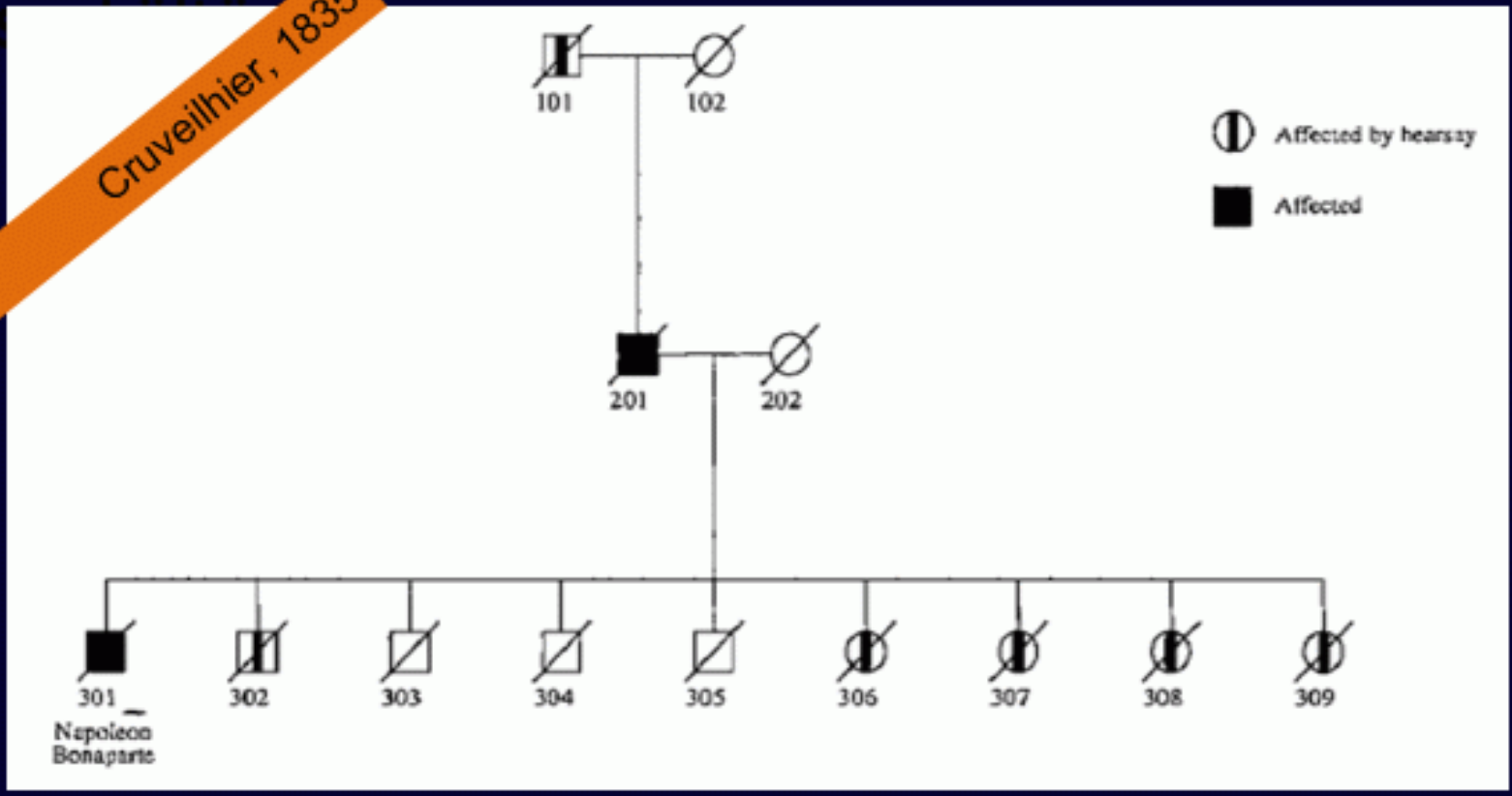
*In addition, in cases where expert pathologists detect carcinoma in situ adjacent to diffuse-type gastric cancer, genetic testing should be considered since this is rarely, if ever, seen in sporadic cases.

Fitzgerald R et al:J Med Genet 47: 436-444, 2010

# MİDE KANSERLERİ

## *Risk Faktörleri*

Cruveilhier, 1835



# Tarihçe

- Mısır papirüslerinde elde edilen bilgiler **MÖ 2500** yılında, Mısırda kanser hakkında zamanın doktorlarının bilgisi olduğu ve zaman koşularına göre mücadele ettiği bilinmektedir.

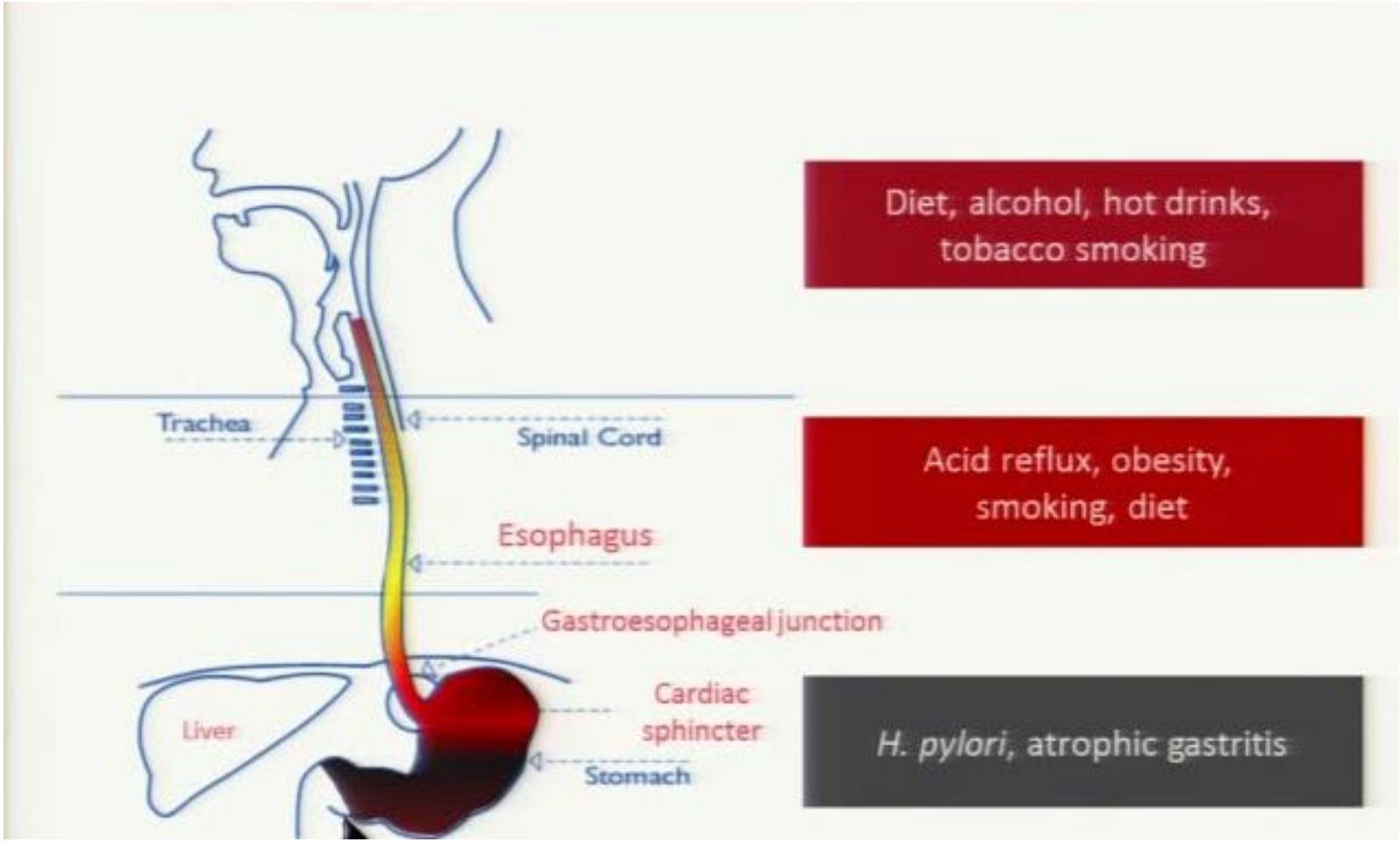
- Bu dönem hakkındaki bilgilere papirüsler ile ulaşıyoruz. 1862 yılında **Edwin Smith** adlı bir antikacının ve Mısır dil bilimci

- **Mısır Luksor** kentinde aldığı bir papirüste, meşhur hekimi olan **İmhotep** ve onun öğretilerinden bahsedilmektedir. Bu öğretilerde kanserden bahsedilmektedir.

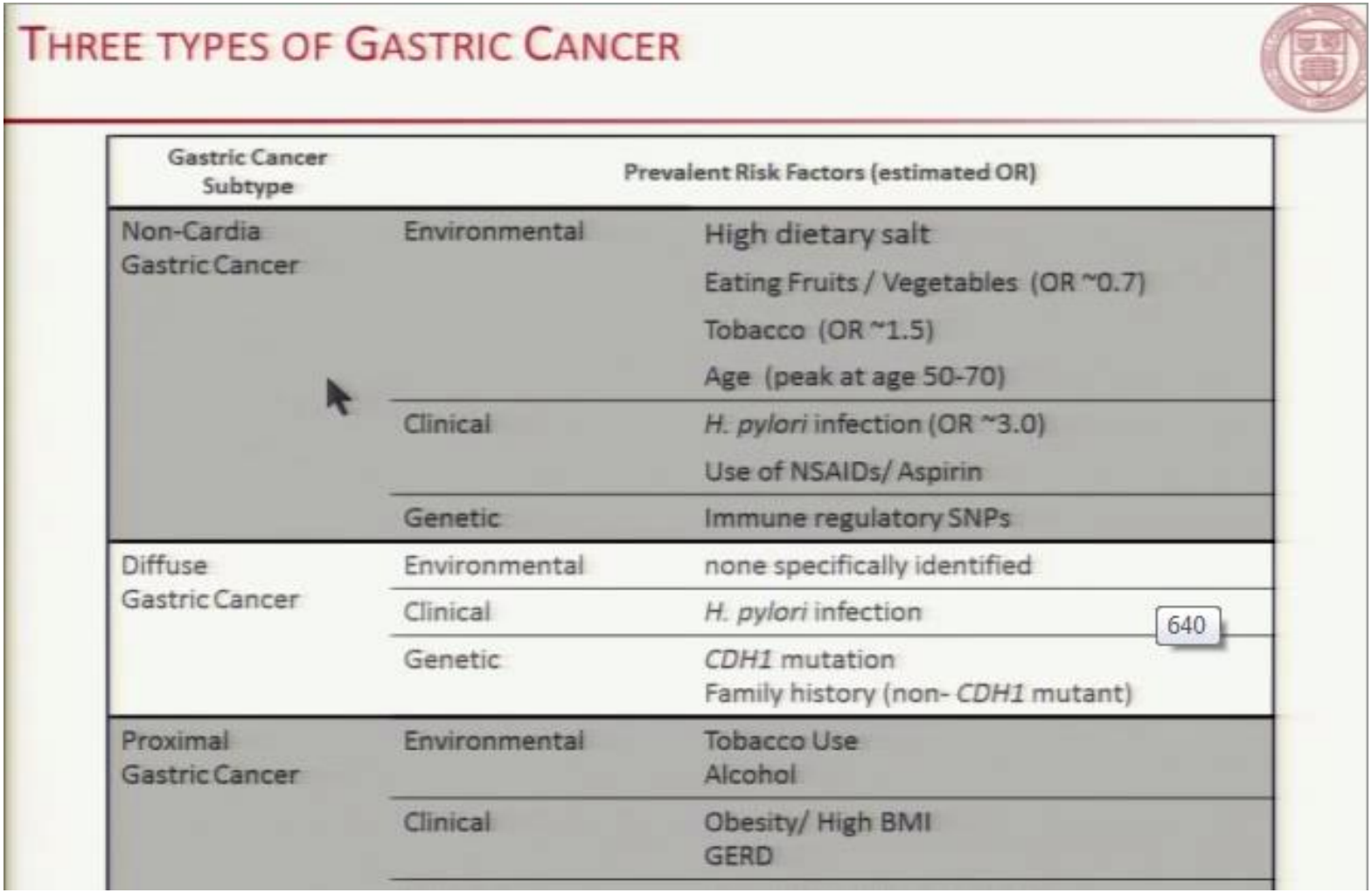
# MİDE KANSERLERİ

## *Risk Faktörleri*


# Mide Kanseri Genetik ve Risk Faktörleri



# Mide Kanseri Risk Faktörleri



## THREE TYPES OF GASTRIC CANCER

| Gastric Cancer Subtype | | Prevalent Risk Factors (estimated OR) |
|---|---|---|
| Non-Cardia Gastric Cancer | Environmental | High dietary salt<br>Eating Fruits / Vegetables (OR ~0.7)<br>Tobacco (OR ~1.5)<br>Age (peak at age 50-70) |
| | Clinical | *H. pylori* infection (OR ~3.0)<br>Use of NSAIDs/ Aspirin |
| | Genetic | Immune regulatory SNPs |
| Diffuse Gastric Cancer | Environmental | none specifically identified |
| | Clinical | *H. pylori* infection |
| | Genetic | *CDH1* mutation<br>Family history (non- *CDH1* mutant) |
| Proximal Gastric Cancer | Environmental | Tobacco Use<br>Alcohol |
| | Clinical | Obesity/ High BMI<br>GERD |

640

# Mide Kanseri Risk Faktörleri

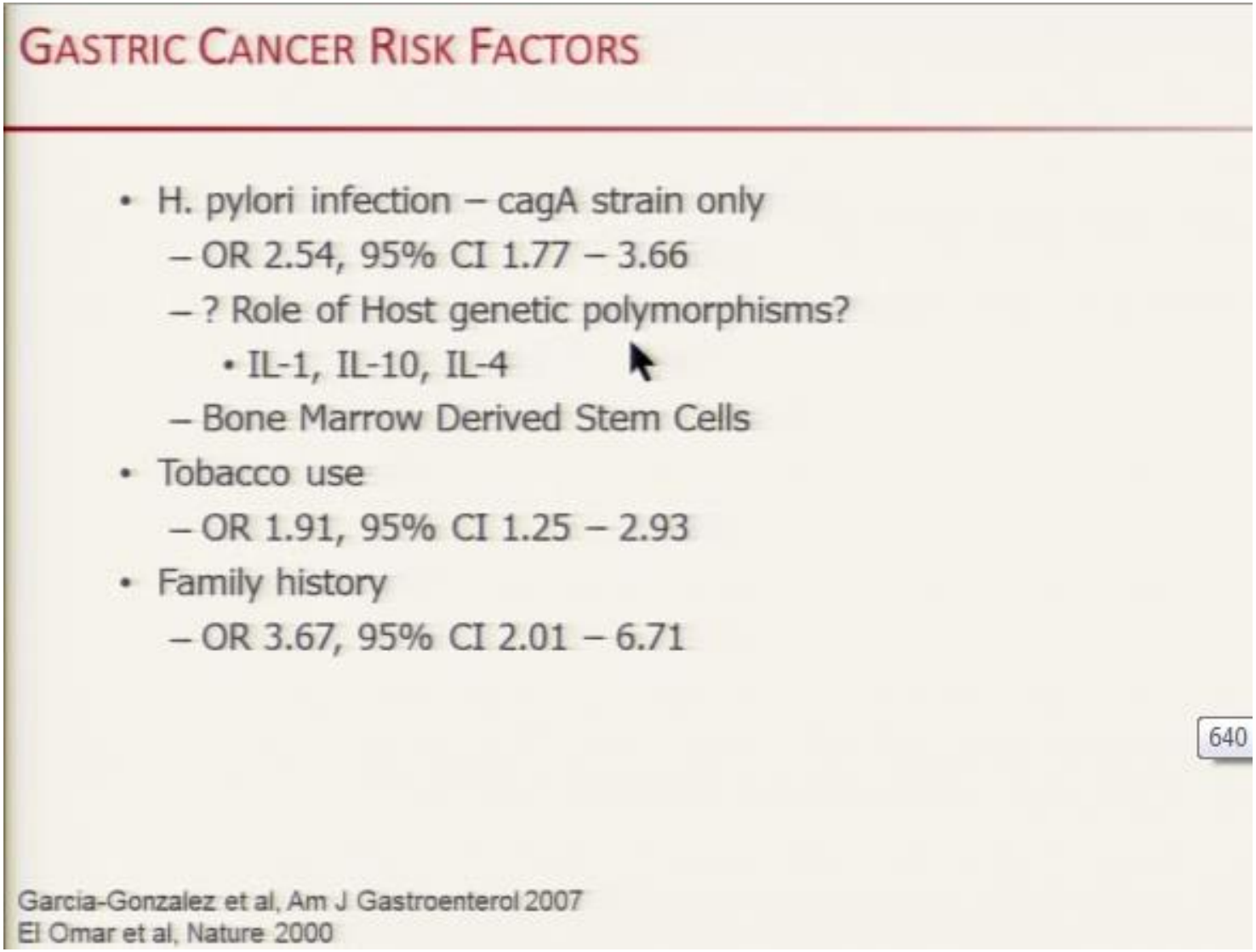
## *Risk Faktörleri*

Alt tipler-Etkenler

| Gastric Cancer Subtype | Type of Risk Factor | Risk Increased | Risk Decreased |
|---|---|---|---|
| Noncardia gastric cancer | Environmental | High dietary salt<br>Tobacco (OR: ~ 1.5)<br>Age (peak: 50-70 yrs) | Eating fruits/vegetables (OR: ~ 0.7) |
| | Clinical | *H pylori* infection (OR: ~ 3.0) | Use of NSAIDs/aspirin |
| | Genetic | Immune regulatory SNPs | |
| Diffuse gastric cancer | Environmental | None specifically identified | |
| | Clinical | ? | |
| | Genetic | *CDH1* mutation<br>Family history (no *CDH1* mutation) | |
| Proximal gastric cancer | Environmental | Tobacco<br>Alcohol | |
| | Clinical | Obesity/high BMI<br>GERD | |
| | Genetic | None specifically identified | |

**Shah** MA, et al. J NCCN 2010

# Mide Kanseri Risk Faktörleri

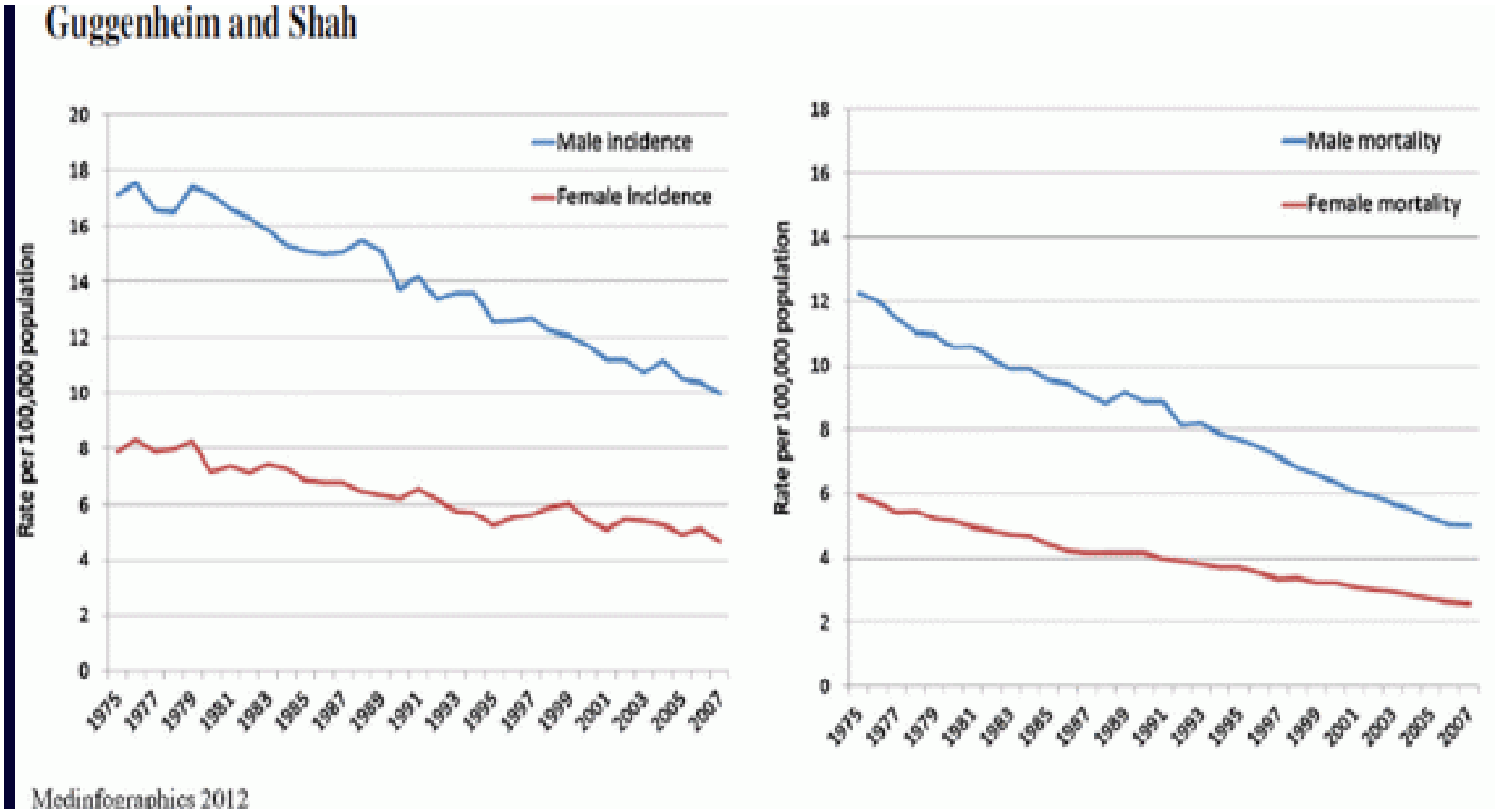


# Mide Kanseri Risk Faktörleri

## GC Genetic Predisposition Syndromes (10-15% of all GC)

- Hereditary Diffuse GC (~3-5%)
- Lynch Syndrome (~1-2%)
  - germline mutations in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2*
  - *Stomach cancers occur in ~11% of Lynch syndrome families*
- FAP (Familial Adenomatous Polyposis) (~1%)
  - *Germline mutation in APC – adenomatous polyposis coli*
  - *Fundic gland polyps*
- Li Fraumeni's syndrome (< 1%)
  - *p53 mutation*
- Peutz-Jeghers syndrome (<1%)
  - Autosomal dominant, hamartomatous polyps of GI tract and mucocutaneous melanin deposits
  - Germline mutations in *STK11 – serine threonine kinase 11.*

# Mide Kanseri İnsidans ve Mortalite



# Mide Kanserinde Klinik Evreleme

- BT
- PET-CT
- EUS
- Laparoskopi

# Mide Kanserinde Klinik Evreleme

**N DOĞRU EVRELEME**

- EUS; %65-92
- BT; %43-82

**T Doğru Evreleme**

- EUS; %50-95
- BT; 50%-70

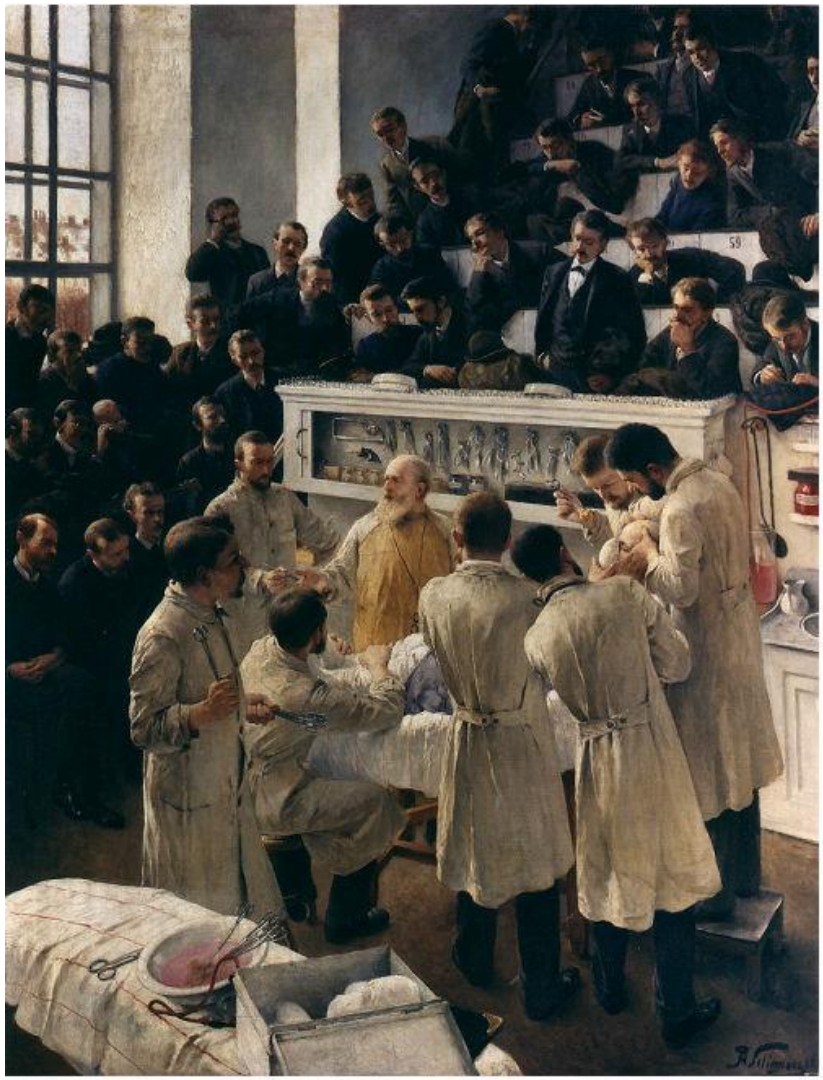
**UZAK METASTAZ SAPTAMA**

- PET-CT, BT Göre %10(≥T3, N+) daha fazla uzak metastaz tespiti ve tedavi değişimi. Diffüz ve müsinöz gastrik kanserlerde FDG tutulumu oranı düşük. Periton metastaz saptama oranı %50.

# Mide Kanseri Klinik Evreleme

**Laparoskopi + peritoneal sitoloji**

- Cerrahi planlanan cT3 , c N+ mide kanseri hastalarında metastazı dışlamak için yapılabilir
- Neoadjuvan Kemoterapi planlanan> cT1b hastalarında önerilir



- 19 yüzyılın ortalarında Lister antiseptiği cerrahi girişimlere sokarak, Cerrahide yeni çığır açıyor.
- Christian Albert Theodor Billroth
- 1881 yılında ilk radikal gastrektomi operasyonu yaptı.

# Mide Kanseri Klinik Evreleme

*Table 1*

**American Joint Committee on Cancer (AJCC)**
**TNM Staging Classification for Carcinoma of the Stomach**
**(7th ed., 2010)**

**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 - 2 regional lymph nodes |
| N2 | Metastasis in 3 - 6 regional lymph nodes |
| N3 | Metastasis in seven or more regional lymph nodes |
| N3a | Metastasis in 7 - 15 regional lymph nodes |
| N3b | Metastasis in 16 or more regional lymph nodes |

**Distant Metastasis (M)**

| | |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**Histologic Grade (G)**

| | |
|---|---|
| GX | Grade cannot be assessed |
| G1 | Well differentiated |
| G2 | Moderately differentiated |
| G3 | Poorly differentiated |
| G4 | Undifferentiated |

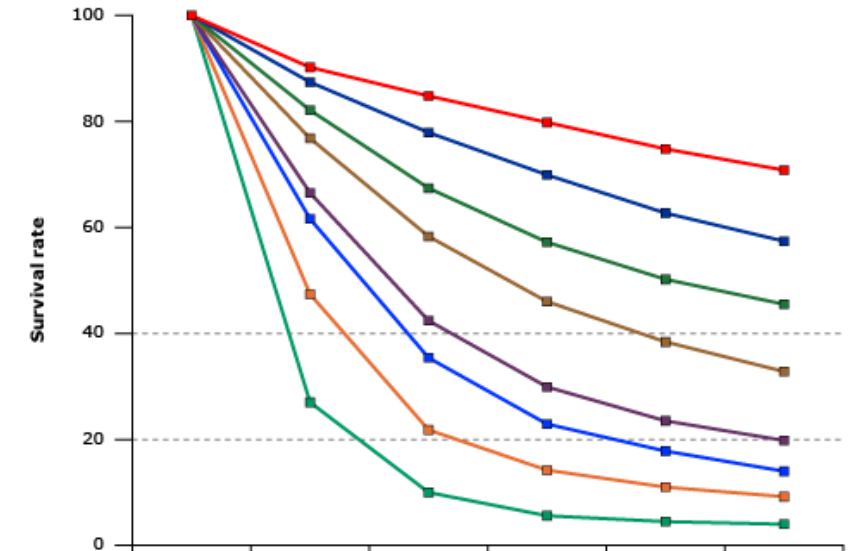
*Note: A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T3. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T4.

**The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

***Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

§A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

# Mide Kanseri Evreye Göre Sağkalım




| | At Dx | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| IA | 100.0 | 90.2 | 84.8 | 79.8 | 74.8 | 70.8 |
| IB | 100.0 | 87.4 | 77.9 | 69.9 | 62.7 | 57.4 |
| IIA | 100.0 | 82.1 | 67.4 | 57.2 | 50.2 | 45.5 |
| IIB | 100.0 | 76.8 | 58.3 | 46.0 | 38.4 | 32.8 |
| IIIA | 100.0 | 66.5 | 42.4 | 29.9 | 23.5 | 19.8 |
| IIIB | 100.0 | 61.6 | 35.4 | 22.9 | 17.8 | 14.0 |
| IIIC | 100.0 | 47.4 | 21.8 | 14.2 | 11.0 | 9.2 |
| IV | 100.0 | 27.0 | 10.0 | 5.6 | 4.5 | 4.0 |

Years from diagnosis

**Data from the SEER 1973-2005 Public Use File diagnosed in years 1991-2000. Stage IA includes 1194; Stage IB, 655; Stage IIA, 1161; Stage IIB, 1195; Stage IIIA; 1031; Stage IIIB, 1660; Stage IIIC, 1053; and stage IV, 6148.**

# Mide Kanseri Tedavi
# Kemoterapi Sonrası Cerrahi

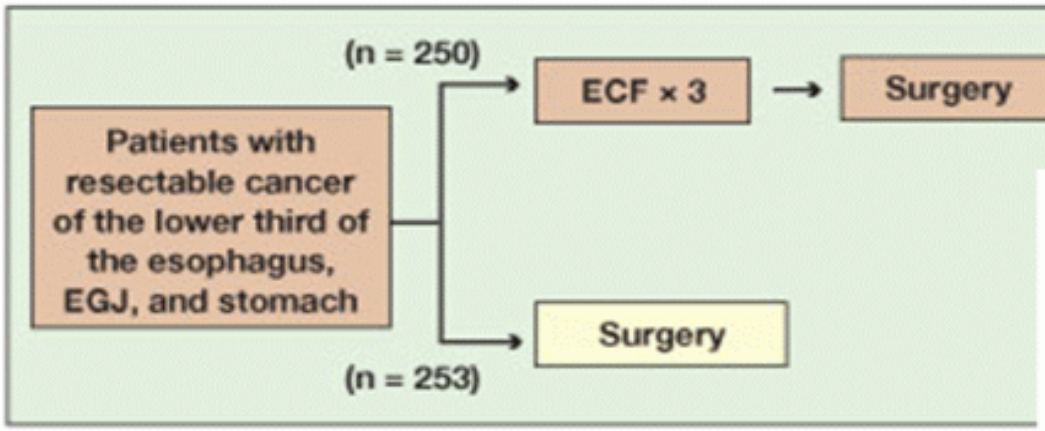
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

## Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

# Mide Kanseri Tedavi
# Kemoterapi Sonrası Cerrahide Kanseri Tedavi




**Eligible patients:**
- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease
- Stage II or greater

**Primary**
Overall survival

**Secondary**
Progression-free survival
Surgical resectability
Quality of Life

**Chemotherapy (ECF):**
Epirubicin 50mg/m2, IV day 1
Cisplatin 60mg/m2, IV day 1
5-FU 200mg/m2/day, continuous infusion, days 1-21
(cycles repeated every 3 weeks)

Recruitment: July 1994-April 2002

Perioperative chemotherapy in operable gastric and lower oesophageal cancer: a randomised controlled trial (the MAGIC trial, ISRCTN 93793971)

D Cunningham, W Allum, S Stenning and S Weeden
on behalf of the UK NCRI Upper GI Clinical Studies Group.
Conducted by the UK Medical Research Council CTU.

NEJM 2006, 355(1): 11-20

Cunningham et al NEJM 2006

# Mide Kanseri Tedavi
# Kemoterapi Sonrası Cerrahi

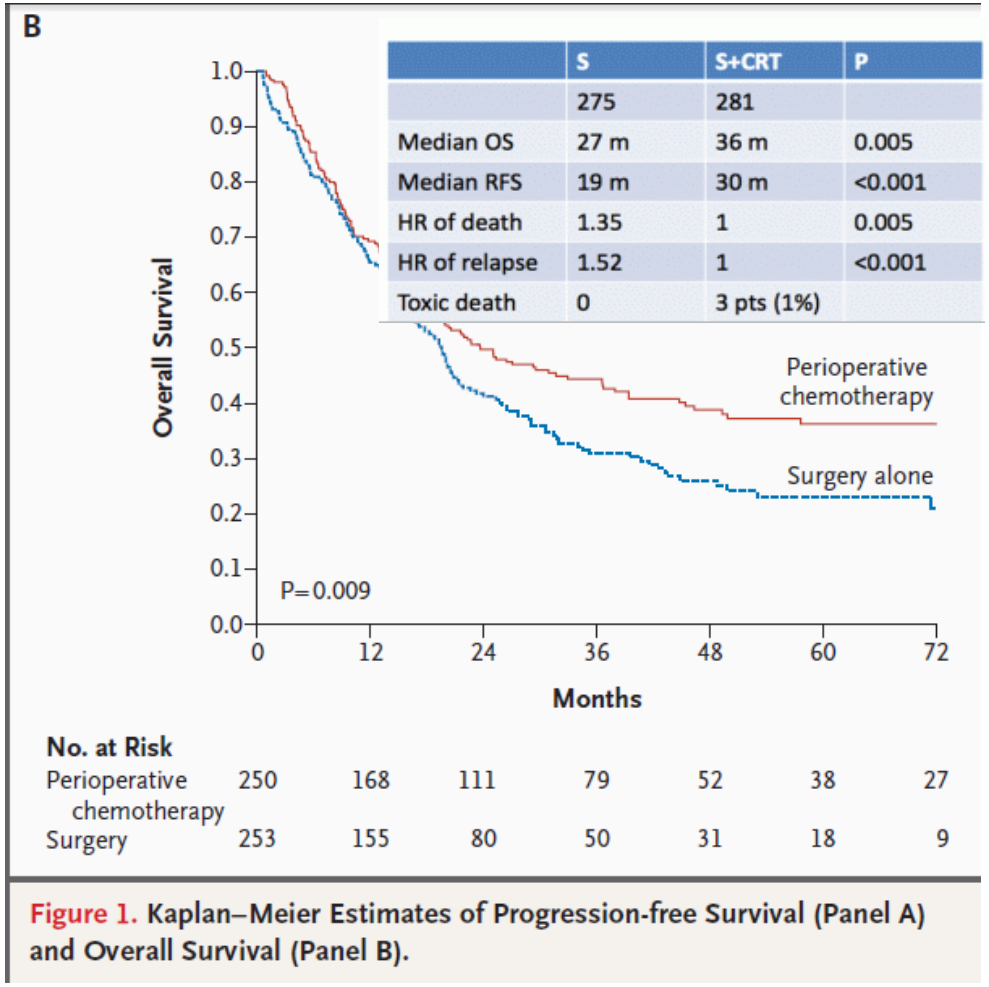



Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

# Mide Kanseri Tedavi
# Kemoterapi Sonrası Cerrahi

| Variable | Perioperative Chemotherapy (no. of deaths/total no.) | Surgery Alone (no. of deaths/total no.) |
|---|---|---|
| Age | | |
| <60 yr | 61/108 | 75/104 |
| 60–69 yr | 56/91 | 59/95 |
| ≥70 yr | 32/51 | 36/54 |
| Total | 149/250 | 170/253 |
| Sex | | |
| Male | 126/205 | 127/191 |
| Female | 23/45 | 43/62 |
| Total | 149/250 | 170/253 |
| WHO performance status | | |
| 0 | 93/169 | 112/173 |
| 1 | 56/81 | 58/80 |
| Total | 149/250 | 170/253 |
| Site of primary tumor | | |
| Lower esophagus | 23/37 | 25/36 |
| Esophagogastric junction | 13/28 | 23/30 |
| Stomach | 113/185 | 122/187 |
| Total | 149/250 | 170/253 |

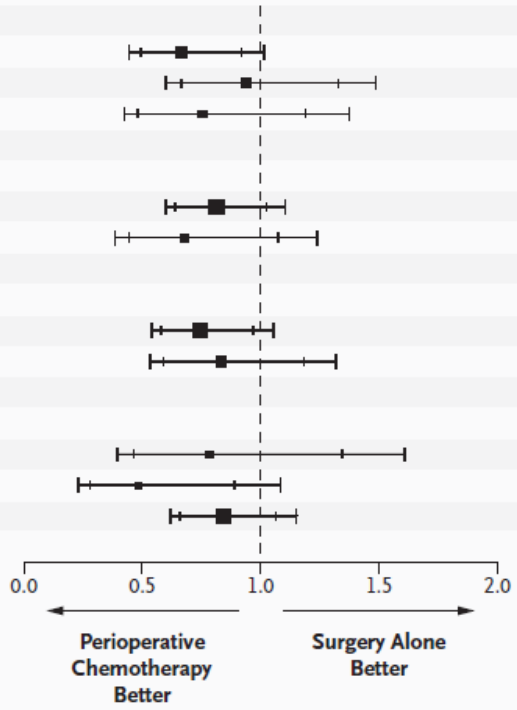
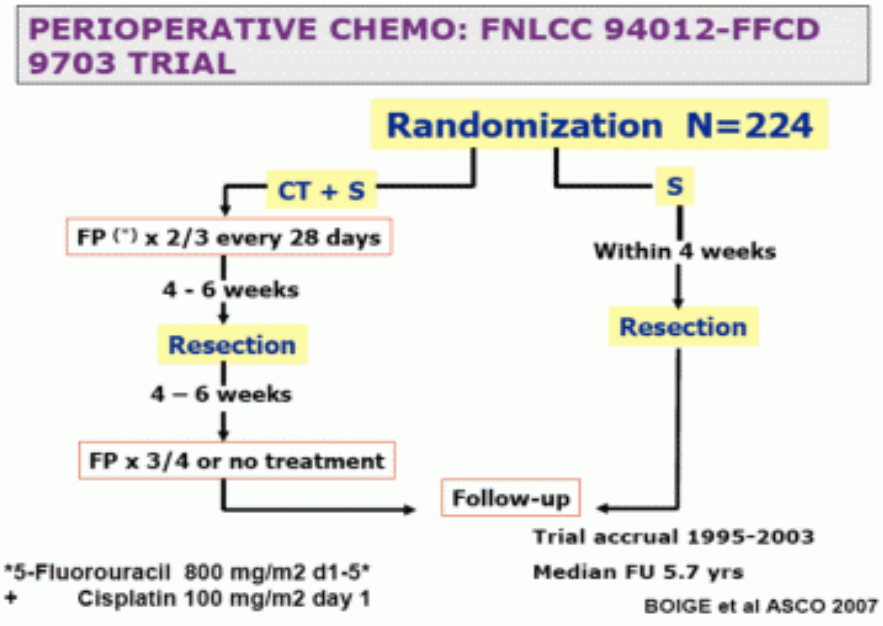



**Figure 2. Tests for Heterogeneity of Treatment Effect According to the Baseline Characteristics of the Patients.**
The hazard ratios show 95 percent (inner tick marks) and 99 percent (outer tick marks) confidence intervals.

# Mide Kanseri Tedavi
# Kemoterapi Sonrası Cerrahi

## Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: A FNCLCC and FFCD Multicenter Phase III Trial

Marc Ychou, Valérie Boige, Jean-Pierre Pignon, Thierry Conroy, Olivier Bouché, Gilles Lebreton, Muriel Ducourtieux, Laurent Bedenne, Jean-Michel Fabre, Bernard Saint-Aubert, Jean Genève, Philippe Lasser and Philippe Rougier



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# Kemoterapi Sonrası Cerrahide Kanseri Tedavi

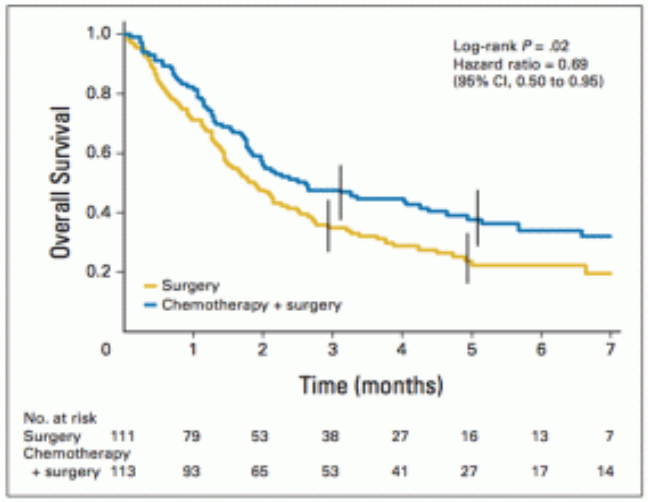



**Fig 2.** Kaplan-Meier curve showing overall survival from date of random assignment.

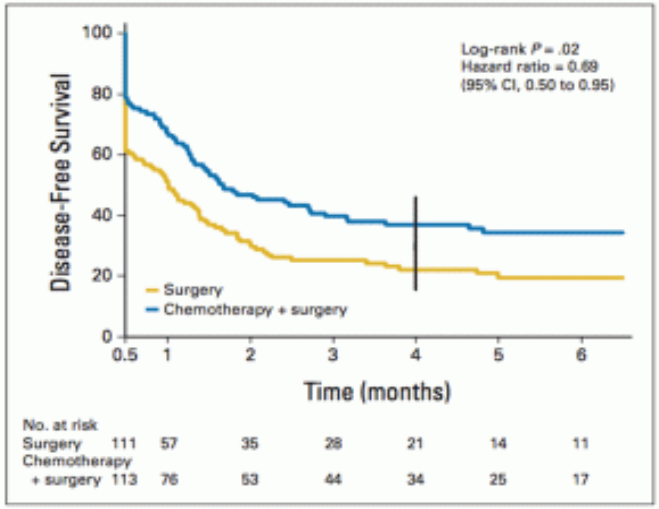


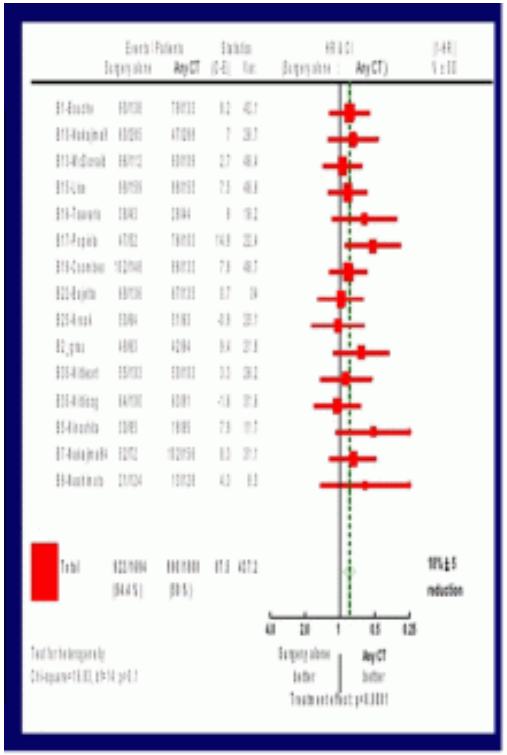

**Fig 3.** Kaplan-Meier curve showing disease-free survival from landmark time of 6 months after the date of random assignment.

# Mide Kanseri Tedavi
# Kemoterapi Sonrası Cerrahi

## SUMMARY OF TRIALS OF PERIOPERATIVE CHEMOTHERAPY FOR LOCALIZED GASTRIC CANCER

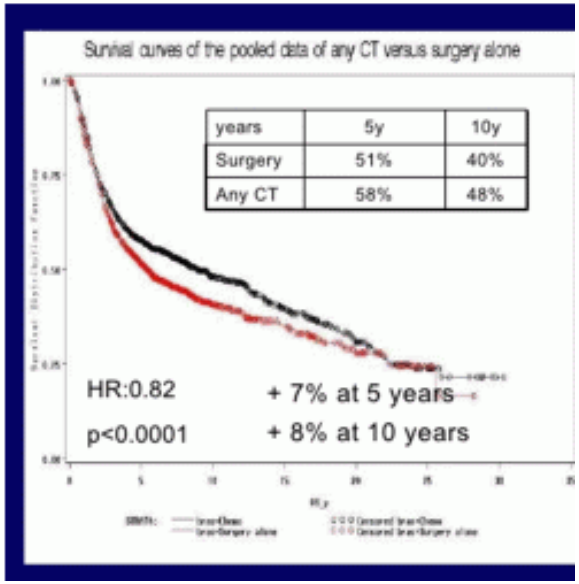
| Trial | CT | Nr. Pts Control | Nr. Pts CT | 5-year Survival Control | 5-year Survival CT | HR (CI at 95%) |
|---|---|---|---|---|---|---|
| Cunningham NEJM 2006 | ECF | 253 No CT | 250 | 23% | 36 % | 0.75 0.60-0.93 p=.009 |
| Boige ASCO 2007 | CDDP 5-FU | 111 No CT | 113 | 24% | 38% | 0.69 0.50-0.95 p=.021 |

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan



Metaanaliz
3514 hasta
Bireysel data
HR: 0.82,
p <0.001

**Adjuvan kemoterapi**



# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KRT

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

- R0 resection of adenocarcinoma of the stomach or gastroesophageal junction (GEJ), presence of complete penetration of the tumor through the muscularis propria and/or involved regional nodes (including 1988 American Joint Committee on Cancer [AJCC] **stages IB to IV with M0**

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KRT

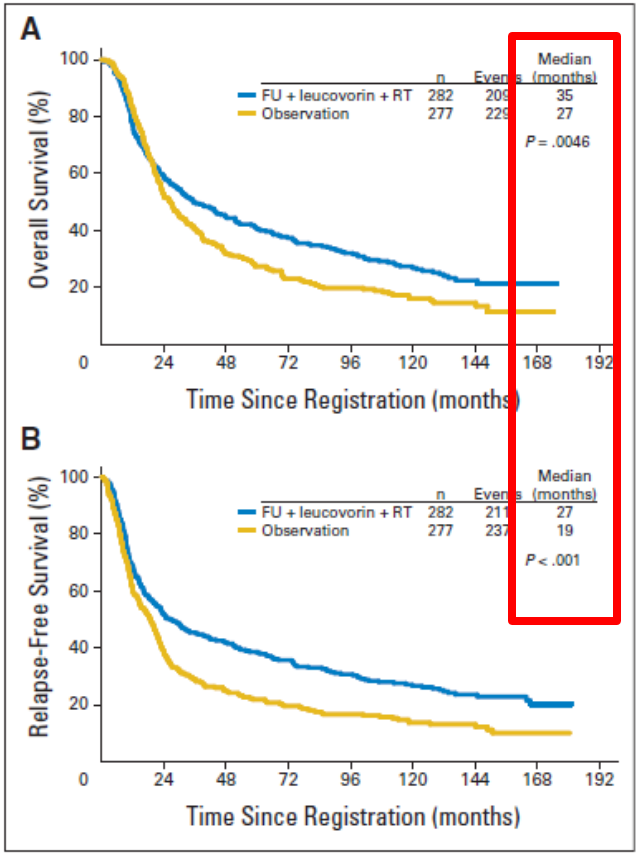
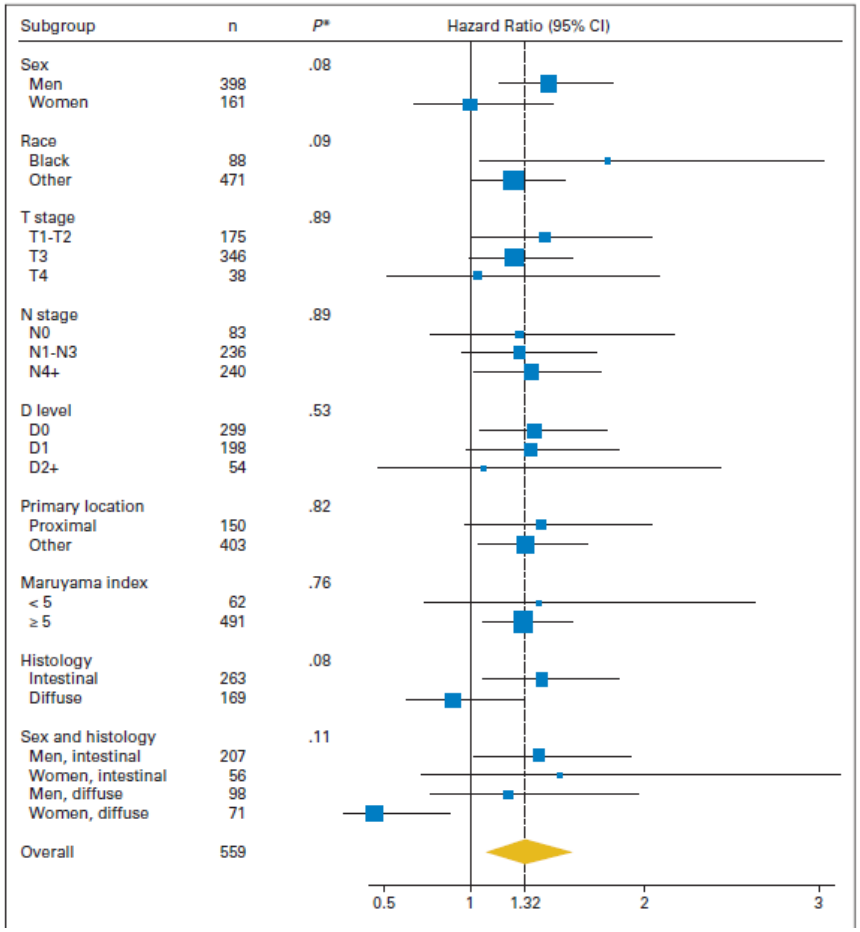



**Fig 2.** (A) Overall survival by arm; (B) relapse-free survival by arm. FU, fluorouracil; RT, radiotherapy.



# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT? KRT?

VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

## Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses

*Se Hoon Park, Tae Sung Sohn, Jeeyun Lee, Do Hoon Lim, Min Eui Hong, Kyoung-Mee Kim, Insuk Sohn, Sin Ho Jung, Min Gew Choi, Jun Ho Lee, Jae Moon Bae, Sung Kim, Seung Tae Kim, Joon Oh Park, Young Suk Park, Ho Yeong Lim, and Won Ki Kang*

See accompanying editorial on page 3082 and article on page 3085

All authors: Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea.

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Both S.H.P. and T.S.S. contributed equally to this work.

Presented in part at the 50th Annual Meeting of the American Society of Clinical Oncology, May 30-June 3, 2014, Chicago, IL.

Clinical trial information: NCT00323830

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Won Ki Kang, MD, Division of Hematology-Oncology, Department of Medicine, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea; e-mail: wkkang@skku.edu.



0732-183X/15/3328w-3130w/$20.00

A B S T R A C T

**Purpose**
The Adjuvant Chemoradiotherapy in Stomach Tumors (ARTIST) trial tested whether the addition of radiotherapy to adjuvant chemotherapy improved disease-free survival (DFS) in patients with D2-resected gastric cancer (GC).

**Patients and Methods**
Between November 2004 and April 2008, 458 patients with GC who received gastrectomy with D2 lymph node dissection were randomly assigned to either six cycles of adjuvant chemotherapy with capecitabine and cisplatin (XP) or to two cycles of XP followed by chemoradiotherapy and then two additional cycles of XP (XPRT). This final update contains the first publication of overall survival (OS), together with updated DFS and subset analyses.

**Results**
With 7 years of follow-up, DFS remained similar between treatment arms (hazard ratio [HR], 0.740; 95% CI, 0.520 to 1.050; $P = .0922$). OS also was similar (HR, 1.130; 95% CI, 0.775 to 1.647; $P = .5272$). The effect of the addition of radiotherapy on DFS and OS differed by Lauren classification (interaction $P = .04$ for DFS; interaction $P = .03$ for OS) and lymph node ratio (interaction $P < .01$ for DFS; interaction $P < .01$ for OS). Subgroup analyses also showed that chemoradiotherapy significantly improved DFS in patients with node-positive disease and with intestinal-type GC. There was a similar trend for DFS and OS by stage of disease.

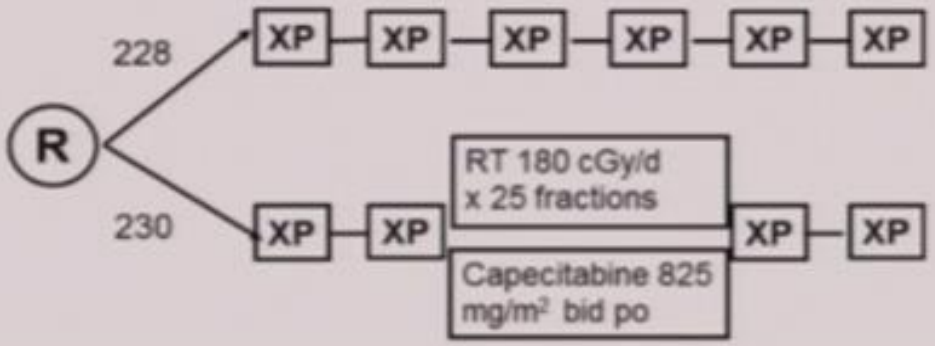
**Conclusion**
In D2-resected GC, both adjuvant chemotherapy and chemoradiotherapy are tolerated and equally beneficial in preventing relapse. Because results suggest a significant DFS effect of chemoradiotherapy in subsets of patients, the ARTIST 2 trial evaluating adjuvant chemotherapy and chemoradiotherapy in patients with node-positive, D2-resected GC is under way.

*J Clin Oncol 33:3130-3136. © 2015 by American Society of Clinical Oncology*

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT? KRT?

## ARTIST
### : ChemoRT vs Chemo after D2 surgery

- N = 458 patients with curatively resected (D2) stomach cancer (postop stage IB, II, III, IVM0)
- XP regimen
  - Capecitabine 1,000 mg/m2 bid po D1-14
  - Cisplatin 60 mg/m2 iv D1, every 3 weeks



# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT? KRT?

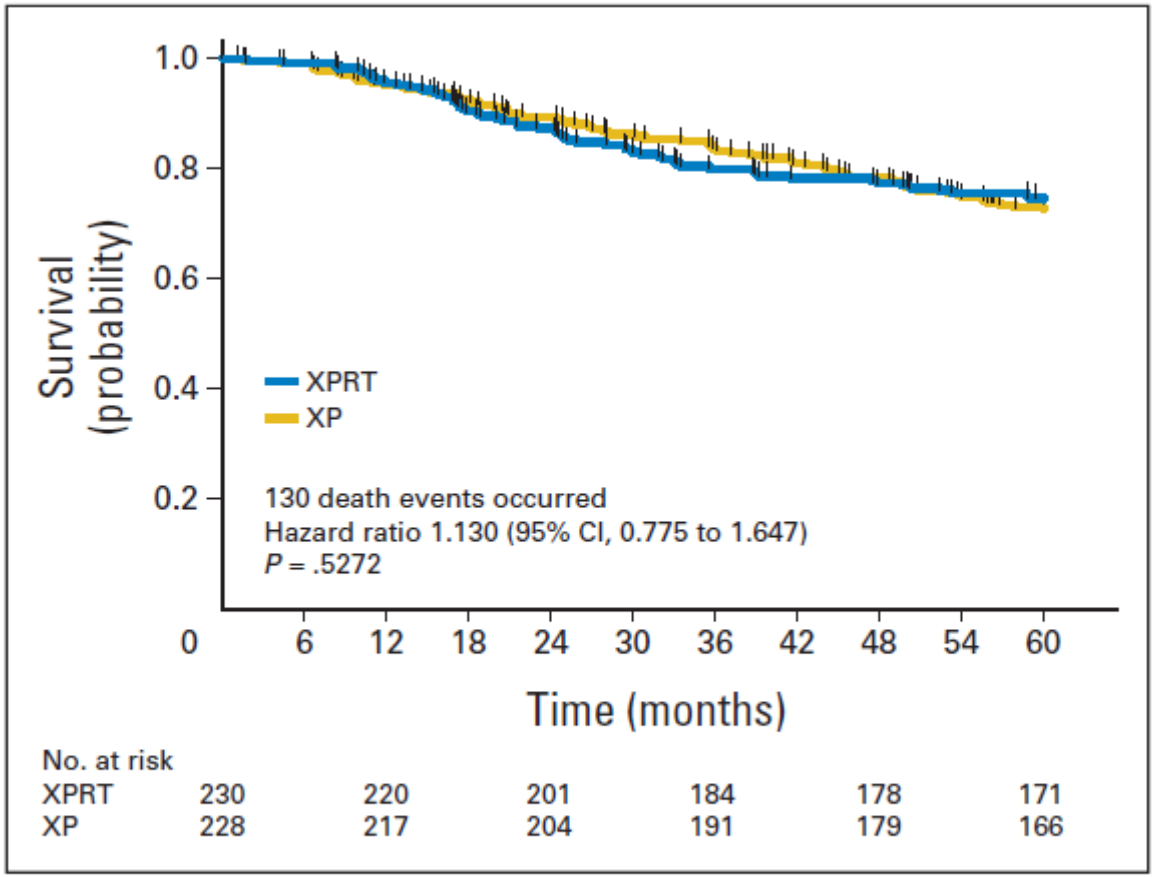



**Fig 3.** Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT? KRT?

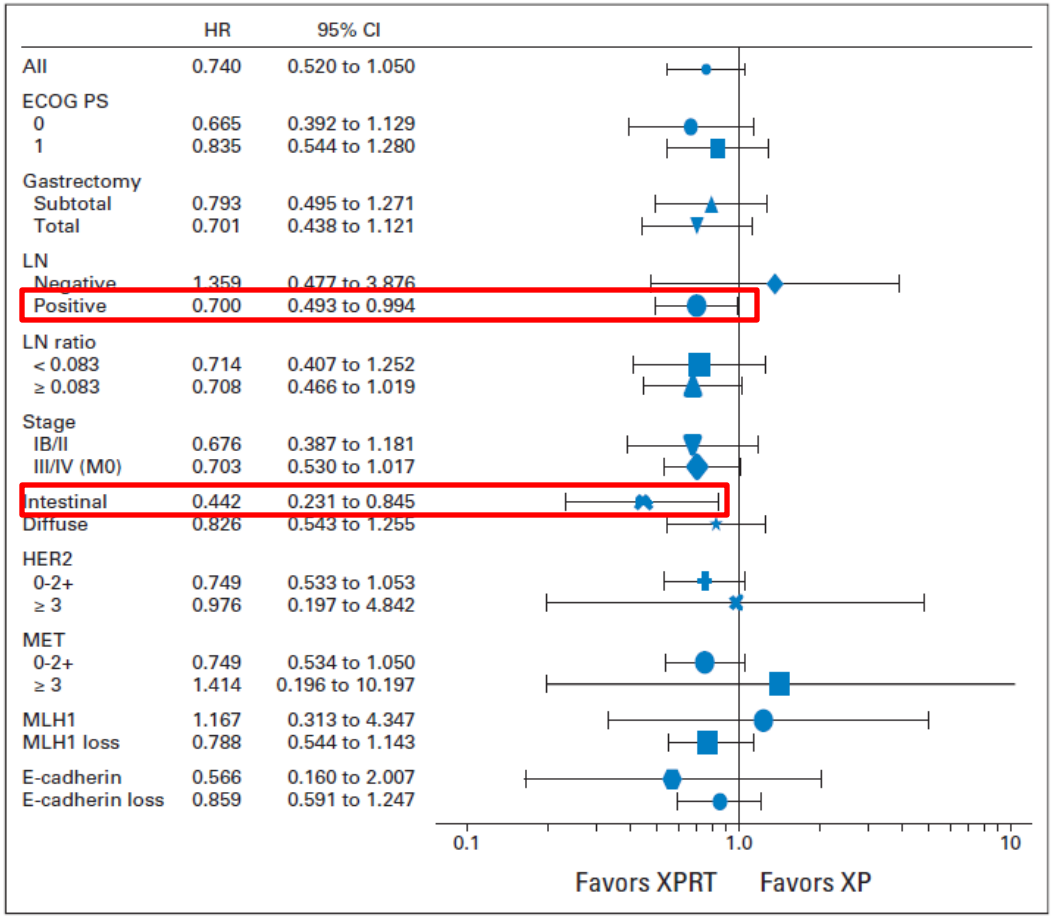



**Fig 4.** Forest plot of hazard ratios (HRs) and 95% CIs for disease-free survival. ECOG PS, Eastern Cooperative Oncology group performance status; HER2, human epidermal growth factor receptor 2; LN, lymph node; XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT

## Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial

Yung-Jue Bang*, Young-Woo Kim, Han-Kwang Yang, Hyun Cheol Chung, Young-Kyu Park, Kyung Hee Lee, Keun-Wook Lee, Yong Ho Kim, Sang-Ik Noh, Jae Yong Cho, Young Jae Mok, Yeul Hong Kim, Jiafu Ji, Ta-Sen Yeh, Peter Button, Florin Sirzén, Sung Hoon Noh*, for the CLASSIC trial investigators†

### Summary

**Background** D2 gastrectomy is recommended in US and European guidelines, and is preferred in east Asia, for patients with resectable gastric cancer. Adjuvant chemotherapy improves patient outcomes after surgery, but the benefits after a D2 resection have not been extensively investigated in large-scale trials. We investigated the effect on disease-free survival of adjuvant chemotherapy with capecitabine plus oxaliplatin after D2 gastrectomy compared with D2 gastrectomy only in patients with stage II–IIIB gastric cancer.

**Methods** The capecitabine and oxaliplatin adjuvant study in stomach cancer (CLASSIC) study was an open-label, parallel-group, phase 3, randomised controlled trial undertaken in 37 centres in South Korea, China, and Taiwan. Patients with stage II–IIIB gastric cancer who had had curative D2 gastrectomy were randomly assigned to receive adjuvant chemotherapy of eight 3-week cycles of oral capecitabine (1000 mg/m² twice daily on days 1 to 14 of each cycle) plus intravenous oxaliplatin (130 mg/m² on day 1 of each cycle) for 6 months or surgery only. Block randomisation was done by a central interactive computerised system, stratified by country and disease stage. Patients, and investigators giving interventions, assessing outcomes, and analysing data were not masked. The primary endpoint was 3 year disease-free survival, analysed by intention to treat. This study reports a prespecified interim efficacy analysis, after which the trial was stopped after a recommendation by the data monitoring committee. The trial is registered at ClinicalTrials.gov (NCT00411229).

**Findings** 1035 patients were randomised (520 to receive chemotherapy and surgery, 515 surgery only). Median follow-up was 34·2 months (25·4–41·7) in the chemotherapy and surgery group and 34·3 months (25·6–41·9) in the surgery only group. 3 year disease-free survival was 74% (95% CI 69–79) in the chemotherapy and surgery group and 59% (53–64) in the surgery only group (hazard ratio 0·56, 95% CI 0·44–0·72; p<0·0001). Grade 3 or 4 adverse events were reported in 279 of 496 patients (56%) in the chemotherapy and surgery group and in 30 of 478 patients (6%) in the surgery only group. The most common adverse events in the intervention group were nausea (n=326), neutropenia (n=300), and decreased appetite (n=294).

**Interpretation** Adjuvant capecitabine plus oxaliplatin treatment after curative D2 gastrectomy should be considered as a treatment option for patients with operable gastric cancer.

**Funding** F Hoffmann-La Roche and Sanofi-Aventis.

*Lancet* 2012; 379: 315–21

Published Online January 7, 2012 DOI:10.1016/S0140-6736(11)61873-4

See Comment page 291

* Both authors contributed equally

† CLASSIC trial investigators listed at the end of Article

Department of Internal Medicine (Prof Y-J Bang MD), and Department of Surgery (Prof H-K Yang M D), Seoul National University College of Medicine, Seoul, South Korea; Gastric Cancer Branch, Research Institute and Hospital, National Cancer Center, Goyang-si, Gyeonggi-do, South Korea (Y-W Kim M D); Department of Surgery (Prof S H Noh M.D), and Department of Medical Oncology, Yonsei Cancer Center, Cancer Metastasis Research Centre (Prof H C Chung MD, Prof J Y Cho M.D), Yonsei University College of Medicine, Seoul, South Korea; Department of Surgery, Chonnam National University Hwasun Hospital, Jeonnam, South Korea (Prof Y-K Park M.D);

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT

| | Surgery only (n=515) | Capecitabine and oxaliplatin (n=520) |
|---|---|---|
| Age (years) | 55·8 (11·6) | 56·1 (11·1) |
| Men | 358 (70%) | 373 (72%) |
| Karnofsky performance status (%) | 90% (90–100) | 90% (90–100) |
| Body surface area ($m^2$) | 1·62 (0·15) | 1·62 (0·15) |
| Time since surgery (months) | 1·14 (0·17) | 1·14 (0·17) |
| AJCC/UICC[7] stage | | |
| IB | 0 (0%) | 1 (<1%) |
| II | 261 (51%) | 253 (49%) |
| IIIA | 184 (36%) | 193 (37%) |
| IIIB | 69 (13%) | 73 (14%) |
| IV | 1 (<1%) | 0 (0%) |
| Tumour stage | | |
| T1 | 3 (1%) | 8 (2%) |
| T2 | 282 (55%) | 282 (54%) |
| T3 | 229 (44%) | 227 (44%) |
| T4 | 1 (<1%) | 3 (1%) |
| Tumour location* | | |
| Antrum | 234 (45%) | 237 (46%) |
| Body | 172 (33%) | 166 (32%) |
| Body and antrum | 29 (6%) | 31 (6%) |
| Fundus | 40 (8%) | 46 (9%) |
| Fundus and body | 13 (3%) | 10 (2%) |
| Gastro-oesophageal junction | 9 (2%) | 15 (3%) |
| Whole gastric | 6 (1%) | 6 (1%) |
| Other† | 12 (2%) | 9 (2%) |
| Lymph nodes examined | 43·6 (16·7) | 45·0 (17·4) |
| Nodal status | | |
| N0 | 56 (11%) | 47 (9%) |
| N1 | 308 (60%) | 313 (60%) |
| N2 | 151 (29%) | 160 (31%) |

Data are mean (SD), n (%), or median (IQR). Intention-to-treat population; all patients were Asian. AJCC/UICC=American Joint Cancer Committee/Union Internationale Contre le Cancer. *Antrum is the lower third, body the middle third, and fundus the upper third. †Includes multiple localisations.

***Table 1:*** **Baseline patient characteristics**

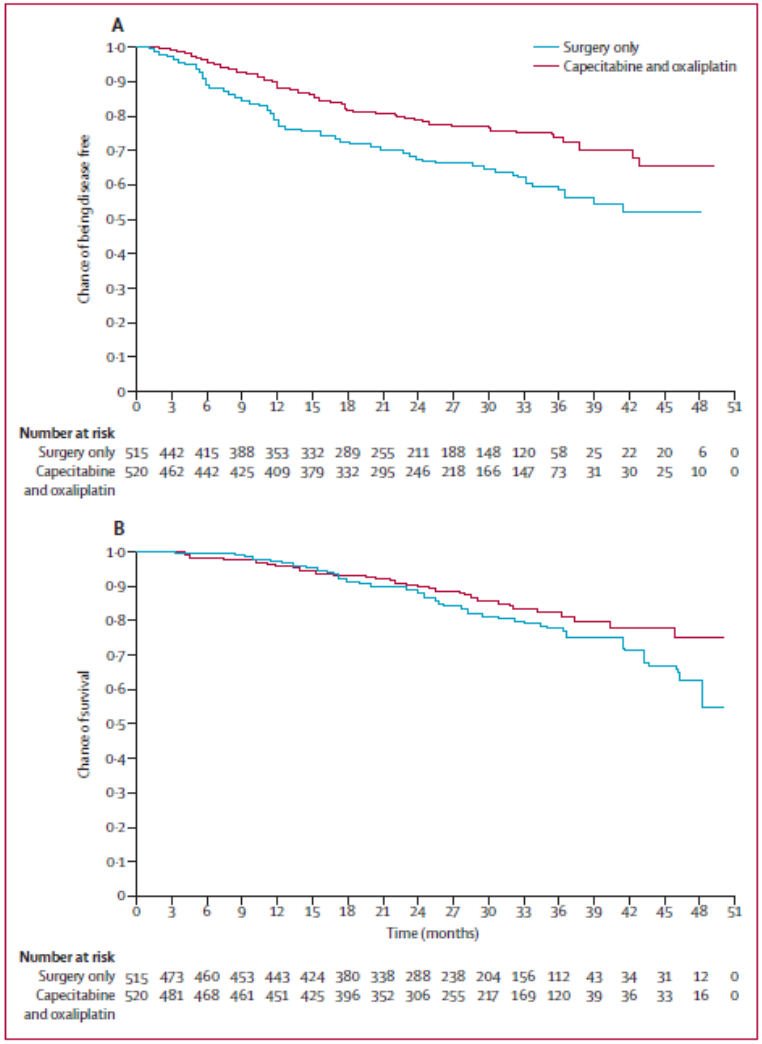



***Figure 2:*** **3 year disease-free survival (A) and preliminary overall survival (B) in the intention-to-treat population**

# Mide Kanseri Tedavi
# Cerrahi Sonrası Adjuvan KT

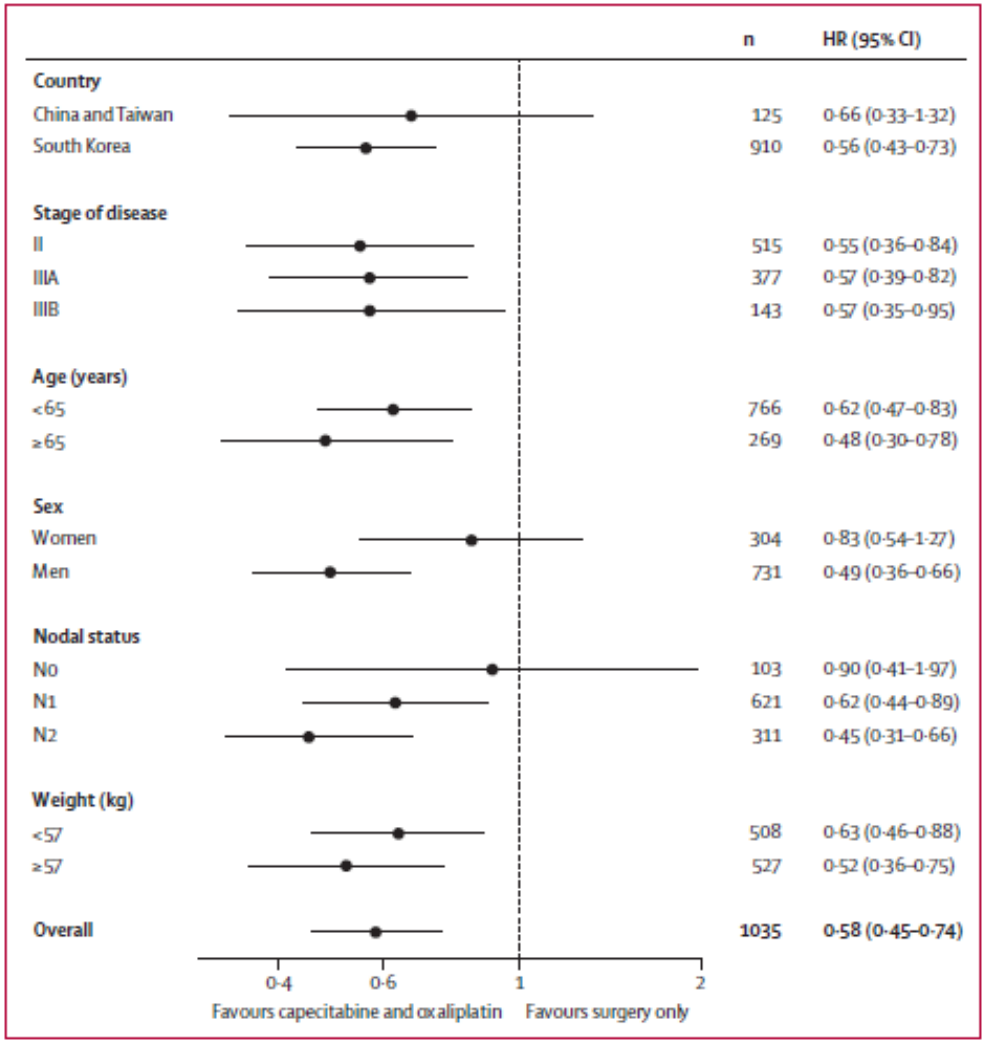



*Figure 3:* 3 year disease-free survival by stratification and prognostic factors in the intention-to-treat population

# Mide Kanseri Tedavi

| | MAGIC[1] (N=503) | | INT116[2] (N=556) | |
|---|---|---|---|---|
| | Peri-op chemo + surgery N=250 | Surgery only N=253 | Post-op chemoRT + surgery N=282 | Surgery only N=277 |
| 2 year survival | 50% | 41% | 58%* | 50%* |
| 5 year survival | 36% | 23% | 40%* | 26%* |
| Median survival | 24 months | 20 months | 35 months | 27 months |
| Hazard ratio (95% CI) | 0.75 (0.60-0.93) P=0.009 | | 0.76 (0.62-0.93) P=0.006 | |

# Mide Kanseri Tedavi

## Comparison of Survival

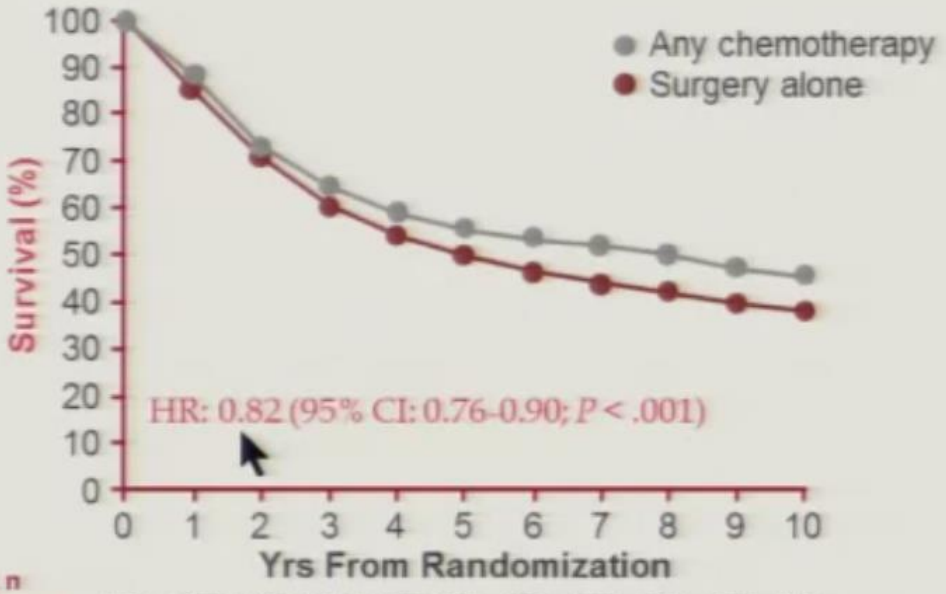
| | Trial | N | RFS Tx vs No | OS Tx vs No |
|---|---|---|---|---|
| West | INT-0116 | 556 | 3y RFS: 48% vs 31% | 3y OS: 50% vs 41% |
| | MAGIG | 503 | 5y PFS: 32% vs 15% | 5y OS: 36% vs 23% |
| East | ACTS-GC | 1059 | 3y RFS: 72% vs 60% | 3y OS: 81% vs 70% |
| | CLASSIC | 1035 | 3y DFS: 74% vs 59% | 3y OS: 83% vs 78% |

# Mide Kanseri Tedavi

## META-ANALYSIS

### SURGERY VS SURGERY + ANY ADJ CT IN RESECTABLE GC

- Survival benefit for addition of chemotherapy




| Pts at Risk, n | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Any chemotherapy | 1924 | 1688 | 1385 | 1217 | 1080 | 929 | 709 | 526 | 390 | 297 | 243 |
| Surgery along | 1857 | 1568 | 1300 | 1092 | 952 | 782 | 583 | 407 | 267 | 172 | 138 |

GASTRIC Group, et al. JAMA. 2010;303:1729-1737.

# Mide Kanseri Tedavi

## Chemotherapy in Resectable Gastric Cancer

- However, resounding lack of progress in improving patient outcomes with any specific CT/CRT regimen vs any other chemotherapy regimen

| Study | Regimens | Primary Endpoint | Primary Endpoint Results | *P* Value |
|---|---|---|---|---|
| CALGB 80101[1] | Postop 5-FU/LV CRT vs ECF CRT | OS | 37 vs 38 mos | .80 |
| ARTIST[2] | Postop CT vs CRT (capecitabine/cisplatin) | 3-yr DFS | 74% vs 78% | .086 |


1. Fuchs CS, et al. ASCO 2011. Abstract 4003.
2. Lee J, et al. J Clin Oncol. 2012;30:268-273.

# Metastatik Mide Kanseri

MSKCC Experience from June 1985-June 2000
1172 R0 resections → 367 recurrences (568 sites)

| Pattern of Failure | # pts (%) |
|---|---|
| Locoregional (LN, anastomosis, gastric bed) | 199 (54%) |
| Peritoneal Seeding | 109 (30%) |
| Distant Metastases | 188 (51%) |
| Liver | 90 (25%) |
| Lung | 39 (11%) |
| Bone | 39 (11%) |
| Lymph Nodes | 35 (10%) |
| Brain | 15 (5%) |

D' Angelica et al. Ann Surg, 2004

# Metastatik Mide Kanseri

## PALLIATIVE CT: OS

| Reference | Trial | Chemo, n | BSC, n | HR for OS | 95% CI |
|---|---|---|---|---|---|
| Murad Cancer 1993 | FAMTX | 30 | 10 | 0.33 | 0.17-0.64 |
| Pyrhönen BJC 1995 | FEMTX | 21 | 20 | 0.25 | 0.25-0.47 |
| Scheithauer Ann Hematol 1996 | ELF | 52 | 51 | 0.49 | 0.33-0.74 |
| **Total** | | **103** | **81** | **0.37** | **0.24-0.55** |

Effective: 11 vs 4.3 mos; $P < .00001$

# Metastatik Mide Kanseri

## Single agent activity in Advanced GC

| Agents | Response rate (%) |
|---|---|
| Mitomycin C | 30 |
| Doxorubicin | 17 |
| Epirubicin | 19 |
| Cisplatin | 19 |
| BCNU | 18 |
| 5-Fluorouracil | 21 |
| Etoposide (oral) | 21 |
| Hydroxurea | 19 |
| UFT | 27 |
| Capecitabine | 19 |
| S-1 | 45 |
| Paclitaxel | 17-23 |
| Docetaxel | 17-29 |
| CPT-11 | 18 |

**RR: ~20%**

Response duration: short

→ **RR: ~20%**

*1960-1970:true activity overestimated d/t methodology*

# Metastatik Mide Kanseri

## WHICH COMBINATION IS BETTER?

### NEW GENERATION REGIMENS SINCE 2000

| Study | Treatment | No.Pt | RR (%) | TTP (month) | OS (month) | *p* - value |
|---|---|---|---|---|---|---|
| Van Cutsem (V325) | CDDP+5FU | 224 | 25 | 3.7 | 8.6 | 0.02 |
| | Doce+CDDP+5FU | 221 | 37 | 5.6 | 9.2 | |
| Dank (V306) | CDDP+5FU | 163 | 26 | 4.2 | 8.7 | NS |
| | Irinotecan+5FU/LV | 170 | 32 | 5.0 | 9.0 | |
| Cunningham (REAL-2) | ECF | 263 | 41 | 6.2 | 9.9 | 0.02 |
| | EOF | 245 | 42 | 6.5 | 9.3 | |
| | ECX | 250 | 46 | 6.7 | 9.9 | |
| | EOX | 244 | 48 | 7.0 | 11.2 | |
| Kang | CDDP+5FU | 137 | 29 | 5.0 | 9.3 | NS |
| | CDDP+capecitabine | 139 | 41 | 5.6 | 10.5 | |
| Boku (JCOG9912) | 5FU | 234 | 9 | 2.9 | 10.8 | NS |
| | CDDP+irinotecan | 236 | 38 | 4.8 | 12.3 | |
| | S-1 | 234 | 28 | 4.2 | 11.4 | |
| Narahara (SPIRITS) | S-1 | 150 | 31 | 4.0 | 11.0 | 0.036 |
| | CDDP+S-1 | 148 | 54 | 6.0 | 13.0 | |
| Ajani (FLAGS) | CDDP+5-FU | 508 | 31.9 | 5.5 | 7.9 | 0.198 |
| | CDDP+S-1 | 521 | 29.1 | 4.8 | 8.6 | |

# Metastatik Mide Kanseri

## REAL-2 Trial

Phase III Comparing Capecitabine With 5-FU and Oxaliplatin With Cisplatin

**ECF** (N=263)

| | |
|---|---|
| Epirubicin | 50 mg/m$^2$ iv 3 wkly |
| Cisplatin | 60 mg/m$^2$ iv 3 wkly |
| 5 FU | 200 mg/m$^2$/d iv given continuously |

**ECX** (N=250)

| | |
|---|---|
| Epirubicin | 50 mg/m$^2$ iv 3 wkly |
| Cisplatin | 60 mg/m$^2$ iv 3 wkly |
| Capecitabine | 625 mg/m$^2$ bid po continuously |

**EOF** (N=245)

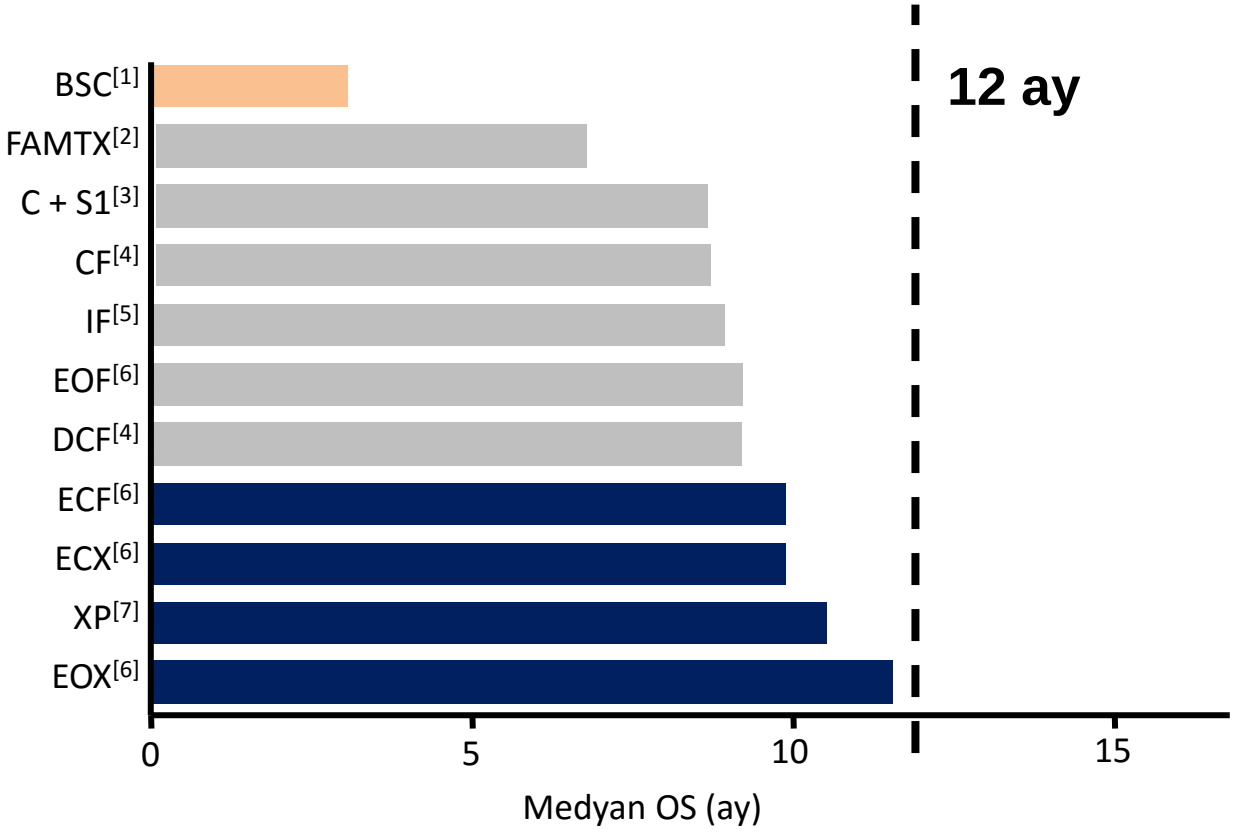
| | |
|---|---|
| Epirubicin | 50 mg/m$^2$ iv 3 wkly |
| Oxaliplatin | 130 mg/m$^2$ iv 3 wkly |
| 5 FU | 200 mg/m$^2$/d iv given continuously |

**EOX** (N=244)

| | |
|---|---|
| Epirubicin | 50 mg/m$^2$ iv 3 wkly |
| Oxaliplatin | 130 mg/m$^2$ iv 3 wkly |
| Capecitabine | 625 mg/m$^2$ bid po continuously |

- **2 X 2 Randomization, 8 cycles**
- **Non-inferiority of X over F and O over C with 1-yr survival of 35% with a 1 side α of 5%**

# Metastatik mide kanserinde medyan genel sağkalım




1. Murad AM, et al. Cancer. 1993;72:37-41. 2. Vanhoefer U, et al. J Clin Oncol. 2000;18:2648-2657.
3. Ajani JA, et al. J Clin Oncol. 2010;28:1547-1553. 4. Van Cutsem E, et al. J Clin Oncol. 2006;24:4991-4997.
5. Dank M, et al. Ann Oncol. 2008;19:1450-1457. 6. Cunningham D, et al. N Engl J Med. 2008;358:36-46.
7. Kang YK, et al. Ann Oncol. 2009;20:666-673. 8. Bang YJ, et al. Lancet. 2010;376:687-697.

# Gastrik kanserde HER2 pozitifliği

- Gastrik kanserde HER2 pozitiflik oranı %7-34 arasında bildirilmiştir.
- Gastrik kanserde HER 2 pozitifliği;
  - ✓ kötü prognoz,
  - ✓ daha agresif hastalık ve
  - ✓ kısa sağkalımla ilişkilendirilmektedir

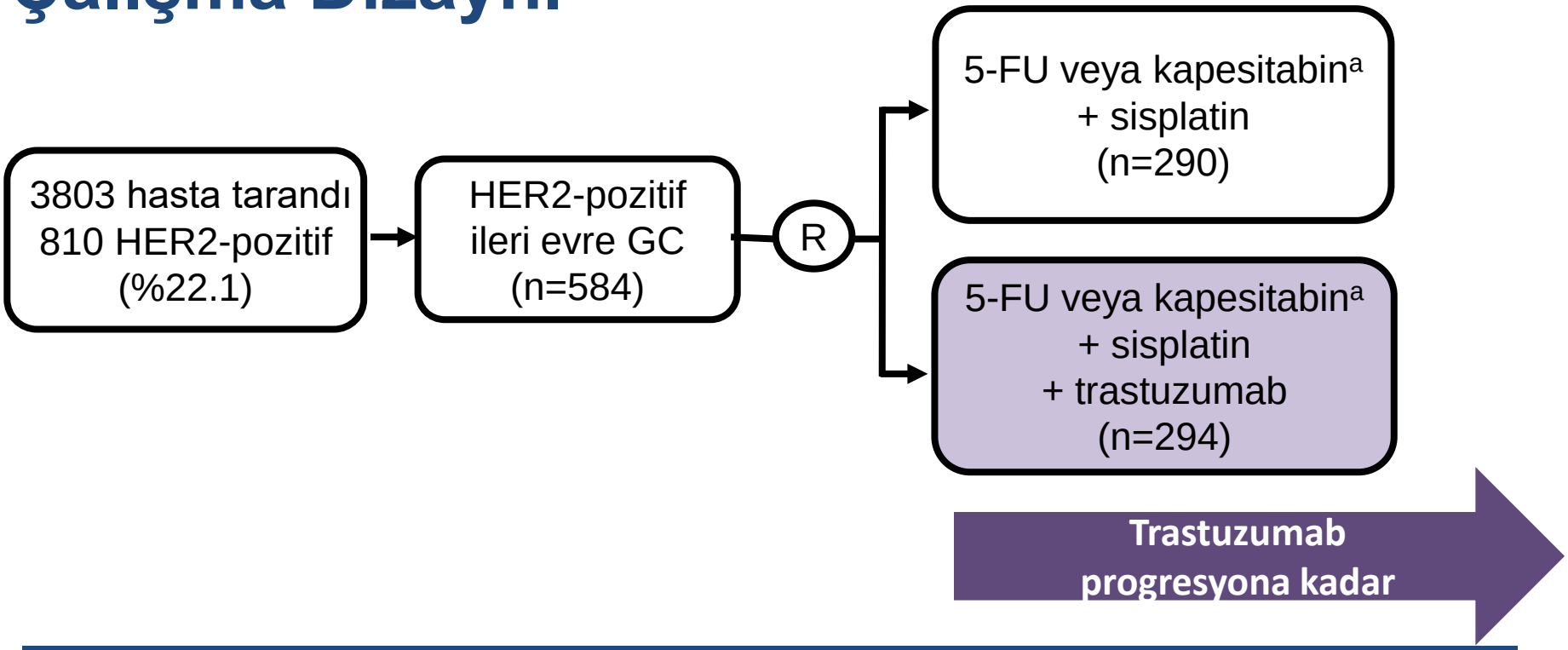
Bang YJ, et al. Lancet. 2010;376:687-697.

# HER2 pozitif ilerlemiş gastrik ya da gastro-özefageal bileşke kanserinin tedavisi için tek başına kemoterapi ve kemoterapi ile kombinasyon halinde trastuzumab kullanımının karşılaştırılması (ToGA): faz III, açık etiketli, randomize kontrollü çalışma

*Yung_Jue Bang, Eric Van Cutsem, Andrea Fevereislova, Hyun C Chung, Lin Shen, Akira Sawaki, Florian Lordick, Atsushi Ohtsu, Yasushi Omuro, Tarah Satoh, Giuseppe Aprile, Evgeny Kulilov, Julie Hill, Michaela Lehle, Josef Rüschoff, Yoon-Koo Kang*

**Bang YJ, et al. Lancet. 2010;376:687-697**.

# Çalışma Dizaynı




- Primer Sonlanım Noktası: Genel Sağkalım
- Sekonder Sonlanım Noktaları: Prograsyonsuz sağkalım (PFS), Progresyona kadar geçen süre (TTP), yanıt oranı (ORR), yanıt süresi (DoR), güvenlilik

**Kapesitabin**: 1000 mg/m$^2$ bid d1-14 q3w x 6
**5-FU**: 800 mg/m$^2$/gün sürekli iv infuzyon d1-5 q3w x 6
**Sisplatin**: 80 mg/m$^2$ q3w x 6
**Trastuzumab**: 8 mg/kg yükleme dozu sonrasında 6 mg/kg q3w progresif hastalığa (PD) kadar

**Bang YJ, et al. Lancet. 2010;376:687-697.**

# ToGA: Histolojik tipe göre HER2 pozitifliği

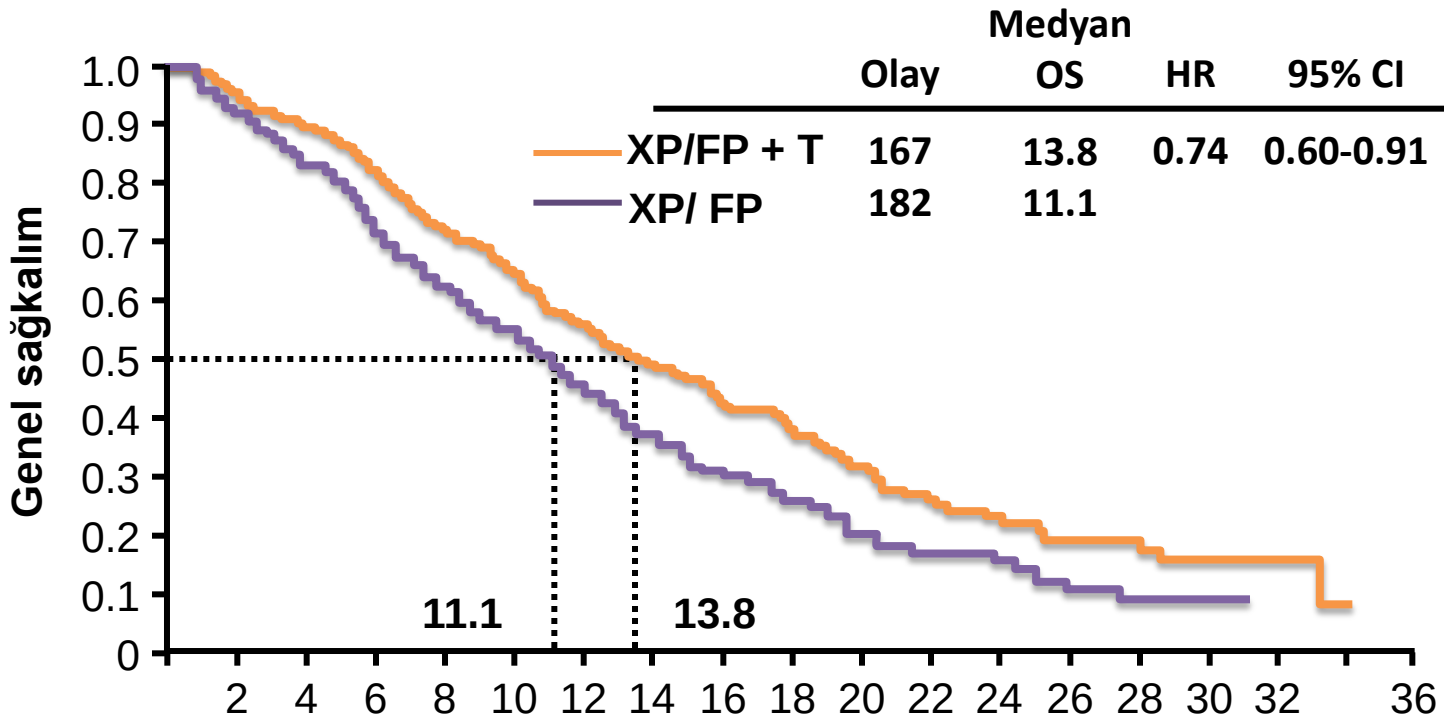
| | Alt tip | HER2 Pozitifliği (%) | *P* |
|---|---|---|---|
| Histolojik tip | Intestinal<br>Diffüz<br>Mikst | 32.2<br>6.1<br>20.4 | < .001 |
| Lokalizasyon | GEJ<br>Gastrik | 33.2<br>20.9 | < .002 |

**Histolojik alt tip ve tümör lokalizasyonu,**
**HER2 ekspresyonu/amplifikasyonu açısından farklılık yaratıyor.**

Bang YJ, et al. ASCO 2009. Abstract 4556.

# ToGA: Genel sağkalım

## ITT Popülasyon



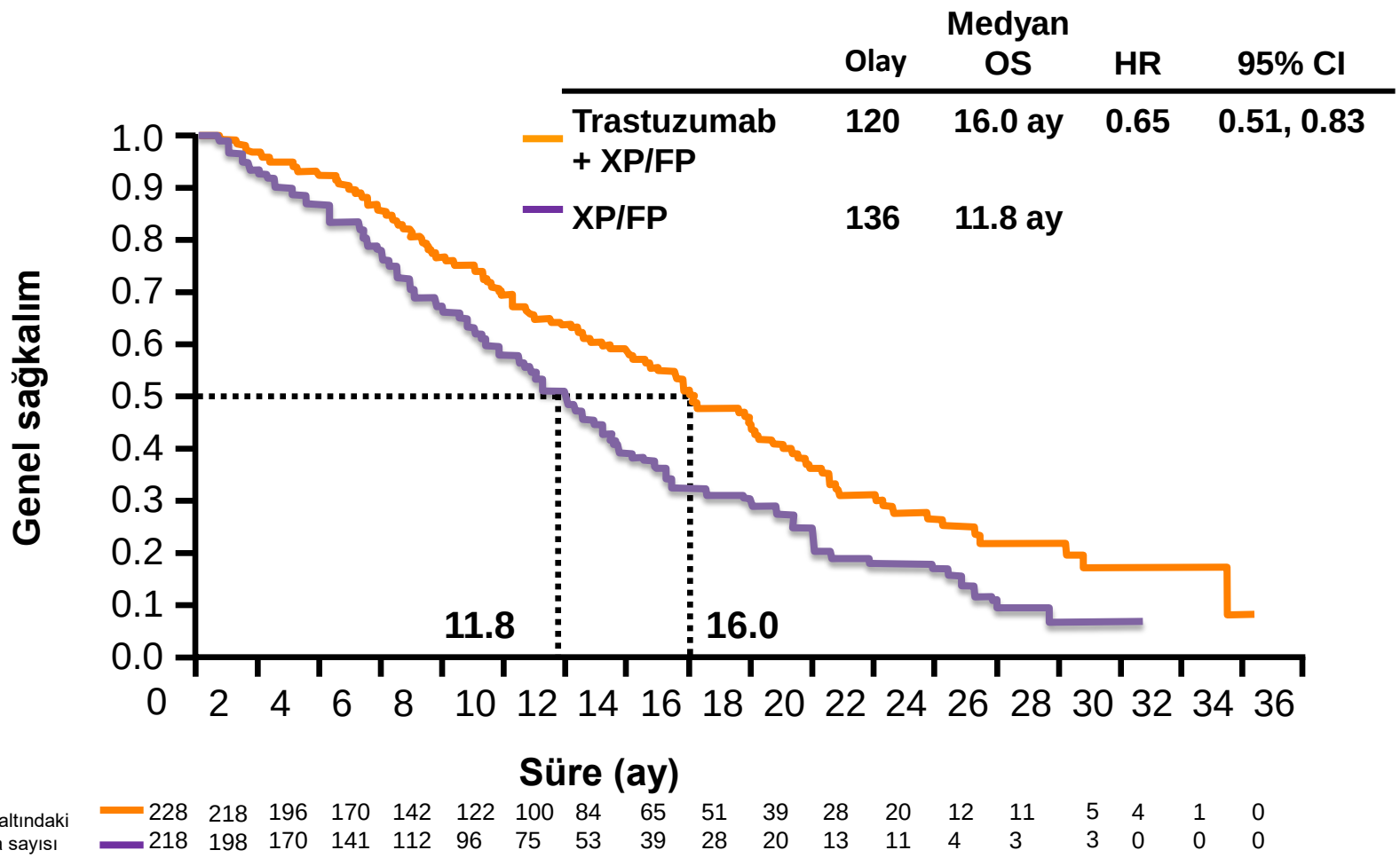

**Risk altındaki hasta sayısı, n**

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 294 | 277 | 246 | 209 | 173 | 147 | 113 | 90 | 71 | 56 | 43 | 30 | 21 | 13 | 12 | 6 | 4 | 1 | 0 |
| | 290 | 266 | 223 | 185 | 143 | 117 | 90 | 64 | 47 | 32 | 24 | 16 | 14 | 7 | 6 | 5 | 0 | 0 | 0 |

Bang YJ, et al. Lancet. 2010;376:687-697.

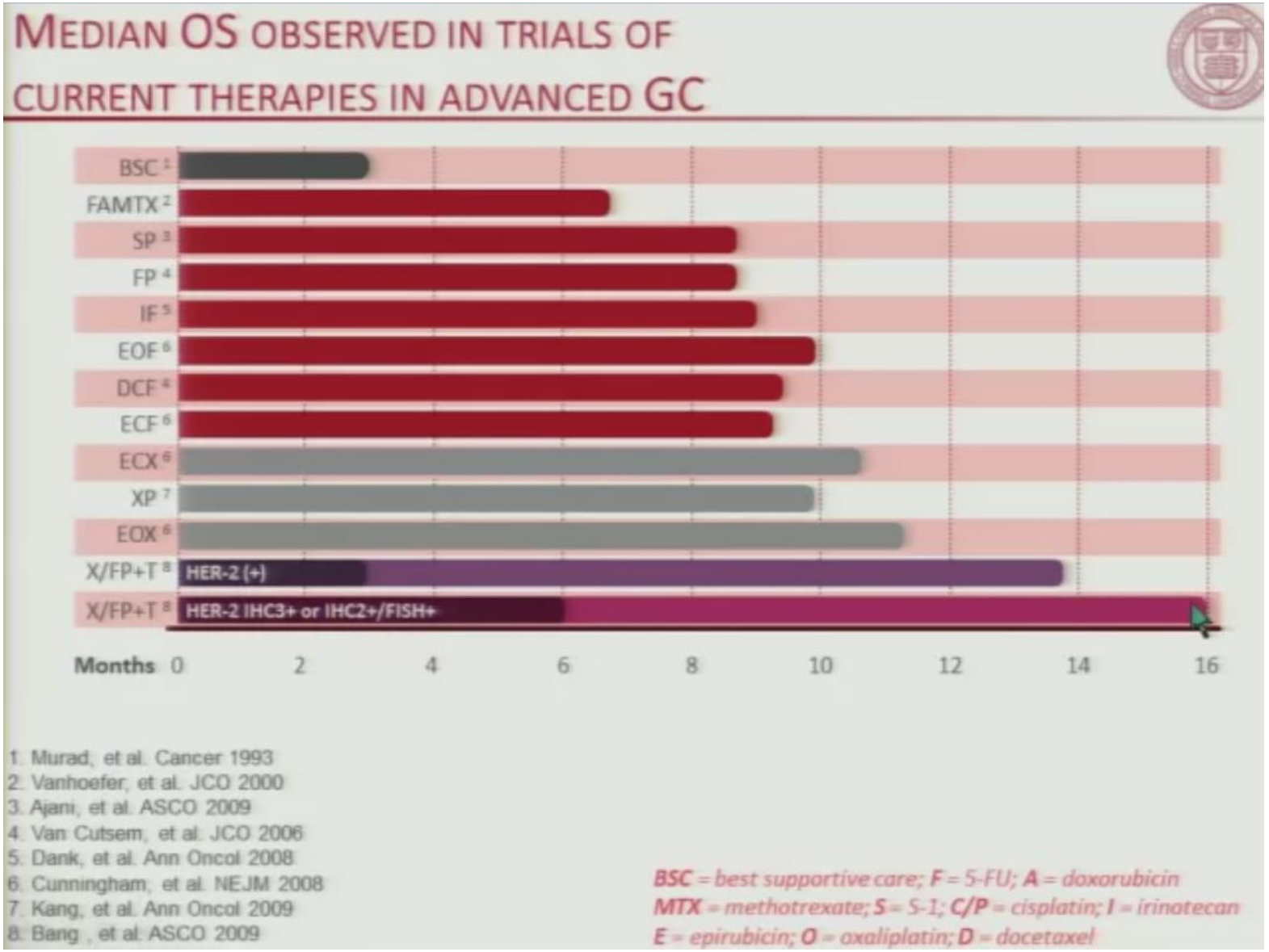
# ToGA: Genel Sağkalım

## HER2'yi eksprese eden grup (IHC 2+/FISH+ ve IHC 3+)

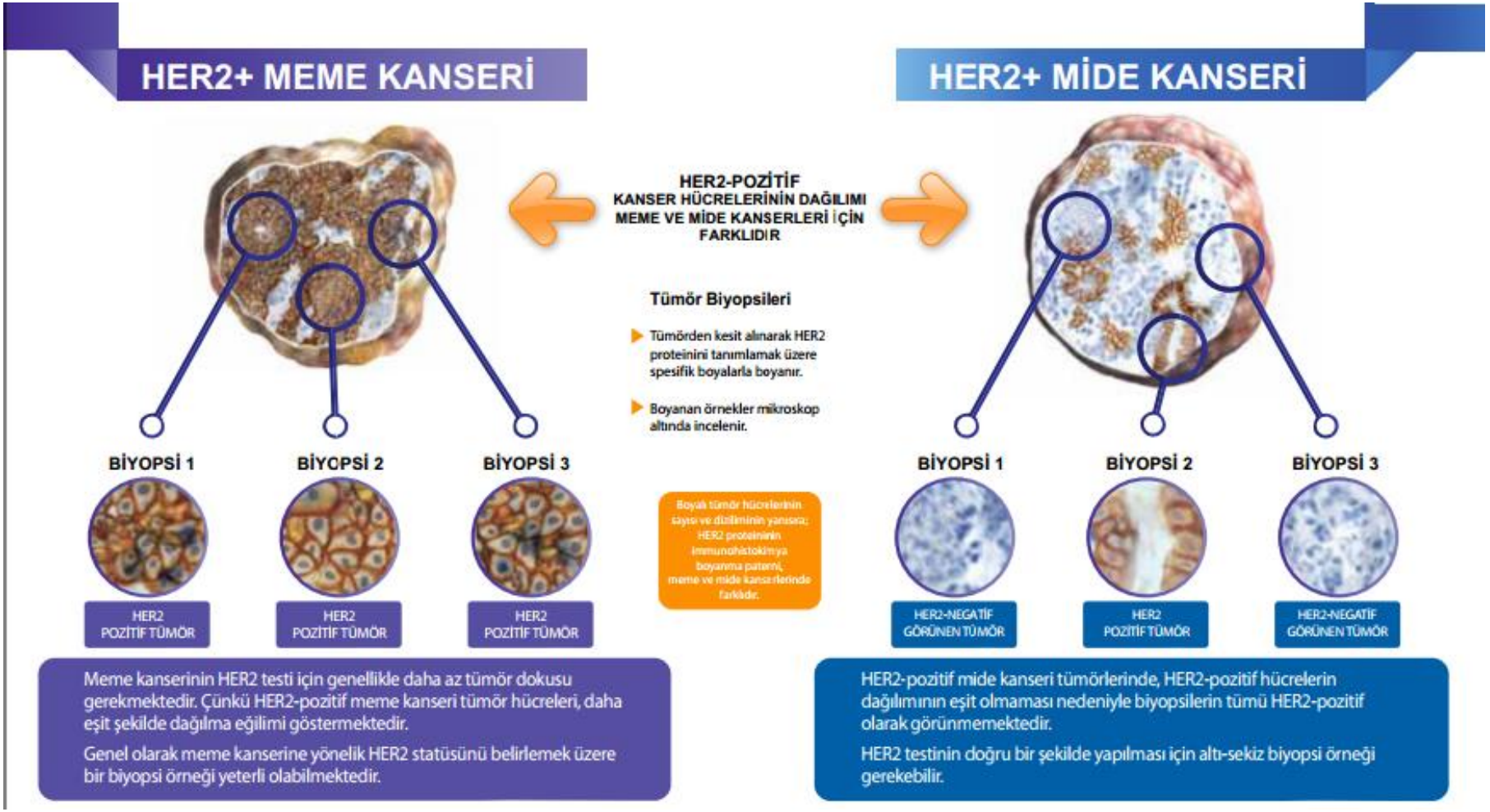



Bang YJ, et al. Lancet. 2010;376:687-697.

# Metastatik Mide Kanseri



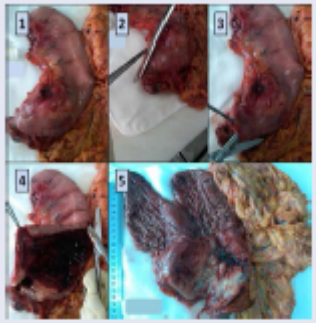
# Mide Kanseri Heterojen yapıdadır




Rüschoff J et al, Wirchows Arch 2010

# Endoskopik biyopsi/ rezeksiyon materyalleri Patoloji Laboratuvarı'na nasıl gönderilmeli?

- Materyal patoloji istem formu eşliğinde en kısa zamanda patoloji laboratuvarına gönderilmeli.
- Materyalin rahat sığabileceği, şeffaf, sızdırmaz plastik ya da cam kaplar kullanılmalı.
- Kabın üzerine hastanın kimlik bilgileri yazılmalı.



## ENDOSKOPİK BİYOPSİLER

- En az 6-8 örnek alınmalı.
- Biyopsi materyali hacminin en az 10 katı hacminde %10'luk formalin solüsyonu içerisine hemen konulmalıdır.

## EKSİZYON MATERYALLERİ

- Gastrektomi ve diğer eksizyon materyalleri, materyalin rahat sığabileceği büyüklükte bir kaba yerleştirilerek en kısa zamanda patoloji laboratuvarına ulaştırılmalıdır.
- Materyal hemen gönderilemeyecek ise lumen usulune uygun açılarak %10'luk formalin solüsyonu içerisinde geniş bir kap içerisinde lumen açık halde fikse edilmelidir.

## PATOLOJİ İSTEM FORMUNUN İÇERMESİ GEREKEN BİLGİLER

| | |
|---|---|
| Hastanın Adı Soyadı / Yaşı ve Cinsiyeti | : |
| Gönderen Doktor | : |
| Gönderen Doktor/Servisin İletişim Bilgileri | : |
| Hasta Hakkında Klinik Bilgi | : |
| Endoskopik Biyopsi | : |
| Endoskopik Bulgular | : |
| Biyopsilerin Alındığı Lokalizasyon/Lokalizasyonlar | : |
| Alınan Biyopsi Sayıları | : |
| Eksizyon | : |
| Eksizyon Tipi (total/subtotal gastrektomi, wedge eksizyon, vb) | : |

Histopatolojik incelemelerin ve gereğinde hedefe yönelik tedaviler için gereken ileri analizlerin güvenilir şekilde yapılabilmesi için dokunun hemen ve uygun şekilde fiksasyonunun yapılması gereklidir.

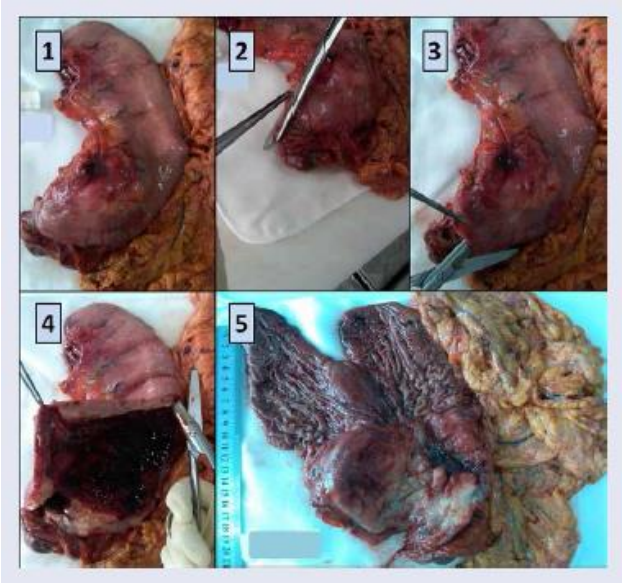
Bu poster Roche Müstahzarları'nın katkılarıyla TPF gastrointestinal çalışma grubu tarafından hazırlanmıştır. 2015

Referans: Rosai and Ackerman's Surgical Pathology, 2011

# Materyaller Patoloji Laboratuvarına nasıl gönderilmeli?

## Endoskopik biyopsi

- 6-8 adet biyopsi alınmalıdır
- Materyal, hacminin 10 katı %10 tamponlu formol solüsyonu içine hemen konulmalıdır.




## Eksizyon materyali

- Gastrektomi ve diğer eksizyon materyali rahatça sığabileceği büyüklükte bir kaba yerleştirilerek en kısa sürede patoloji laboratuvarına gönderilmelidir.
- Materyal hemen gönderilemeyecekse, lümen usulüne uygun açılarak %10 tamponlu formol solüsyonu içinde lümen açık olarak bekletilmelidir.

# Gastrik Kanser Endikasyonu

- HER 2 pozitifliği, hem immunhistokimyasal yöntemle +2/+3 ve hem FISH/CISH ile pozitif olarak saptanan,
- Metastatik mide veya özofagogastrik bileşke yerleşimli adenokanserli ve
- Daha önce metastatik hastalığı için kemoterapi uygulanmamış olan hastalarda,
- Platin ile kapesitabin ya da 5-fluorourasil içeren kemoterapi rejimleri ile kombine olarak kullanımı endikedir

# Metastatik Mide Kanseri Geri Ödemesi

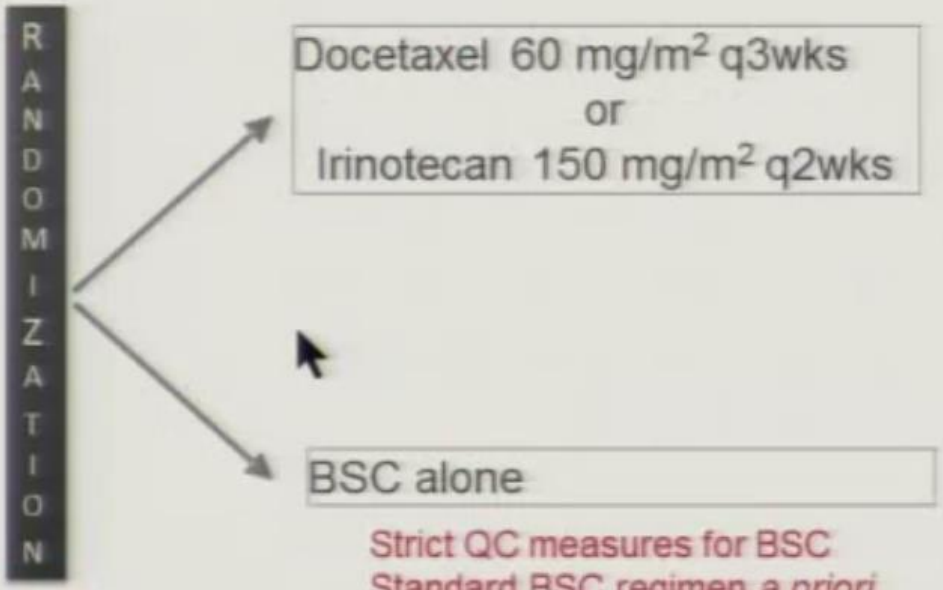
- HER 2 pozitifliği, *hem immunhistokimyasal yöntemle +2/+3 ve hem FISH/CISH/SISH ile pozitif* olarak saptanan,
- Daha önce kemoterapi uygulanmamış olan hastalarda,
- Platin ve kapesitabin ya da platin ve 5-fluorourasil içeren kemoterapi rejimleri ile kombine olarak kullanımı endikedir
- Progresyon gelişmesi halinde tedavi sonlandırılır

Şubat 2015 tarihli SUT metni

# Metastatik Mide Kanseri

## Study Treatments

- Stratified for PS & # prior therapy
- SLC regimen determined by investigators
- SLC continued until progression, toxicities, or withdrawal



# Metastatik Mide Kanseri

## Second-line CT
## First Phase III Trial

- Median age: 56 yrs
- 1 line: 73%; 2 lines: 27%
- PS 0: 54%
- > 1 M+ site: 65%
- < 3-mo treatment-free interval: 74%

| | CT + BSC (n = 133) | BSC (n = 69) | |
|---|---|---|---|
| **OS, mos** | 5.3 | 3.8 | HR: 0.66 (95% CI: 0.48-0.89; *P* = .007) |

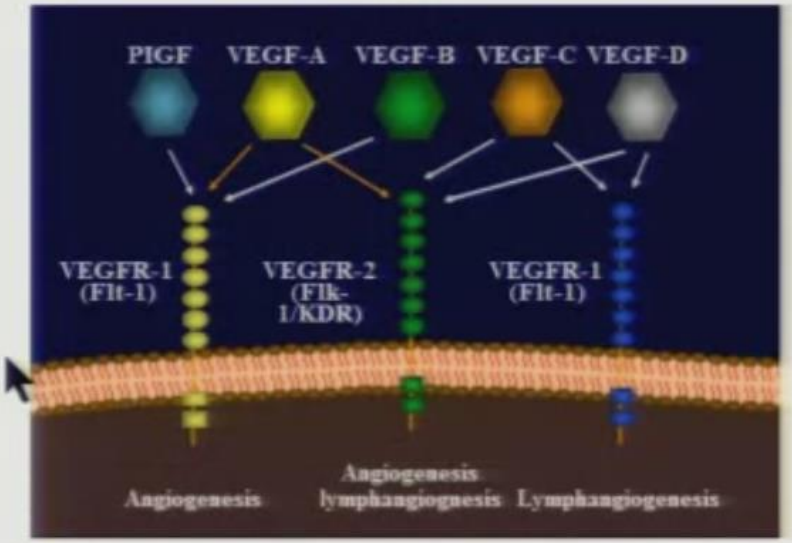
- Further CT, ≥ 3rd line: 40% vs 22%; *P* = .011
- No QoL data

Kang JH, et al. J Clin Oncol. 2012;30:1513-1518.

# Metastatik Mide Kanseri

## TARGETING VEGF IN GASTRIC CANCER

- VEGF is a key mediator of angiogenesis [1]
- VEGF expression is associated with more aggressive disease and poor prognosis in gastric cancer [2,3]
- Bevacizumab:
  - Antibody against VEGF




1. Neufeld G, et al. FASEB J. 1999;13:9-22
2. Kim SE, et al. Gut Liver. 2009;3:88-94
3. Lieto E, et al. Ann Surg Oncol. 2008;15:69-79