Gastrointestinal Maligniteler
Tedavi Yaklaşımları

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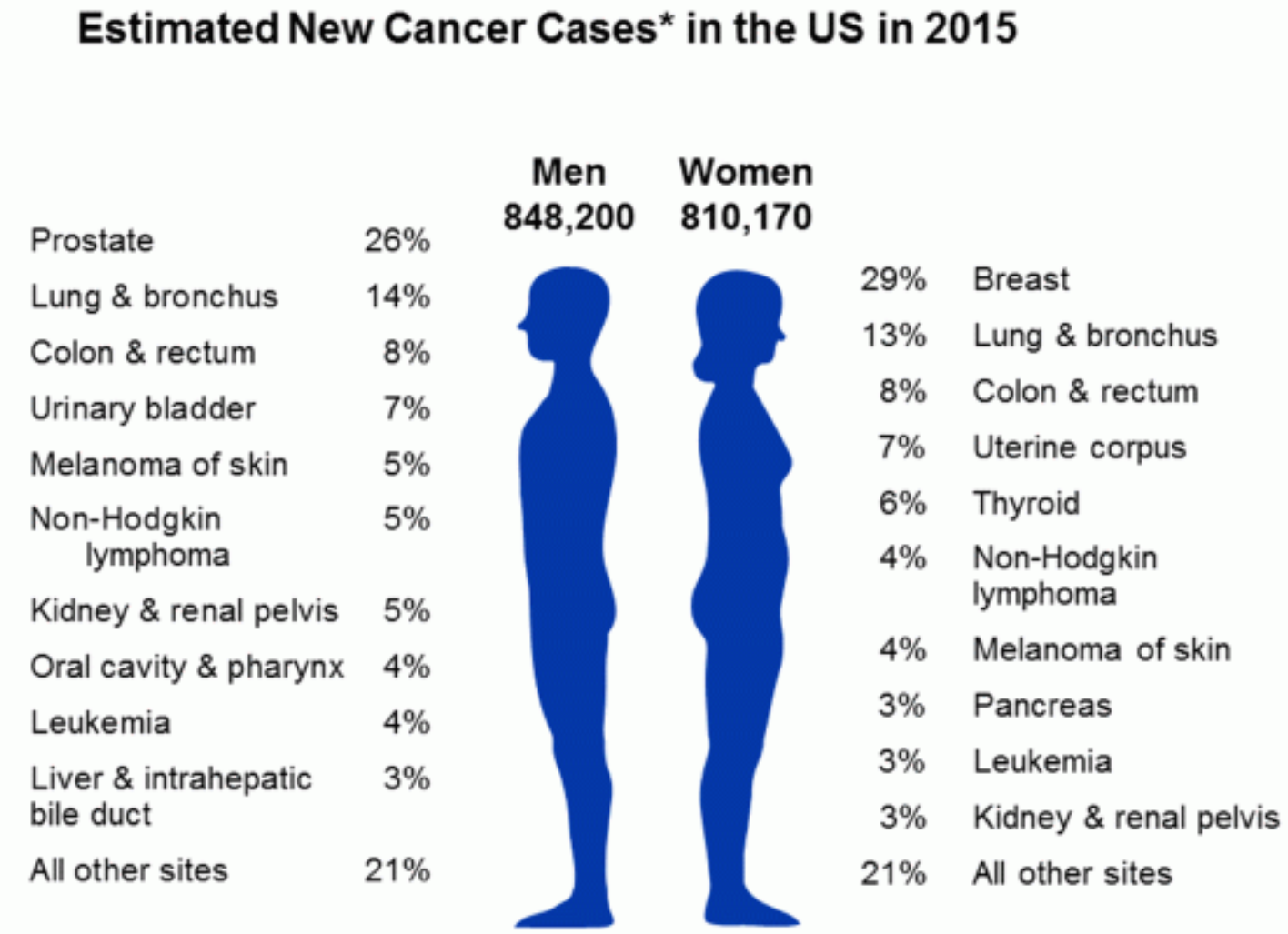
Tıbbi Onkoloji

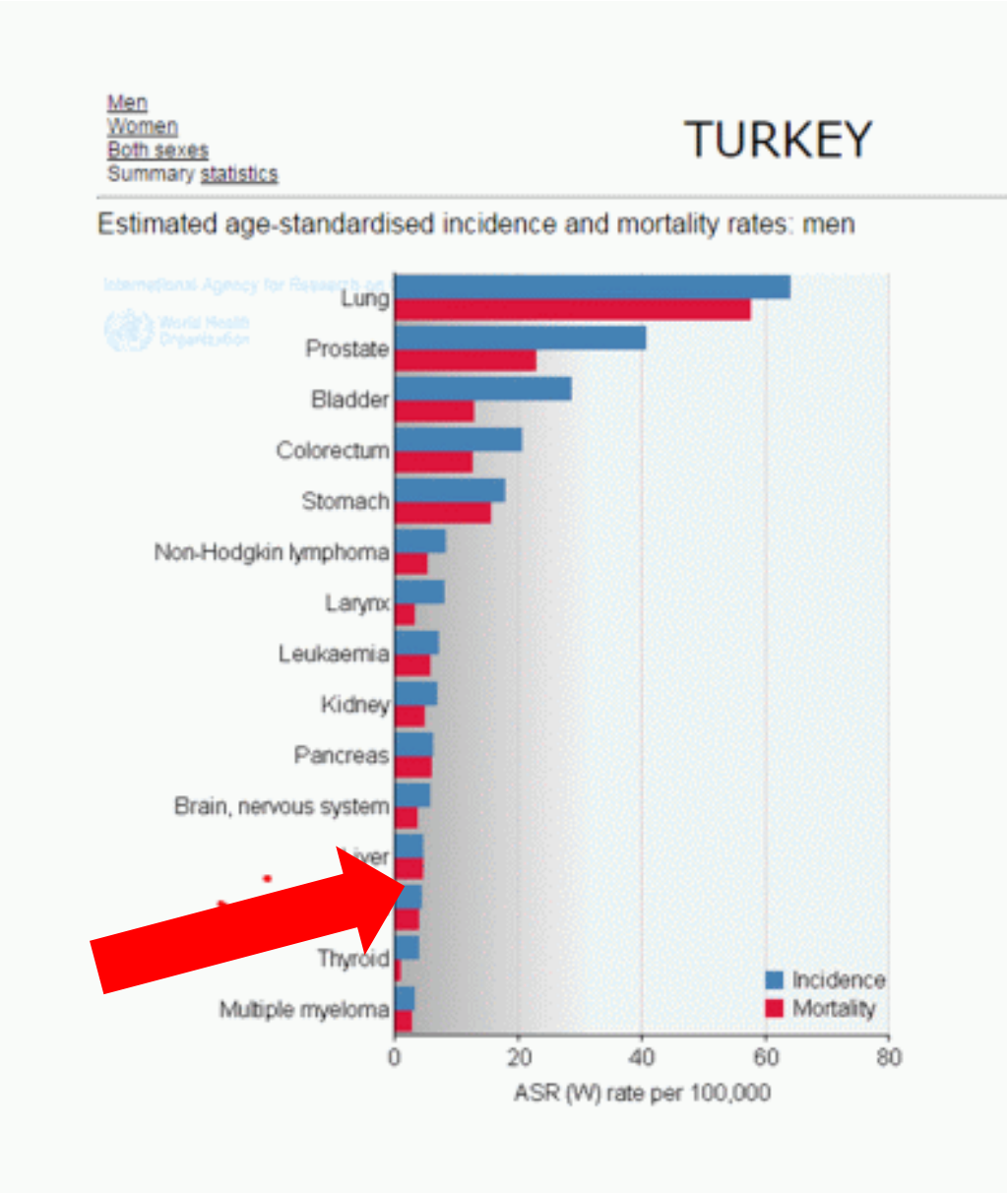
Ders Planı

- Özofagus, distal özofagus –kardia kanserinde tedavi yaklaşımları
- Mide kanserinde tedavi yaklaşımları
- Kolon kanserinde tedavi yaklaşımları
- Rektum kanserinde tedavi yaklaşımları

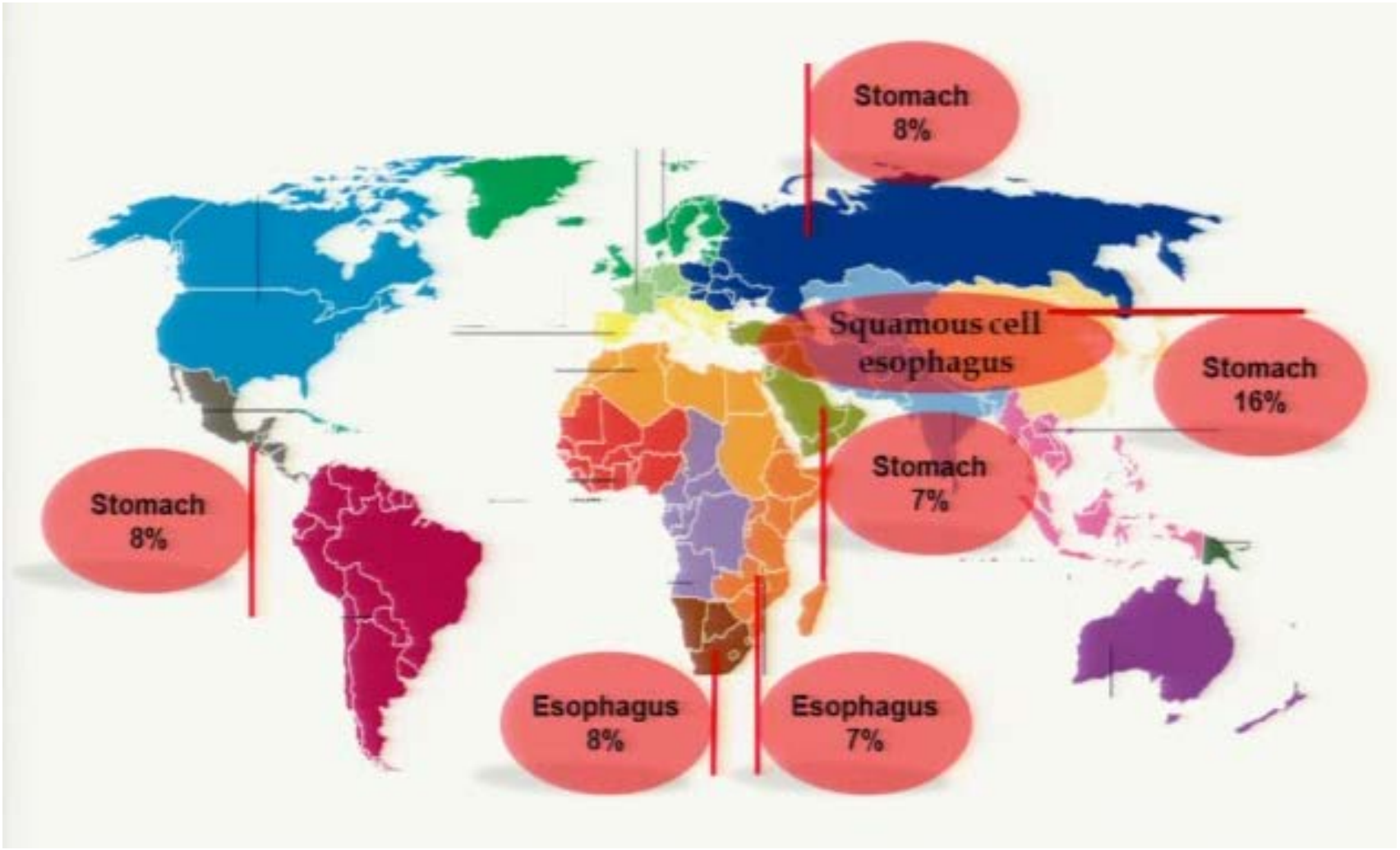
Özofagus Kanseri İnsidans ve Mortalite



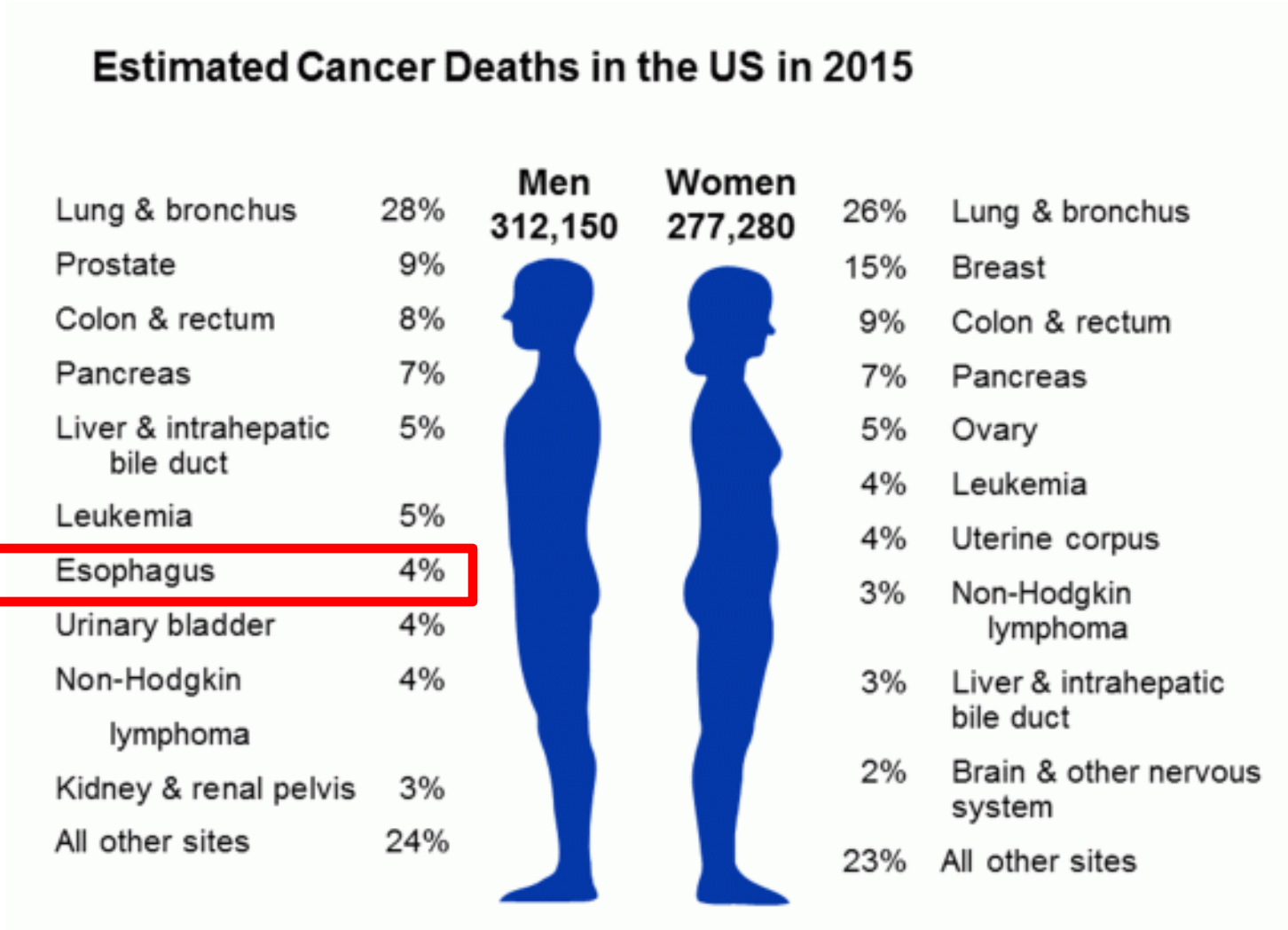
Özofagus Kanseri İnsidans ve Mortalite



Özofagus Kanseri İnsidans ve Mortalite



Özofagus Kanseri İnsidans ve Mortalite

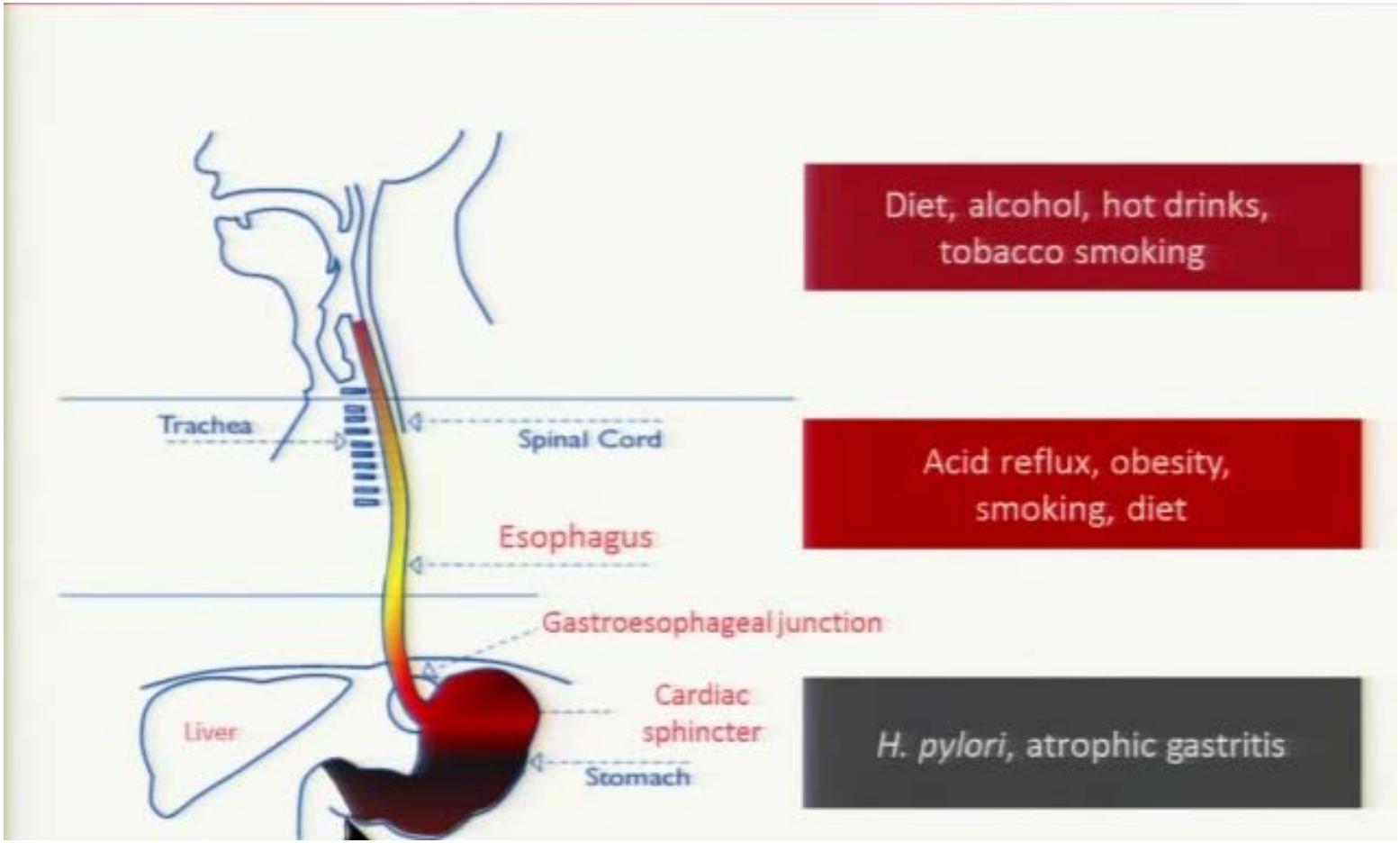


Özofagus Kanseri İnsidans ve Mortalite

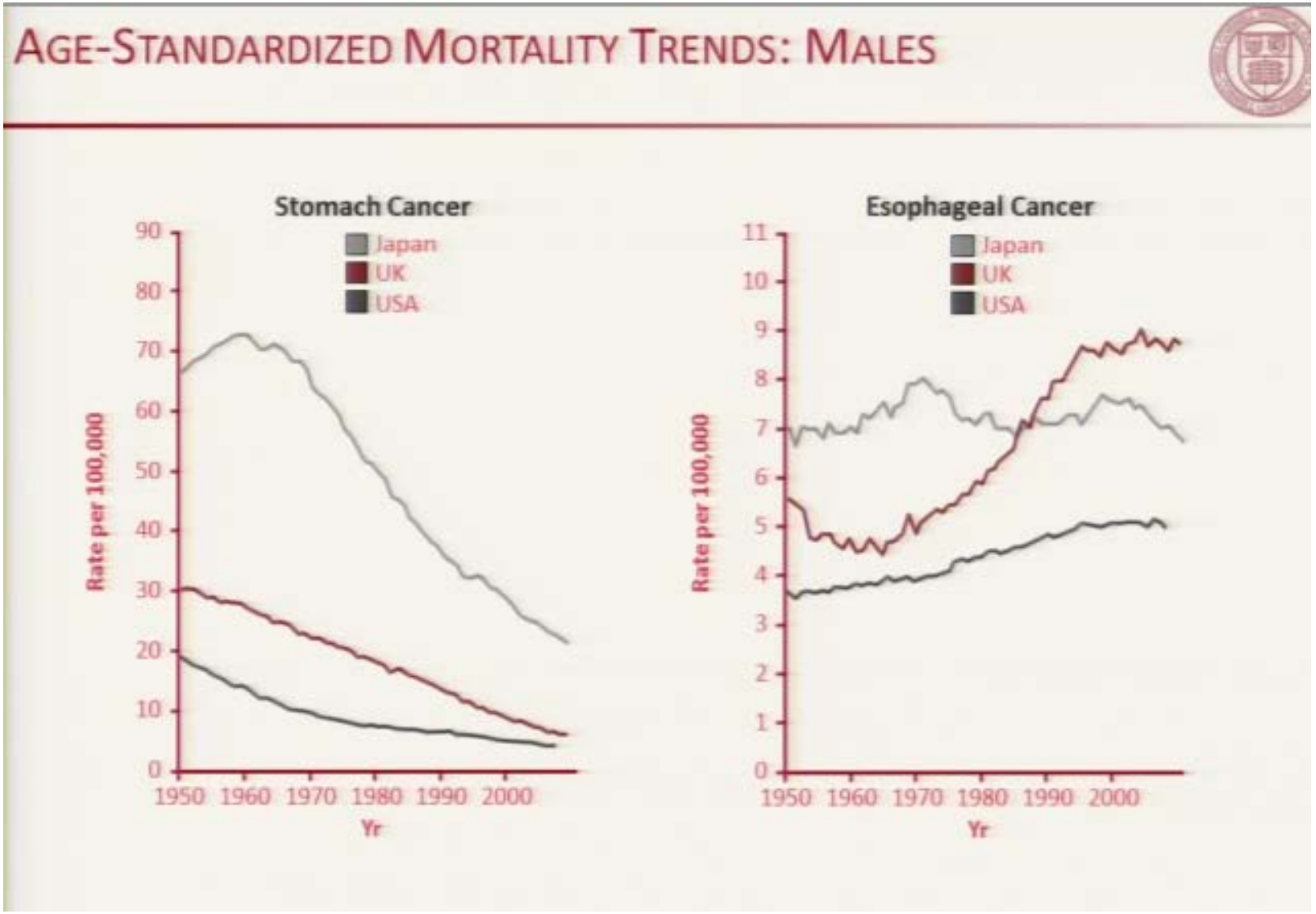
Estimated Number of New Cancer Cases and Deaths by Sex, US, 2015

	Yeni Vakalar	Ölüm	Ölüm Oranı %
Özofagus	16,980	15,590	92
Mide	24,590	10,720	43
İnce barsak	9,410	1,260	13
Kolon	93,090	49,700	53
Rektum	39,610		
Anorektum	7,270	1,010	14
KC- intrahepatik SY	35,660	24,550	69
Safra Kesesi vd SY	10,910	3,700	34
Pankreas	48,960	40,560	83

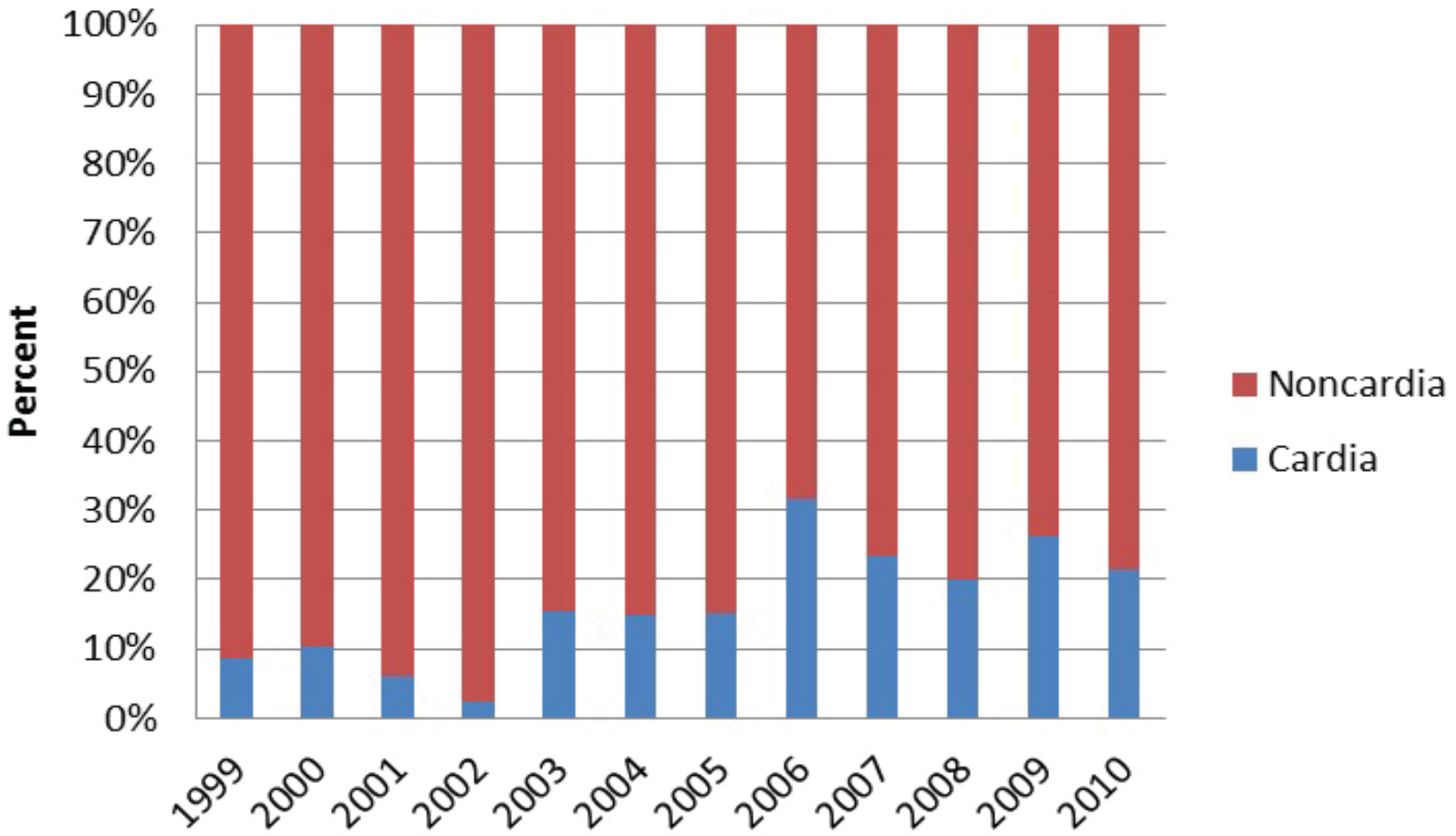
Özofagus Kanseri Genetik ve Risk Faktörleri



Özofagus Kanseri İnsidans ve Mortalite



Özofagus Kanseri İnsidans ve Mortalite



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

Özofagus Kanseri Genetik ve Risk Faktörleri

Adenokarsinom vs SCCa

Patogenetik, epidemiyolojik, tümör biyolojisi ve prognoz açısından farklı

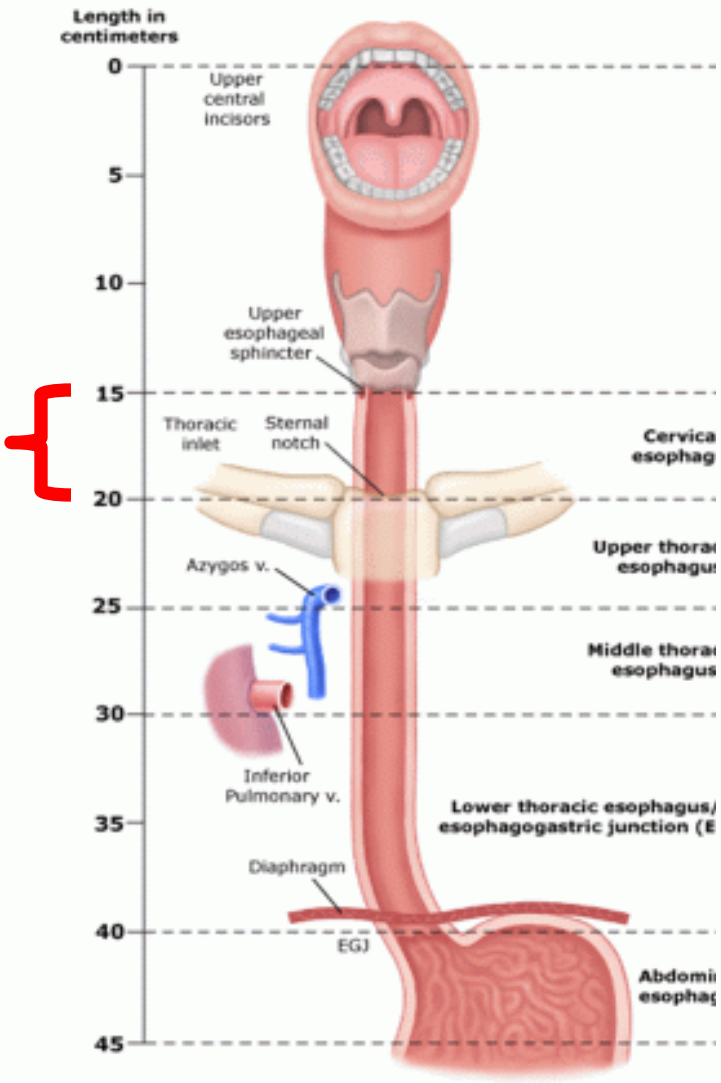
	Adenokarsinom	SCCa
İnsidans	Batıda (gelişmiş ülkeler) artıyor	Endemik (gelişmekte olan ülkeler) bölgelerde
Etyoloji	Obezite ve GÖR, Barret's	Sigara ve alkol
Prekürsör lezyon	Barret özefagus	Epitelyal displazi
Nüks paterni	Uzak nüks	Lokal nüks
Prognoz (özellikle erken evrede)	Daha iyi	Daha kötü
Lokalizasyon	Distal özofagus	Orta özofagus
Erkek / Kadın oranı	7/1	3/1
Siyah / Beyaz ırk	1/4	6/1

Özofagus Kanseri Genetik ve Risk Faktörleri

Syndrome	Gene(s)	Inheritance Pattern	Surveillance Recommendations
Esophageal Cancer, Tylosis With Non-epidermolytic Palmoplantar Keratosis (PPK) and Howel-Evans Syndrome[1,2]	*TEC (17q25)*	Autosomal dominant	Surveillance by upper gastrointestinal endoscopy is recommended in family members with tylosis after 20 years of age.
Familial Barrett's Esophagus (FBE)[3]	*unknown*	Autosomal dominant	Potential family history of BE, EAC, or EGJ adenocarcinoma should be determined for patients presenting with GERD, especially Caucasian males older than 40 years of age.
Bloom Syndrome (BS)[4]	*BLM/RECQL3*	Autosomal recessive	Screening for GERD with or without endoscopy to screen for early cancer after 20 years of age may be considered
Fanconi Anemia (FA)[1,2]	*FANCD1, BRCA2, FANCN (PALB2)*	Autosomal recessive	Endoscopy of the esophagus may be considered as a surveillance strategy in individuals identified with FA.

[1]Lindor NM, Greene MH. The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. J Natl Cancer Inst 1998;90:1039-1071.
[2]Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise handbook of familial cancer susceptibility syndromes - second edition. J Natl Cancer Inst Monogr 2008:1-93.
[3]Sun X, Elston R, Barnholtz-Sloan J, et al. A segregation analysis of Barrett's esophagus and associated adenocarcinomas. Cancer Epidemiol Biomarkers Prev 2010;19:666-674.
[4]Ellis NA, German J. Molecular genetics of Bloom's syndrome. Hum Mol Genet 1996;5 Spec No:1457-1463.

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.

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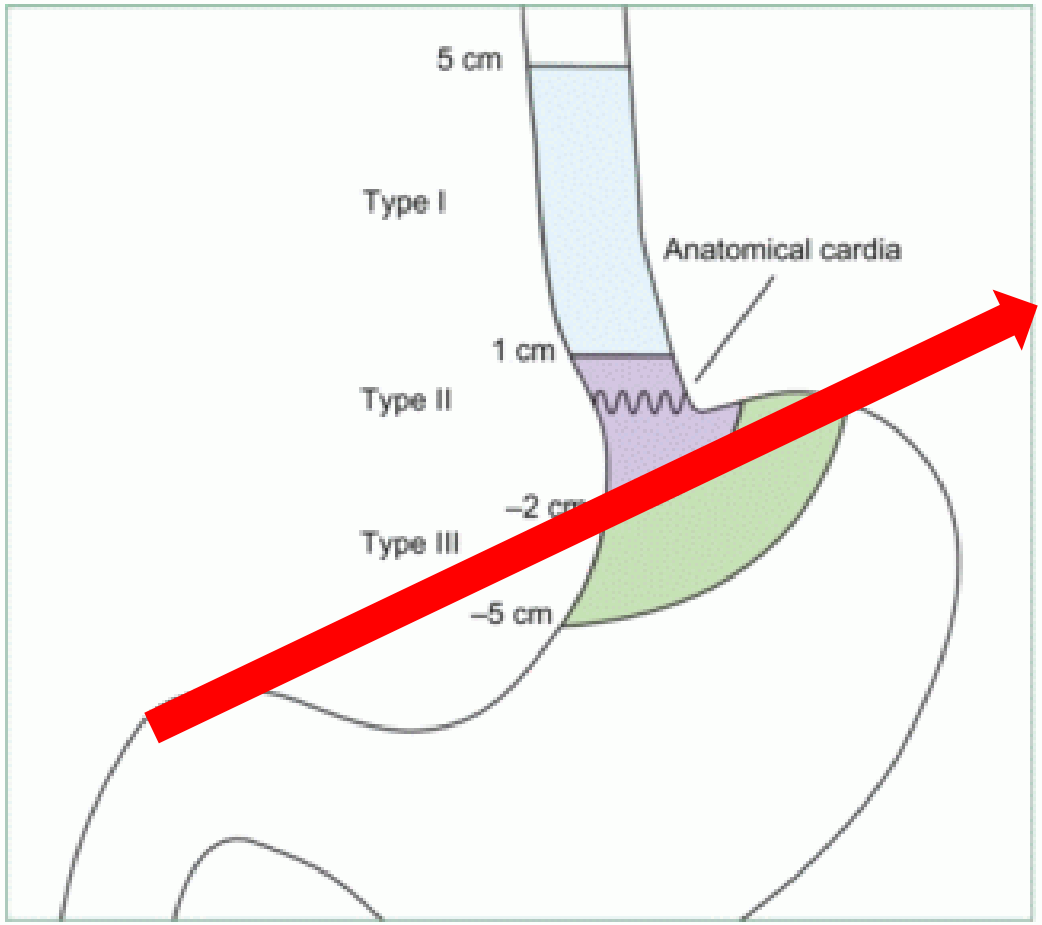
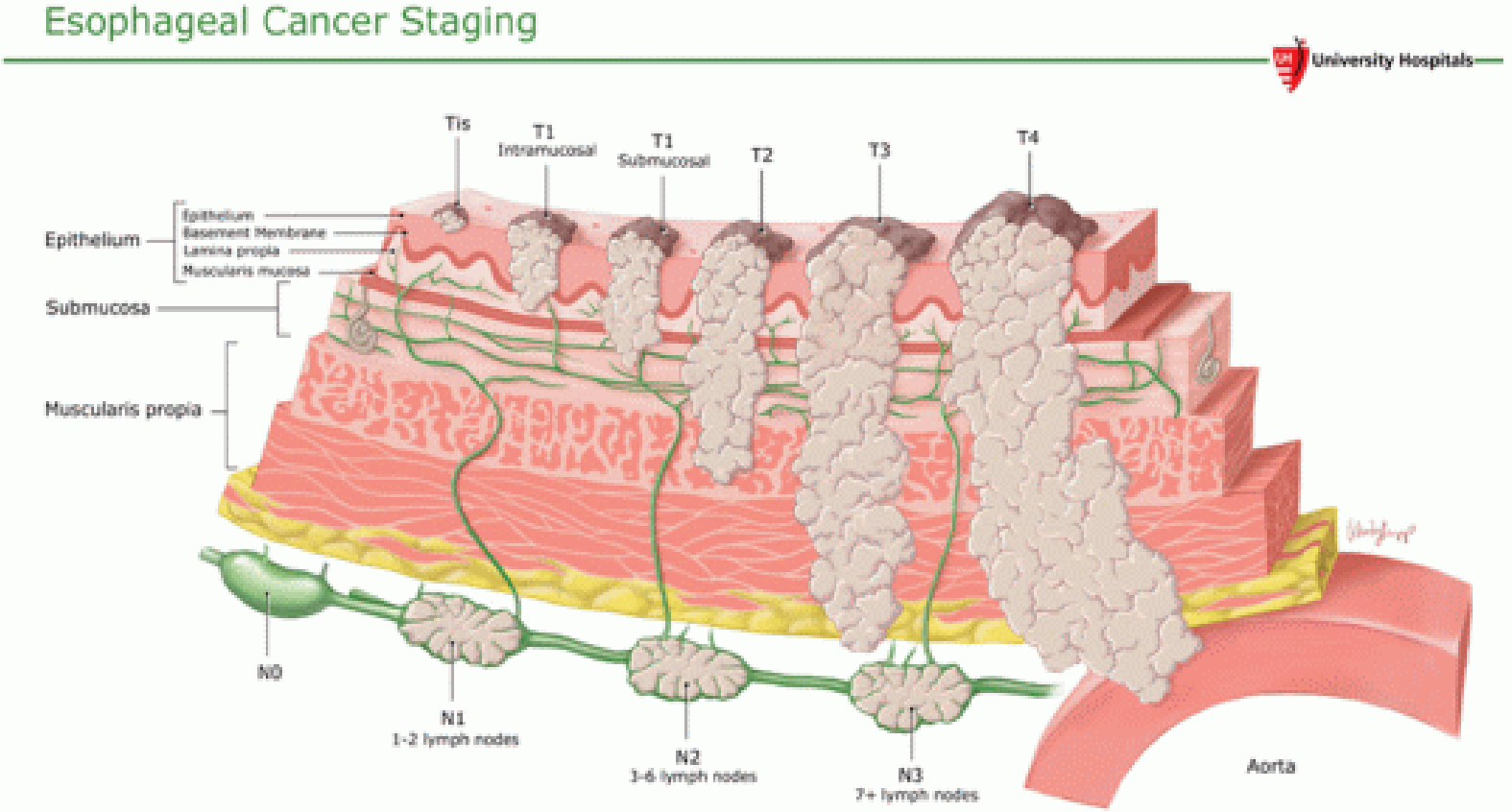
Özofagus Kanserinde Evreleme

Siewert Sınıflaması



Özofagus Kanserinde

Evreleme



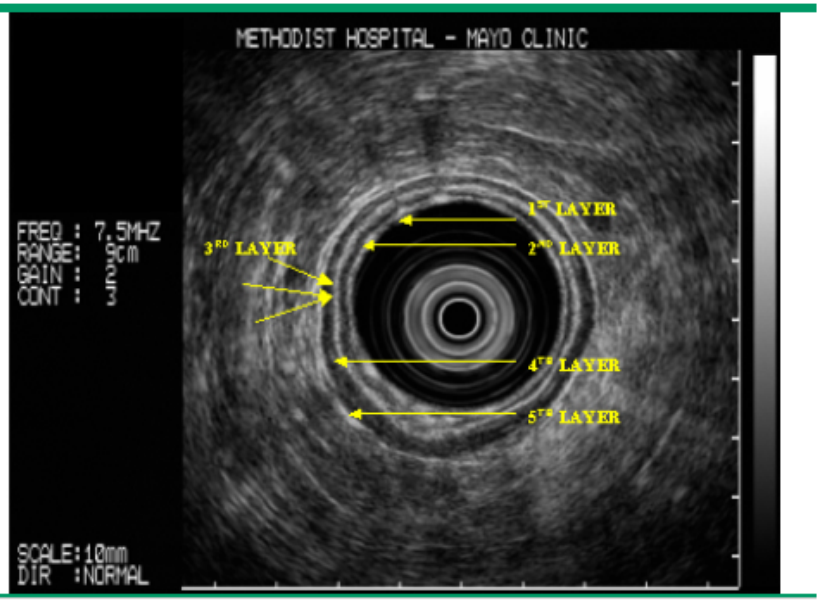
Özofagus duvarının seroza tabakası olmadığından tümör direk yayımla komşu organ ve yapıları (Plevra, trakea, ana bronşlar, perikard, büyük damarlar, duktus torasikus, vertebra) komşuluk yoluyla invaze eder.

Özofagus Kanserinde Evreleme

- BT
- PET-CT
- EUS
- Bronkoskopi
- Laparoskopi

Özofagus Kanserinde Evreleme

Endoscopic ultrasound (EUS) of normal esophagus



EUS examination of the normal esophagus showing the typical five-layer pattern: first hyperechoic layer (interface between lumen and mucosa), second hypoechoic layer (deep mucosa including muscularis mucosa), third hyperechoic layer (submucosa), fourth hypoechoic layer (muscularis propria), and fifth hyperechoic layer (adventitia interface).

Courtesy of Enrique Vazquez-Sequeiros, MD and Maurits J Wiersema, MD.

- ❑ **T evresi doğru saptama %80**
- ❑ **N evresi doğru saptama %90**
- ❑ **T1 yüzeyel tümörleri doğru saptama %67**

Chandawarkar RY, et al. Endosonography for preoperative staging of specific nodal groups associated with esophageal cancer. World J Surg, 1996.
Young PE, et al. Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus. Clin Gastroenterol Hepatol, 2010.

Özofagus Kanserinde Klinik Evreleme

N DOĞRU EVRELEME

- EUS: %80, Çölyak lenf nodları: %85
- BT: %50
- PET-CT: %57

UZAK METASTAZ SAPTAMA

- PET-CT, BT Göre %20 daha fazla uzak metastaz tespiti ve tedavi değişimi

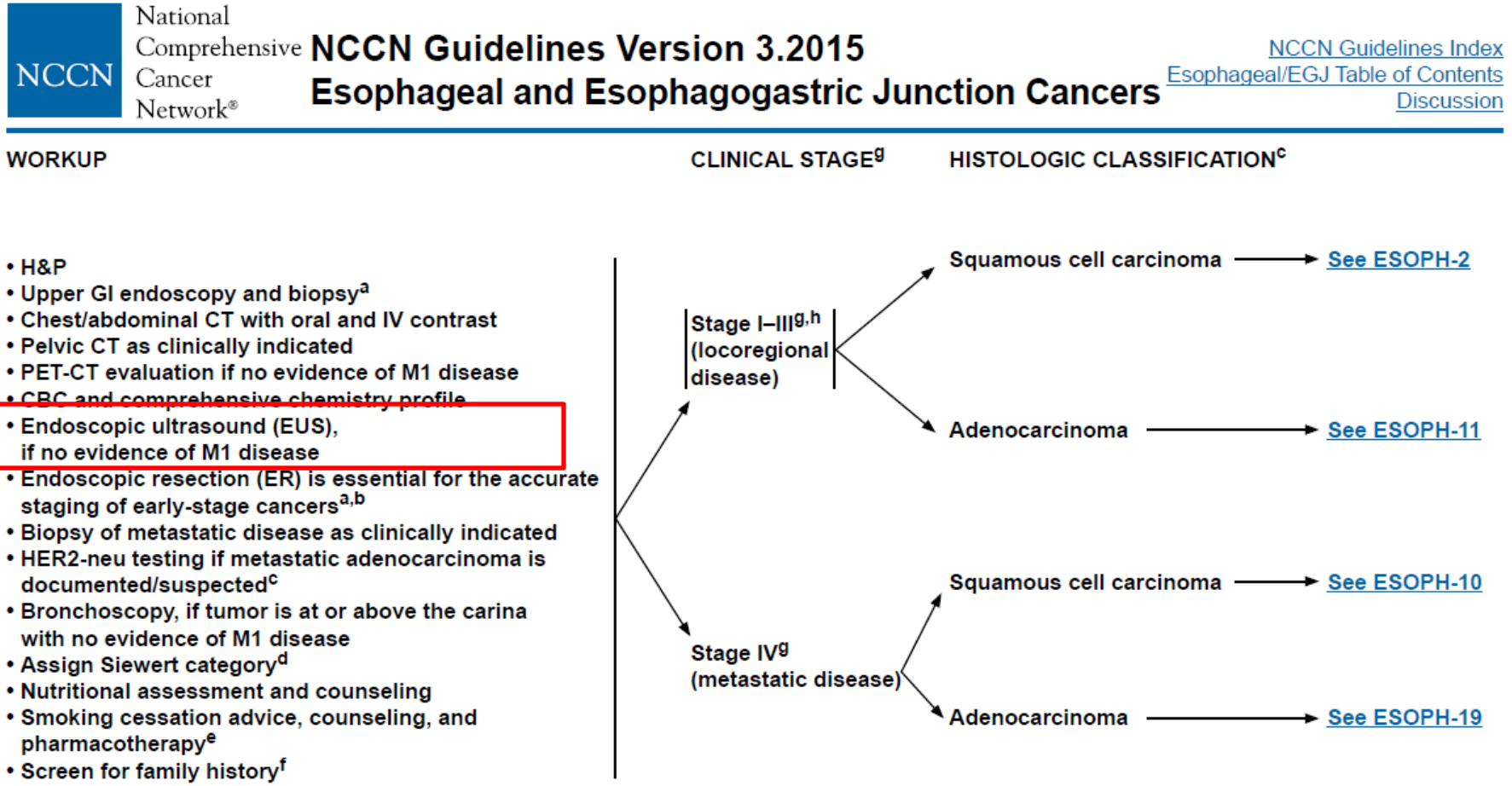
Özofagus Kanserinde Evreleme

- 126 T1 (75 T1a-51 T1b hasta) adenokarsinom içeren retrospektif bir çalışmada LN tutulumu sırasıyla % 1.3 ve % 22 bulunmuştur

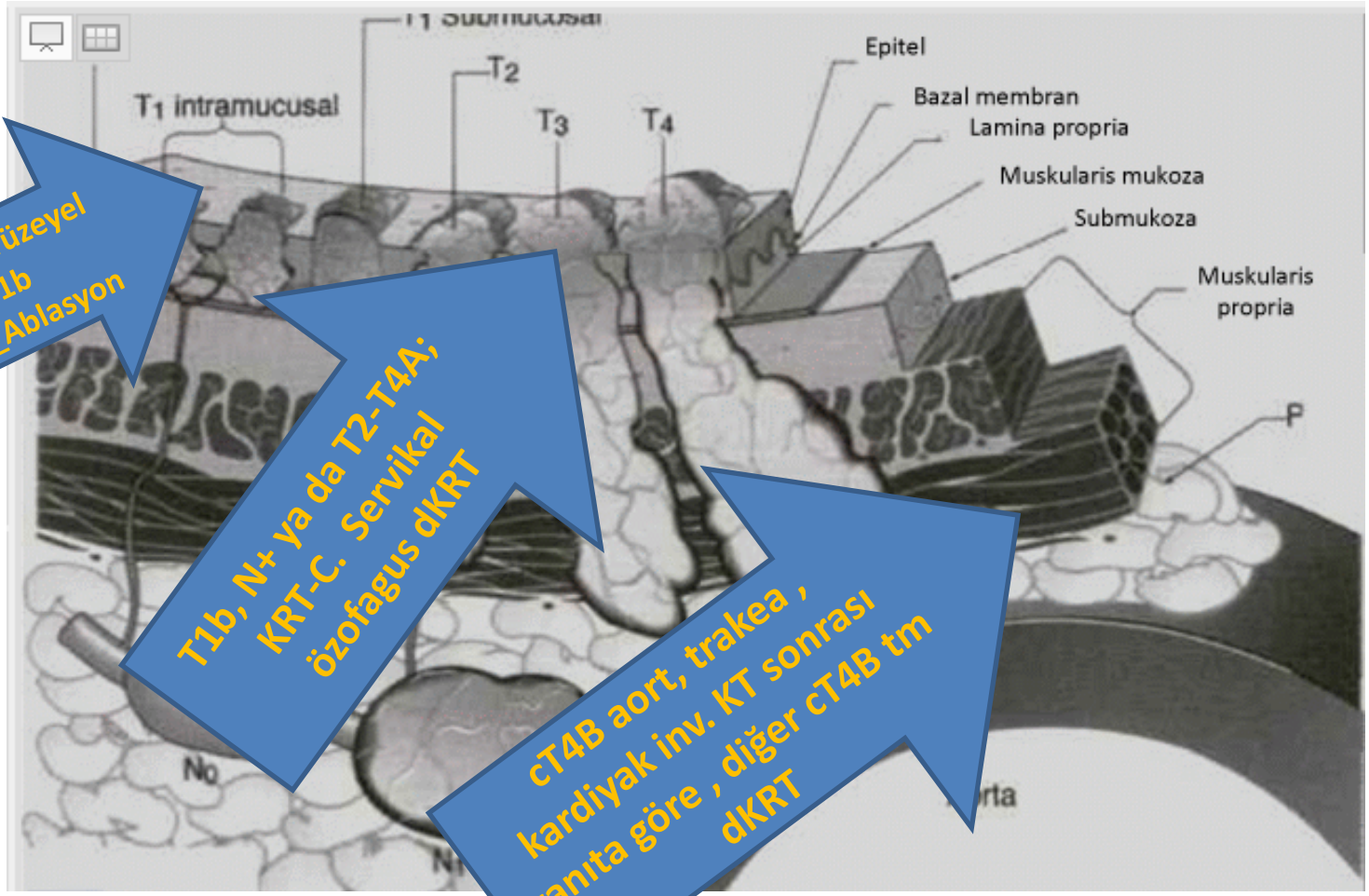
- Vaskuler invazyon, tümör boyutu ve diferansiasyon derecesi LN tutulumunu artıran sebepler arasında sayılabilir

Shimada H, Nabeya Y, Matsubara H, et al. Prediction of lymph node status in patients with superficial esophageal carcinoma: analysis of 160 surgically resected cancers. Am J Surg 2006;191:250-4.

Özofagus Kanserinde Klinik Evreleme
İlk Hangi Tetkik? EUS ? BT, PET-CT?



Özofagus Kanserinde Tedavi Yaklaşımları



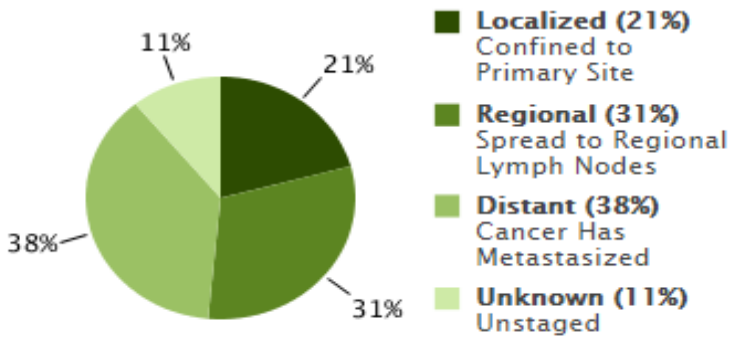
Özofagus Kanserinde Tedavi Yaklaşımları

Survival by Stage

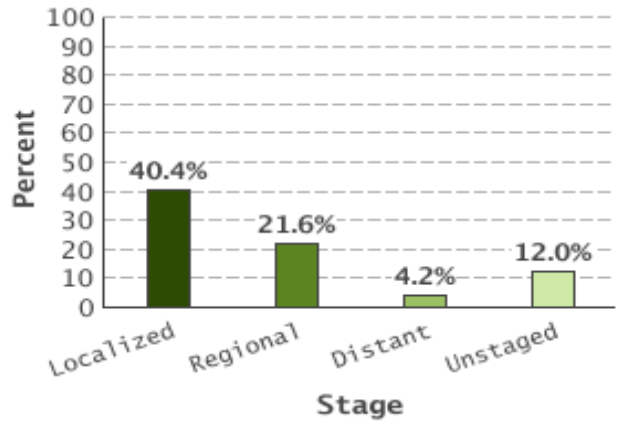
Cancer stage at diagnosis, which refers to extent of a cancer in the body, determines treatment options and has a strong influence on the length of survival. In general, if the cancer is found only in the part of the body where it started it is *localized* (sometimes referred to as stage 1). If it has spread to a different part of the body, the stage is *regional* or *distant*. The earlier esophageal cancer is caught, the better chance a person has of surviving five years after being diagnosed. For esophageal cancer, 20.5% are diagnosed at the local stage. The 5-year survival for localized esophageal cancer is 40.4%.

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

Percent of Cases by Stage



5-Year Relative Survival



SEER 18 2005-2011, All Races, Both Sexes by SEER Summary Stage 2000

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

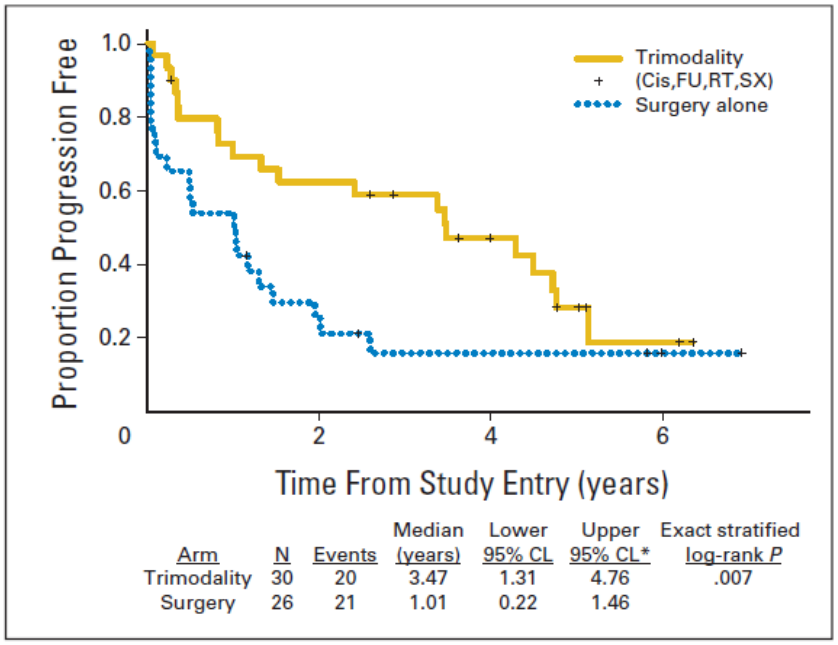
Table 1. CALGB 9781: Patient Characteristics

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 χ^2 test for categorical variables and the Van der Waerden (normal) scores for continuous variables.

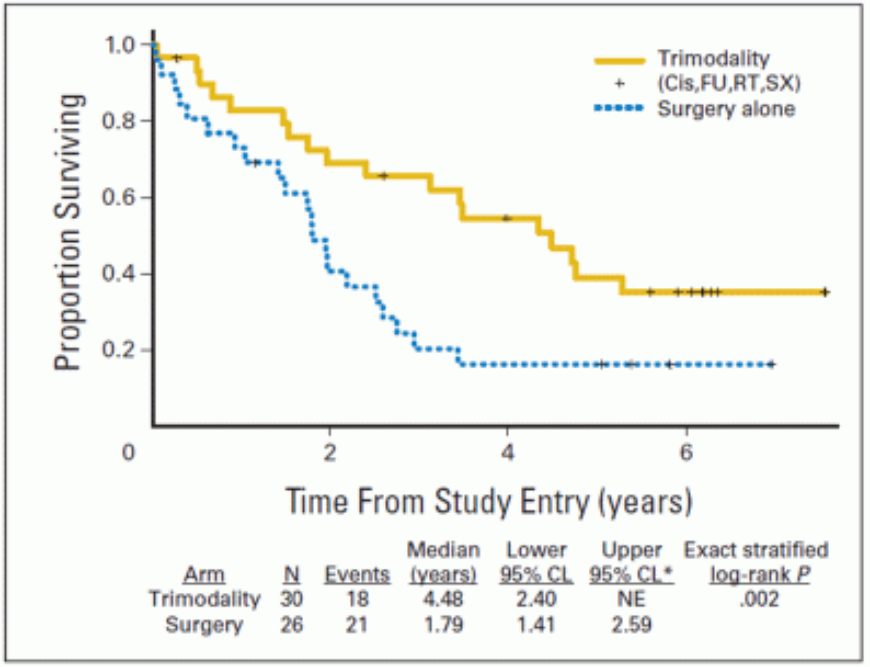
Patients with histologically documented untreated squamous cell carcinoma or adenocarcinoma of the thoracic esophagus (below 20 cm) or gastroesophageal junction and with less than 2cm distal spread into the gastric cardia were eligible

Özofagus Kanserinde Tedavi Yaklaşımları
Cerrahi Öncesi KRT-Cerrahi



Arm	N	Events	Median (years)	Lower 95% CL	Upper 95% CL*	Exact stratified log-rank *P*
Trimodality	30	20	3.47	1.31	4.76	.007
Surgery	26	21	1.01	0.22	1.46	

Fig 3. Kaplan-Meier estimates of progression-free survival (PFS) by treatment arm measured from study entry until documented progression of disease or death from any cause. (*) NE, not estimable. †Asymptotic results for PFS were comparable to those obtained using the exact method.



Arm	N	Events	Median (years)	Lower 95% CL	Upper 95% CL*	Exact stratified log-rank *P*
Trimodality	30	18	4.48	2.40	NE	.002
Surgery	26	21	1.79	1.41	2.59	

Fig 2. Kaplan-Meier estimates of overall survival (OS) by treatment arm measured from study entry until death from any cause. (*) NE, not estimable. †Asymptotic results for OS were comparable to those obtained using the exact method.

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

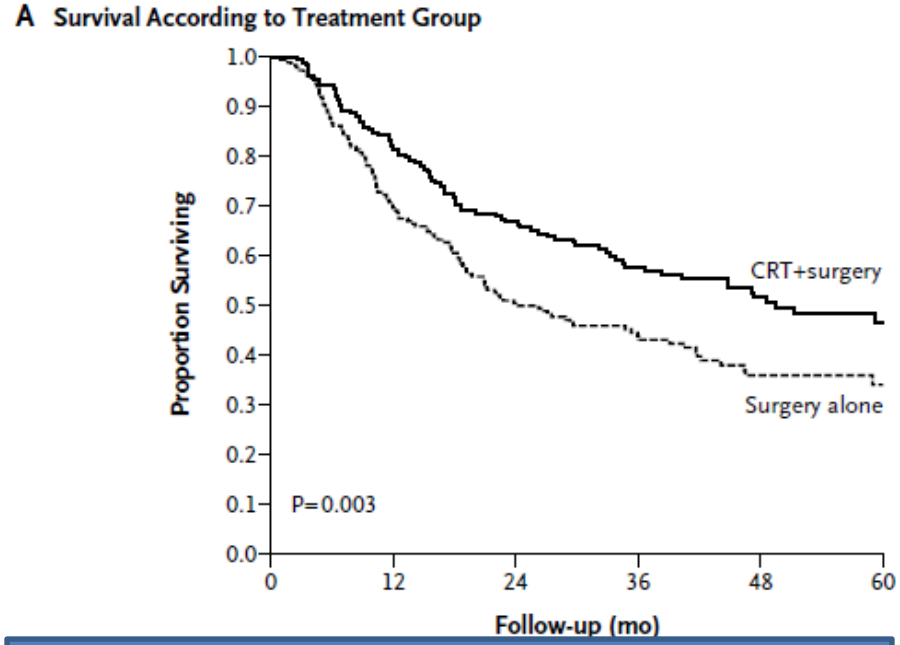
- The length and width of the tumor could not exceed 8 cm and 5 cm, respectively.

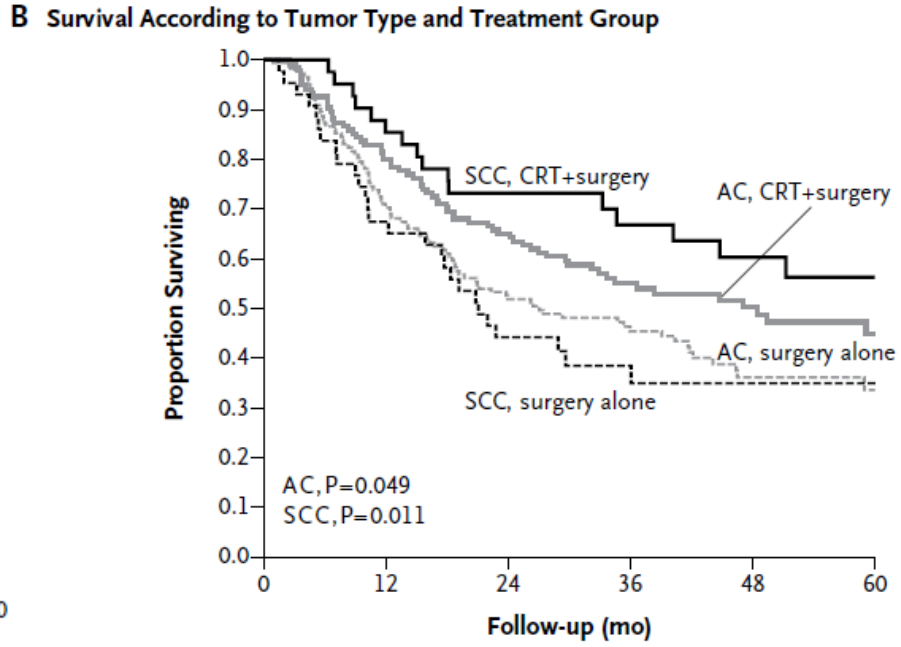
Özofagus Kanserinde Tedavi Yaklaşımları
Cerrahi Öncesi KRT-Cerrahi

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





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

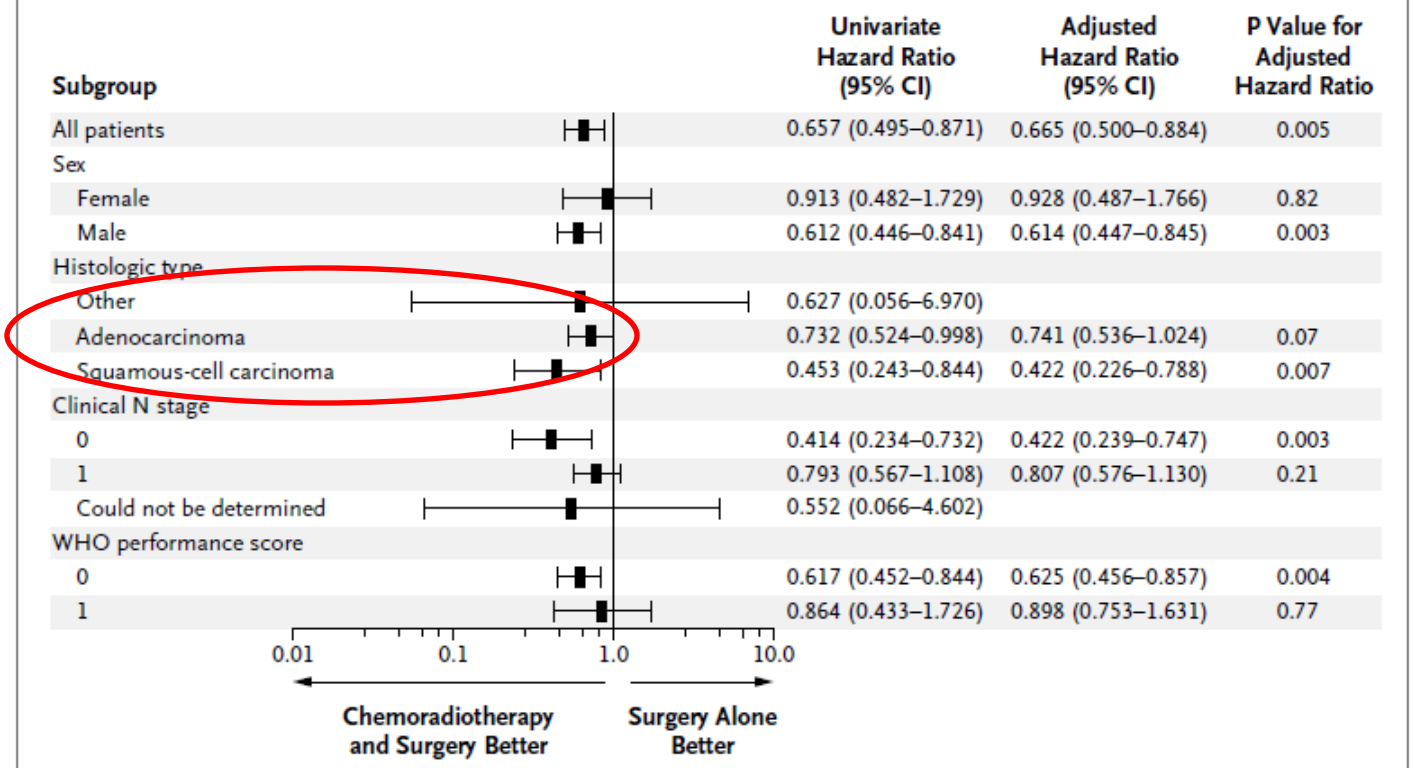


Figure 3. Hazard Ratios for Death.

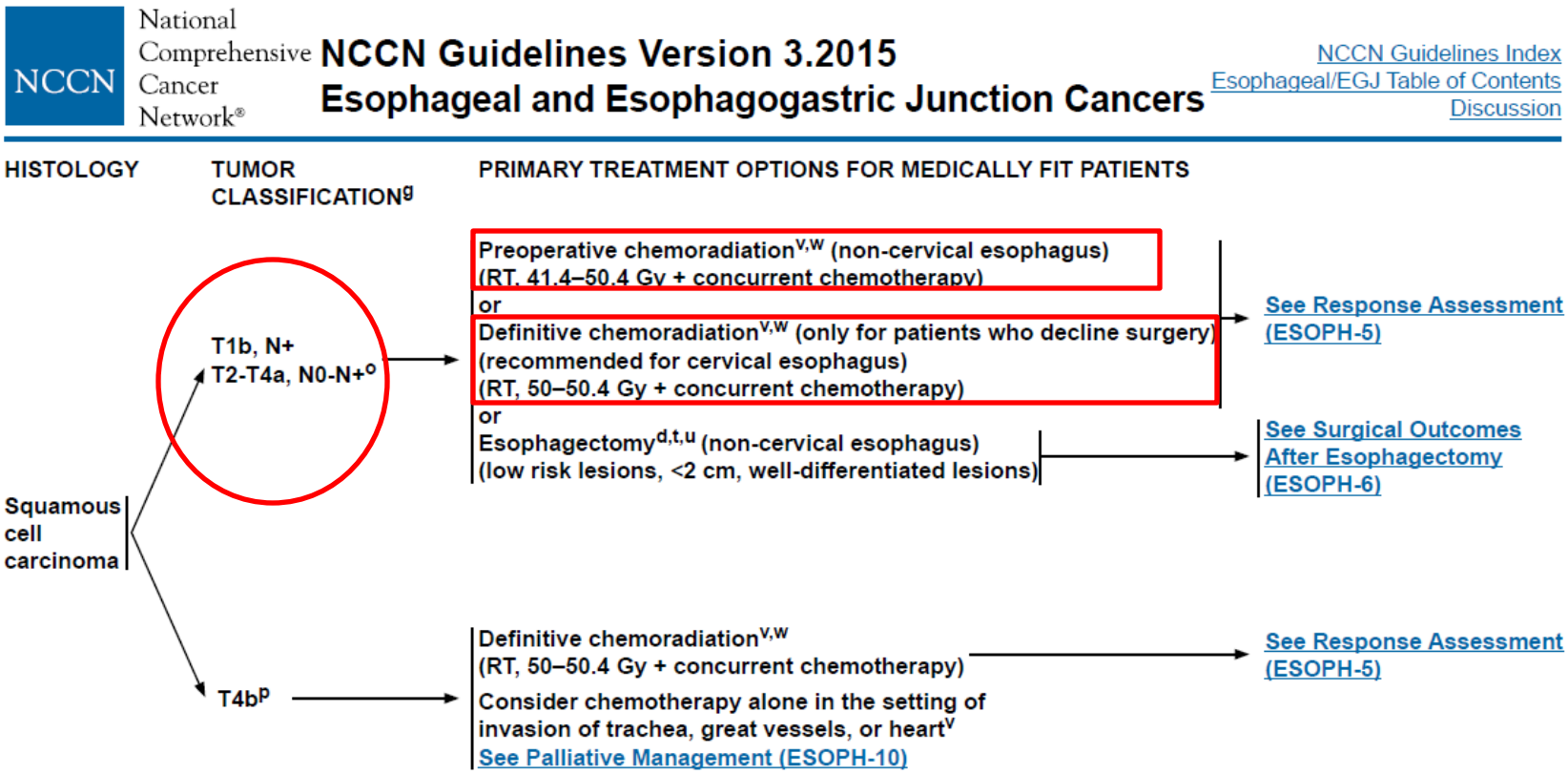
This forest plot shows hazard ratios for death (oblongs) and 95% confidence intervals (I bars) for 366 patients with esophageal or esophagogastric-junction cancer, according to baseline characteristics. Univariate hazard ratios are shown, as well as hazard ratios adjusted for baseline covariates. Clinical 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]

Özofagus Kanserinde Tedavi Yaklaşımları
Cerrahi Öncesi KRT-Cerrahi

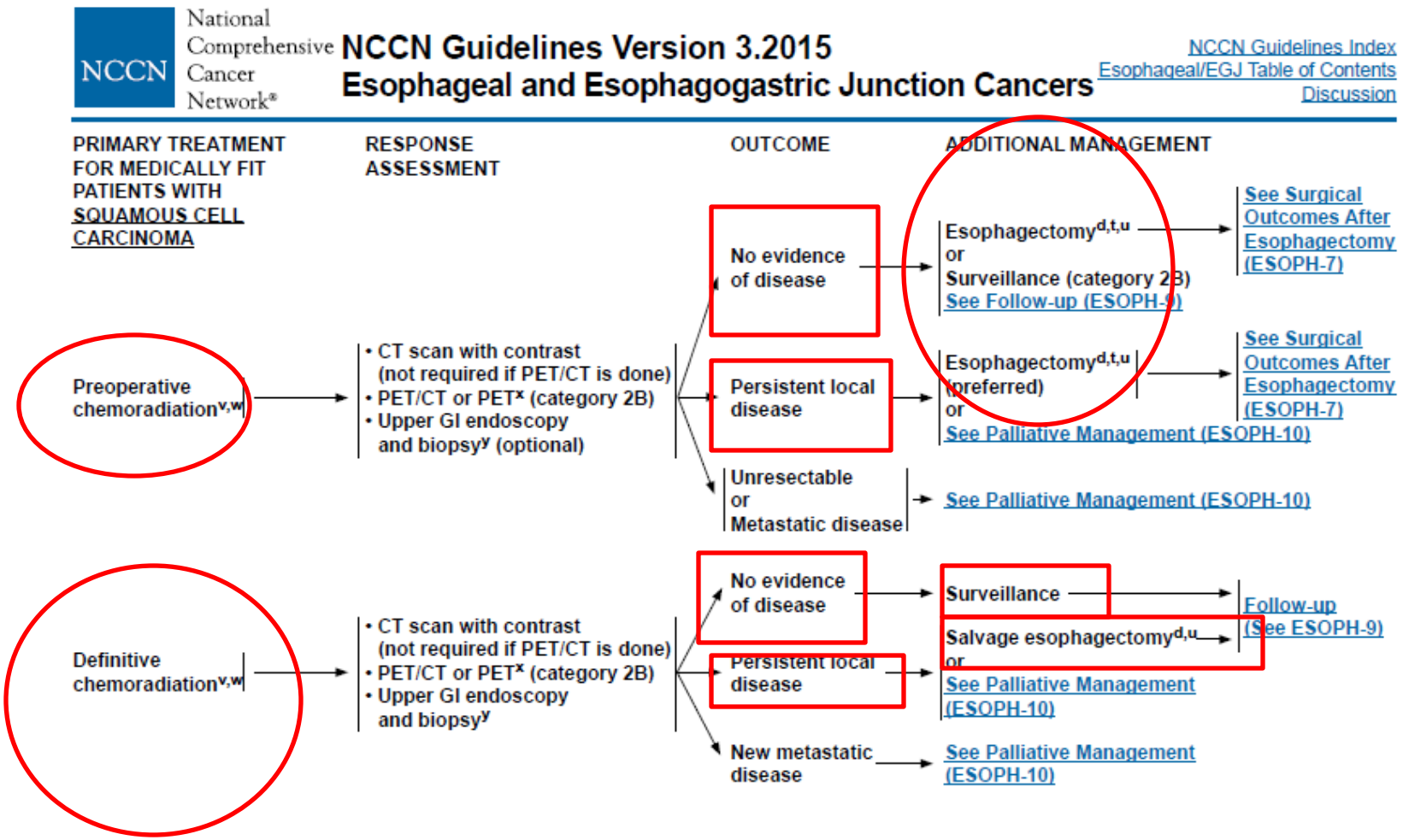
Table 2. Adverse Events during Neoadjuvant Chemoradiotherapy and after Surgery.*

Event	Chemoradiotherapy and Surgery (N=171)	Surgery Alone (N=186)
Postoperative events — no. of patients/total no. (%)†		
Pulmonary complications‡	78/168 (46)	82/186 (44)
Cardiac complications§	36/168 (21)	31/186 (17)
Chylothorax¶	17/168 (10)	11/186 (6)
Mediastinitis‖	5/168 (3)	12/186 (6)
Anastomotic leakage**	36/161 (22)	48/161 (30)
Death		
In hospital	6/168 (4)	8/186 (4)
After 30 days	4/168 (2)	5/186 (3)
Events of any grade during chemoradiotherapy — no. of patients (%)		
Anorexia	51 (30)	
Alopecia	25 (15)	
Constipation	47 (27)	
Diarrhea	30 (18)	
Esophageal perforation	1 (1)	
Esophagitis	32 (19)	
Fatigue	115 (67)	
Nausea	91 (53)	
Neurotoxic effects	25 (15)	
Vomiting	43 (25)	
Leukopenia	103 (60)	
Neutropenia	16 (9)	
Thrombocytopenia	92 (54)	

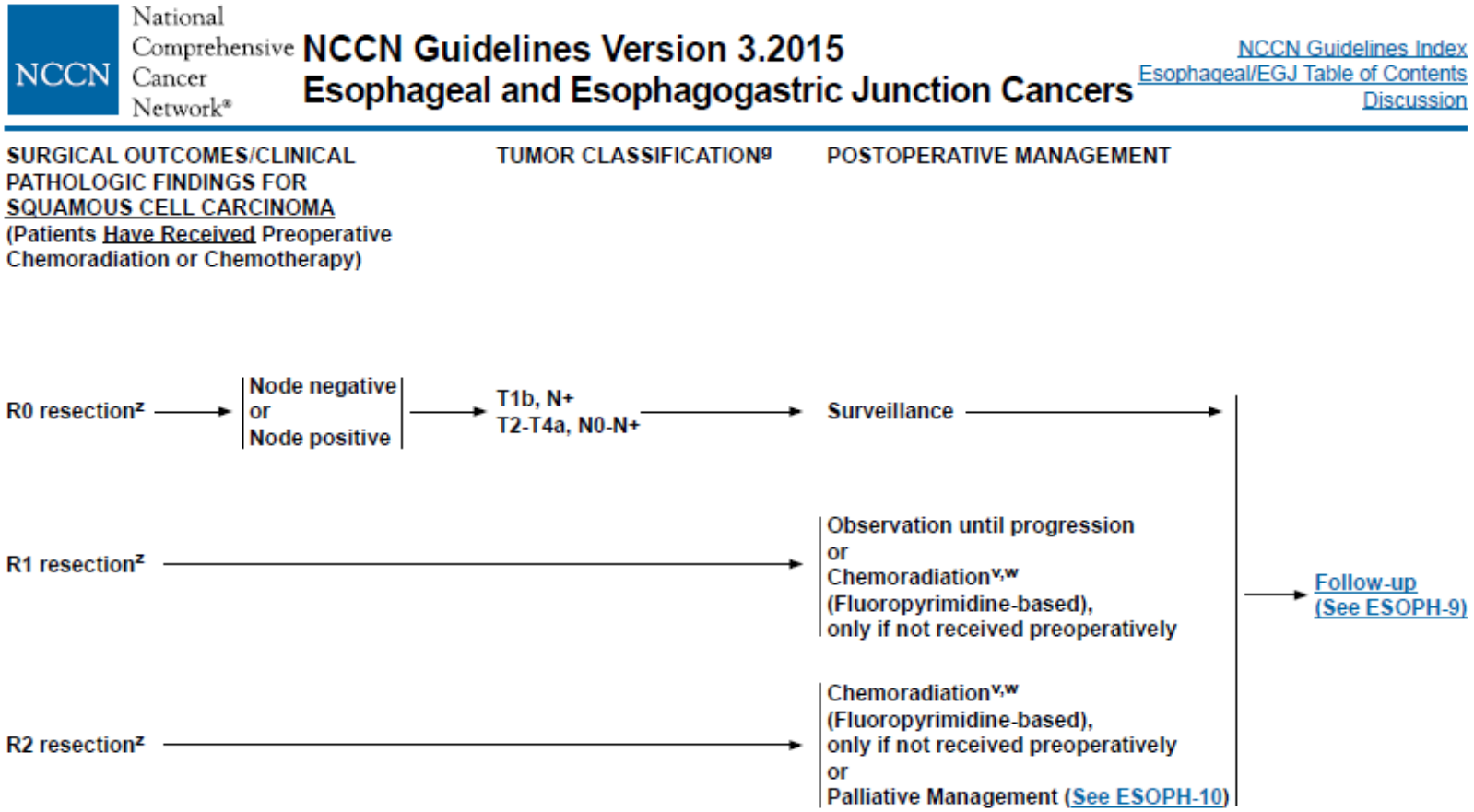
Özofagus Kanseri Tedavi



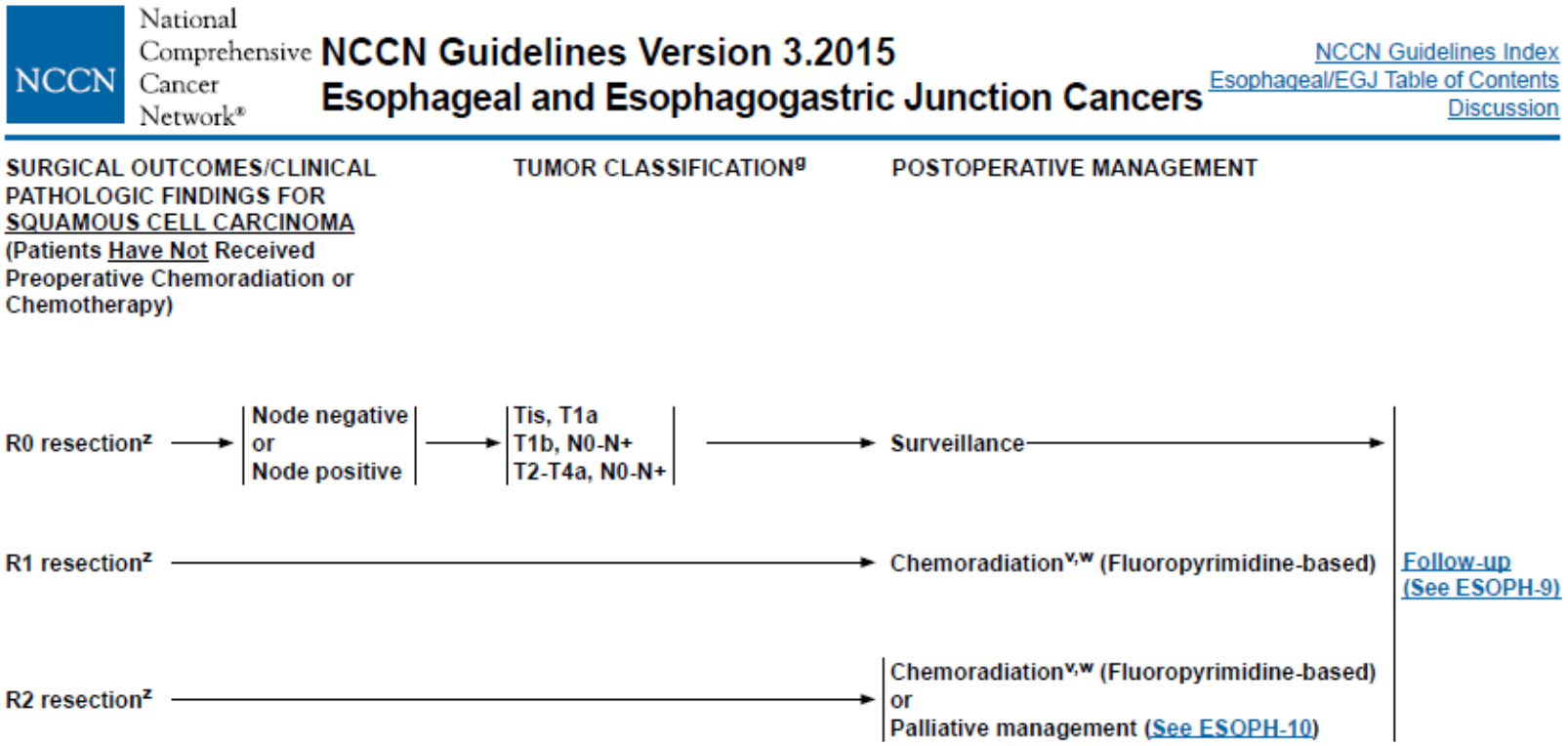
Özofagus Kanseri Tedavi



Özofagus Kanseri Tedavi



Özofagus Kanseri Tedavi



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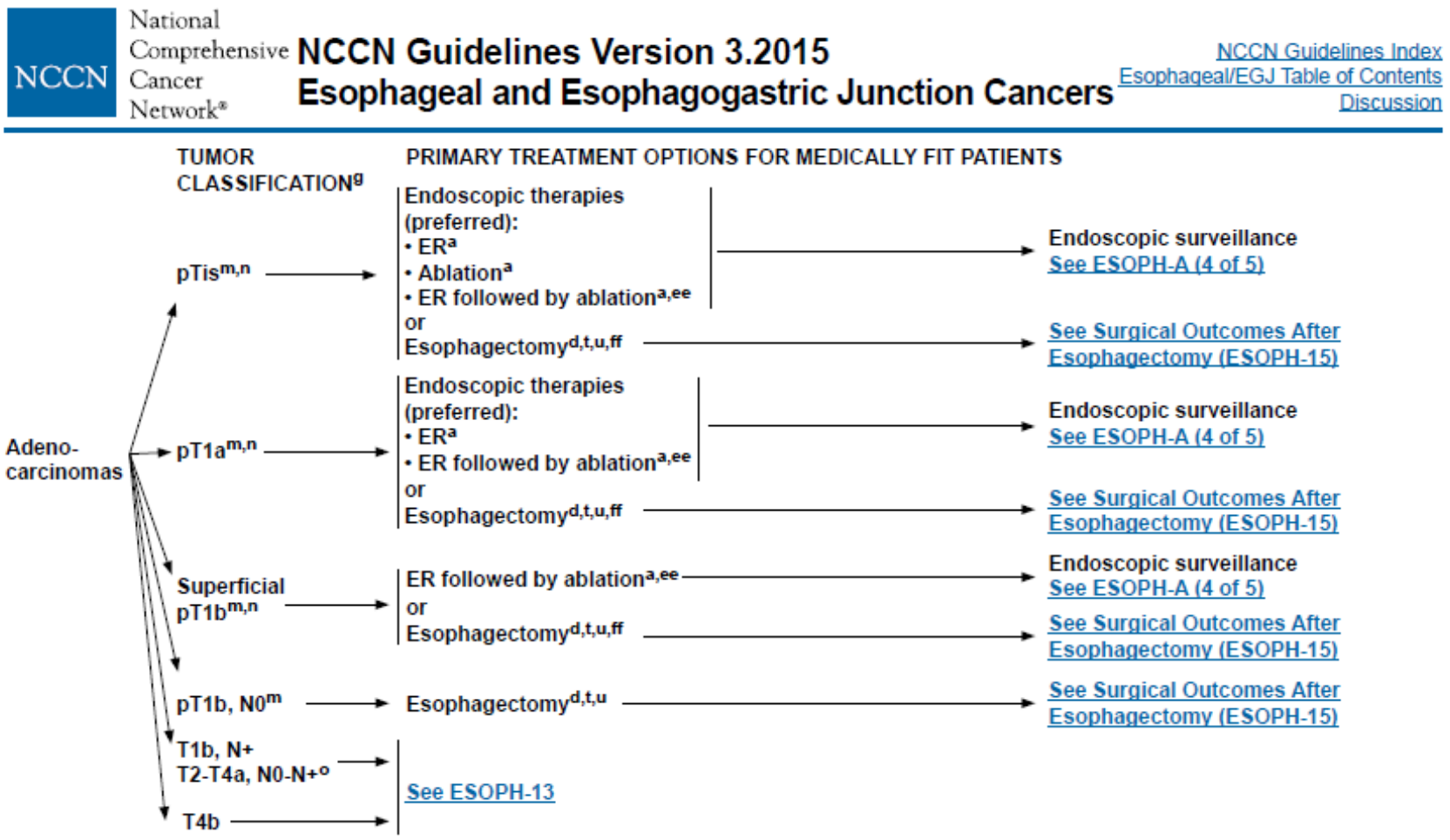

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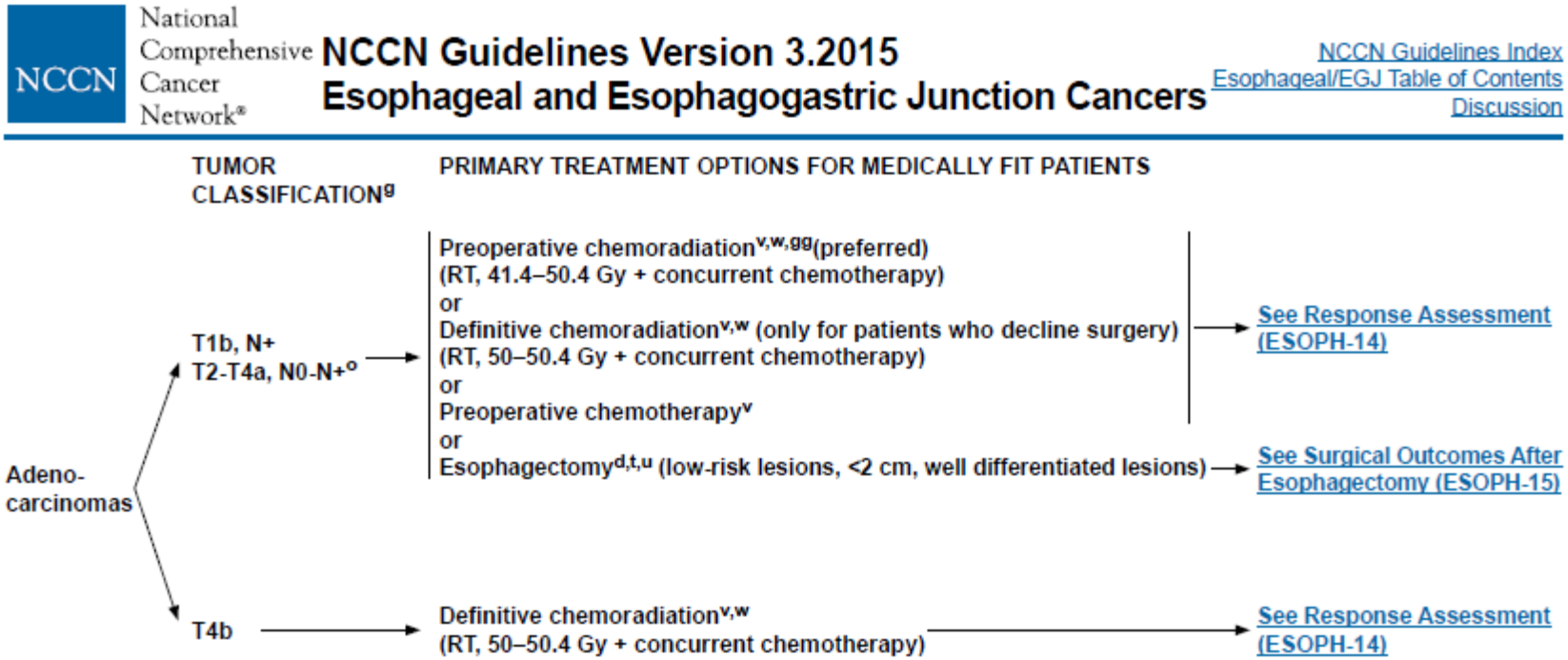

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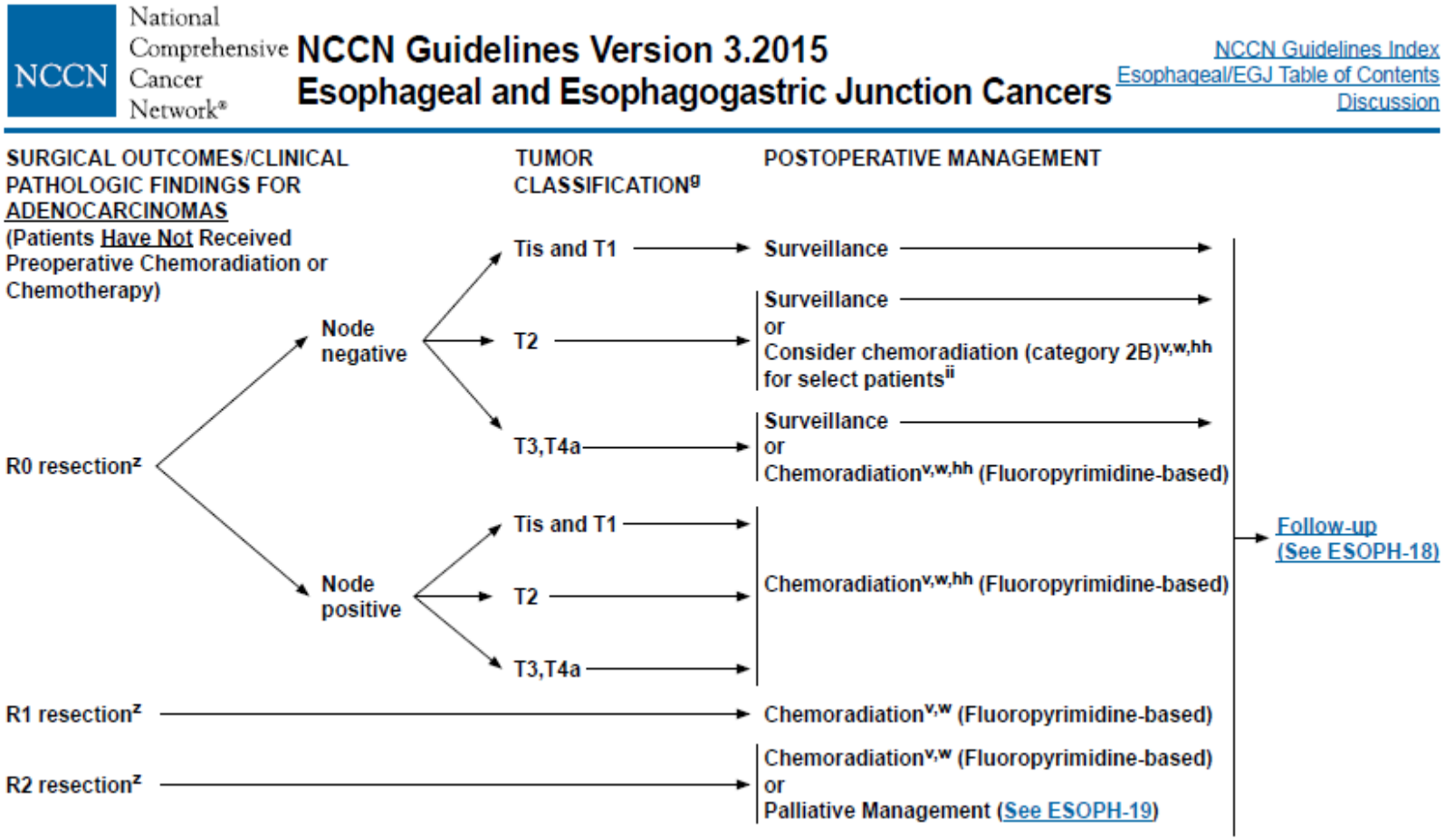

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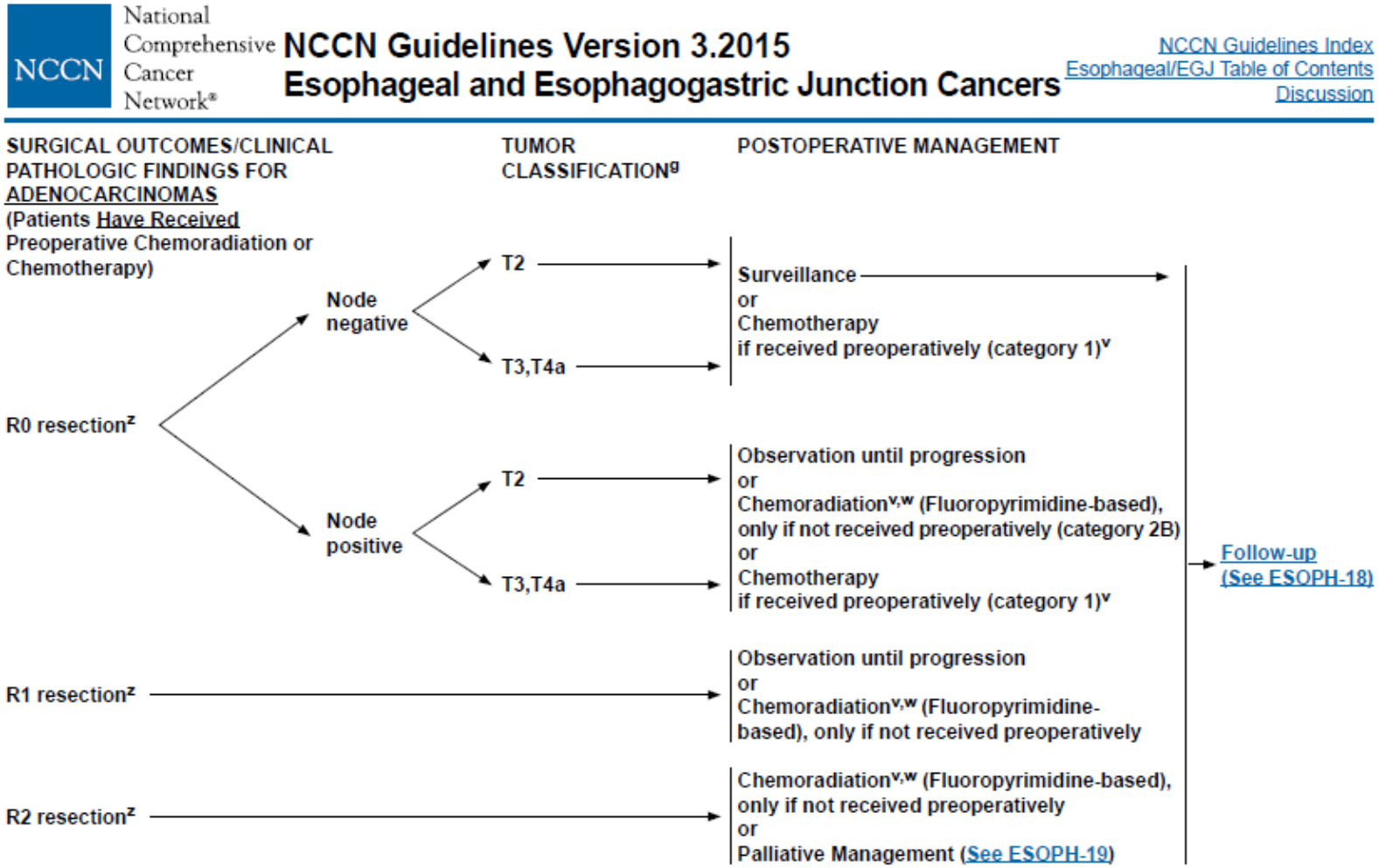


Aşağıdakilerden hangisi skuamöz hücreli özofagus kanseri için risk faktörü değildir?

A-Plummer-Vinson sendromu

B-Gasto-özofageal reflü

C-Akalazya

D-Tilozis

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

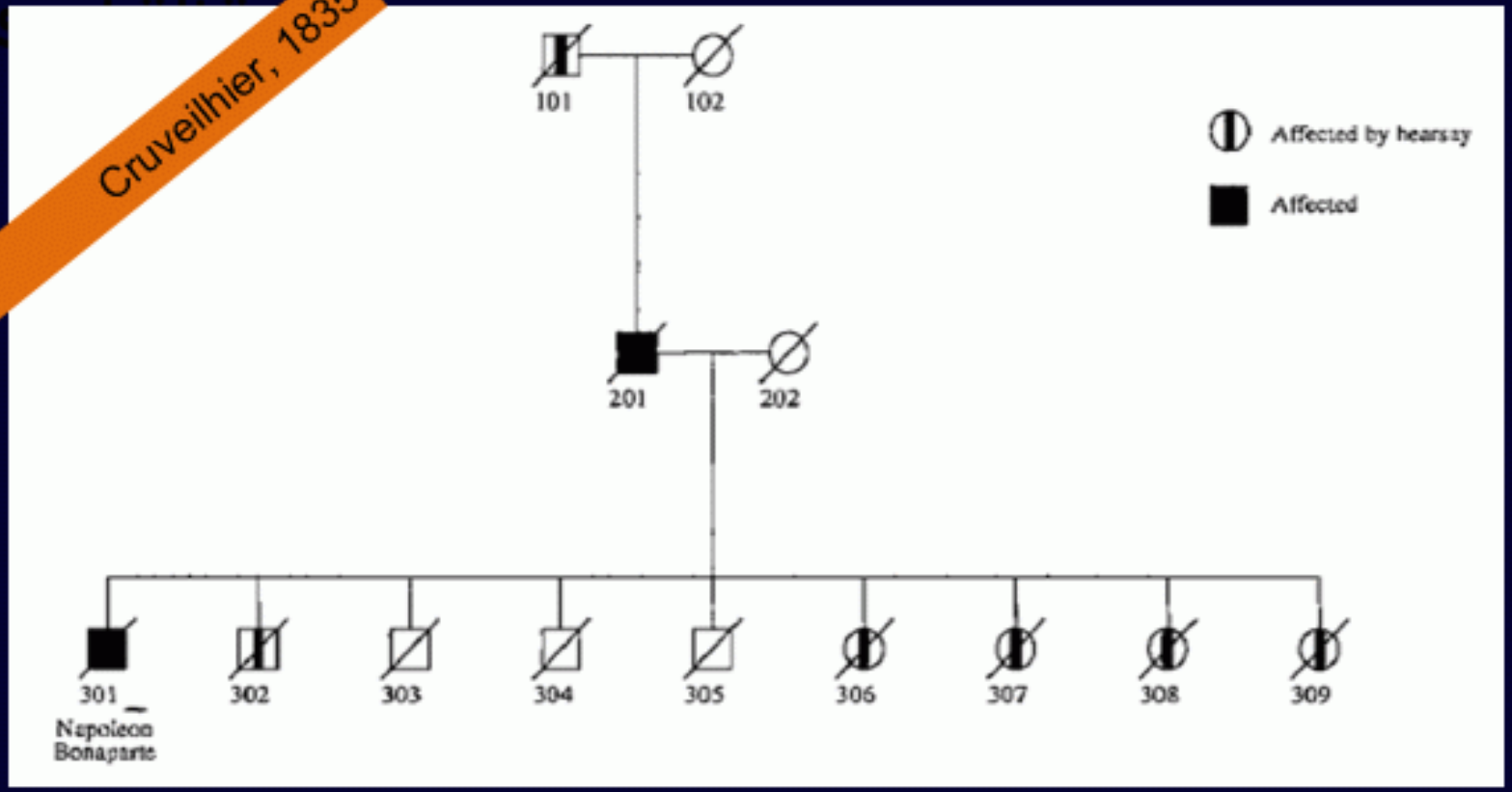
Risk Faktörleri

Sos

MİDE KANSERLERİ

Risk Faktörleri

Cruveilhier, 1835



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 Eating Fruits / Vegetables (OR ~0.7) Tobacco (OR ~1.5) Age (peak at age 50-70)
	Clinical	*H. pylori* infection (OR ~3.0) Use of NSAIDs/ Aspirin
	Genetic	Immune regulatory SNPs
Diffuse Gastric Cancer	Environmental	none specifically identified
	Clinical	*H. pylori* infection
	Genetic	*CDH1* mutation Family history (non- *CDH1* mutant)
Proximal Gastric Cancer	Environmental	Tobacco Use Alcohol
	Clinical	Obesity/ High BMI 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 Tobacco (OR: ~ 1.5) 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 Family history (no *CDH1* mutation)	
Proximal gastric cancer	Environmental	Tobacco Alcohol	
	Clinical	Obesity/high BMI GERD	
	Genetic	None specifically identified	

Shah MA, et al. J NCCN 2010

Mide Kanseri Risk Faktörleri

Gastric Cancer Risk Factors

- H. pylori infection – cagA strain only
  - OR 2.54, 95% CI 1.77 – 3.66
  - ? Role of Host genetic polymorphisms?
    - IL-1, IL-10, IL-4
  - Bone Marrow Derived Stem Cells
- Tobacco use
  - OR 1.91, 95% CI 1.25 – 2.93
- Family history
  - OR 3.67, 95% CI 2.01 – 6.71

640

Garcia-Gonzalez et al, Am J Gastroenterol 2007
El Omar et al, Nature 2000

Mide Kanseri Risk Faktörleri

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

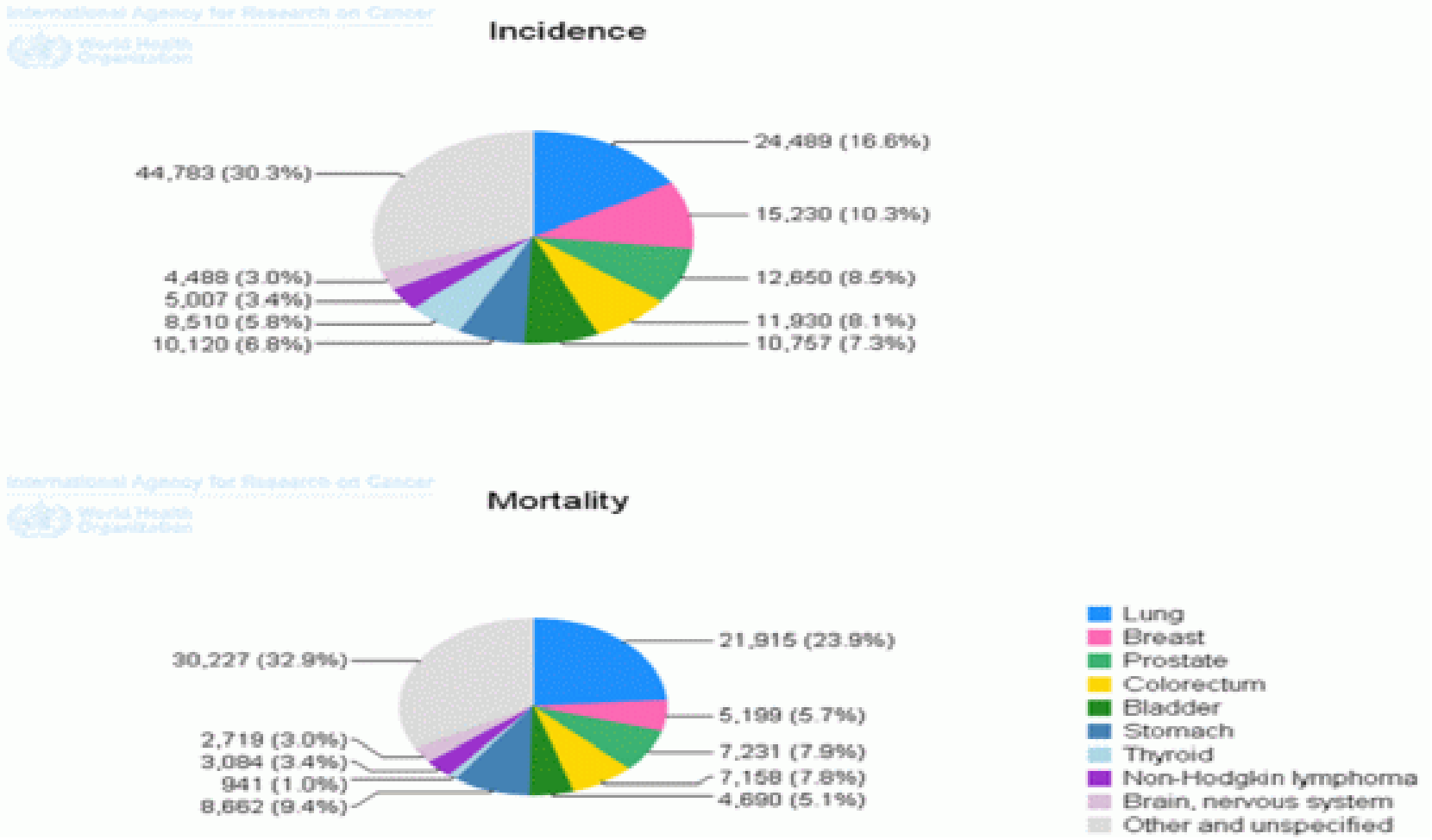
- Hereditary Diffuse GC (~3-5%)
- Lynch Syndrome (~1-2%)
  - germline mutations in one of the mismatch repair genes *MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2*
  - *Stomach cancers occur in ~11% of Lynch syndrome families*
- FAP (Familial Adenomatous Polyposis) (~1%)
  - *Germline mutation in APC – adenomatous 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

Epidemiyoloji

GLOBOCAN 2012-

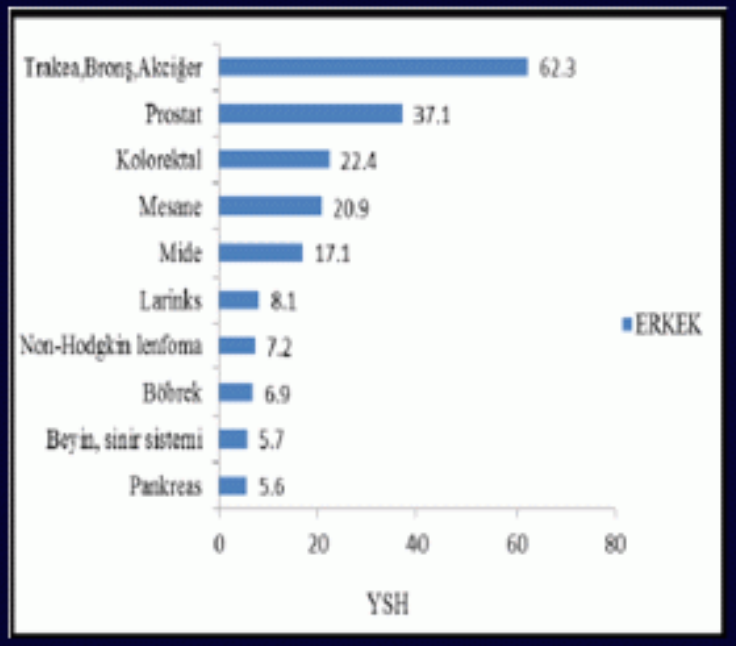
Türkiye

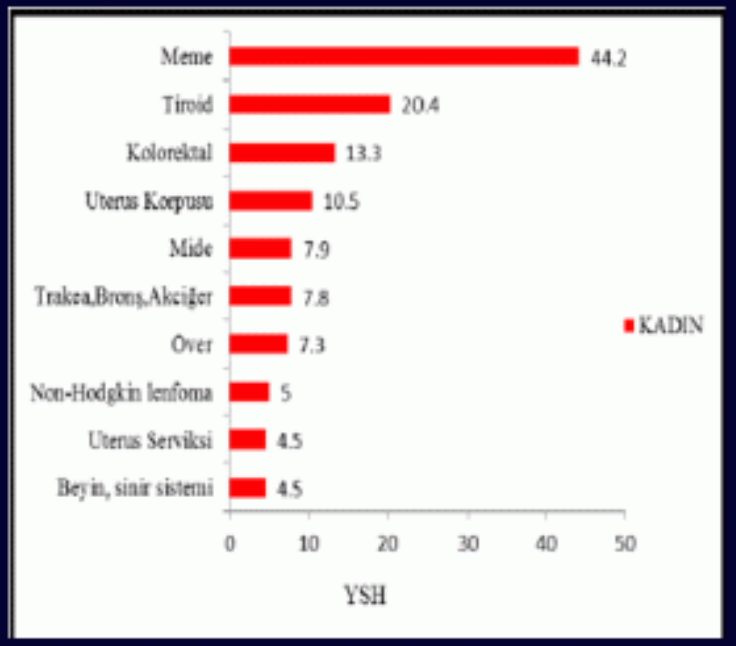


Mide Kanseri İnsidans ve Mortalite

Epidemiyoloji Türkiye 2011

verileri

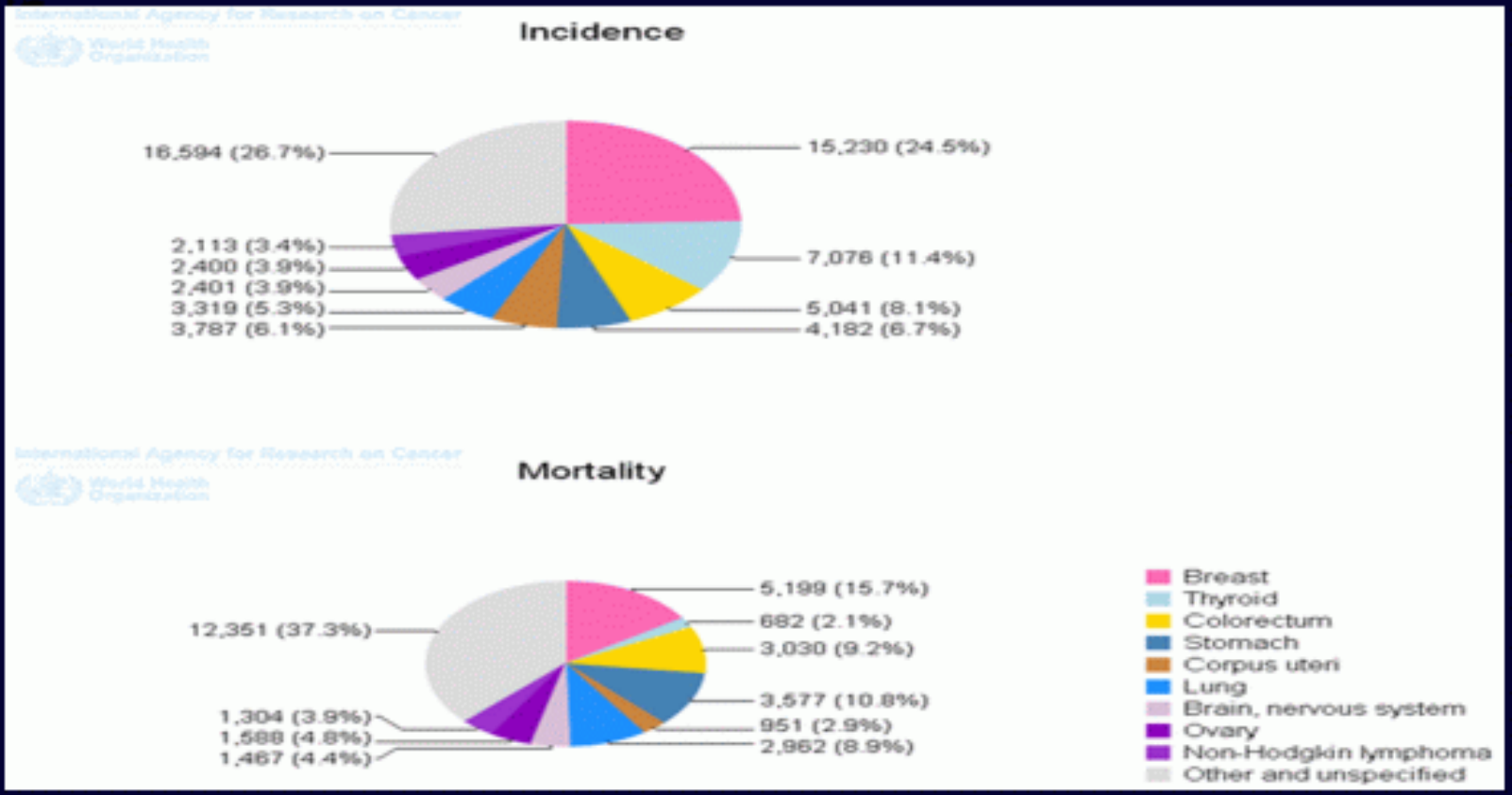




En sık 10 tümörün yaşa göre standardize edilmiş hızları (100.000 kişide)

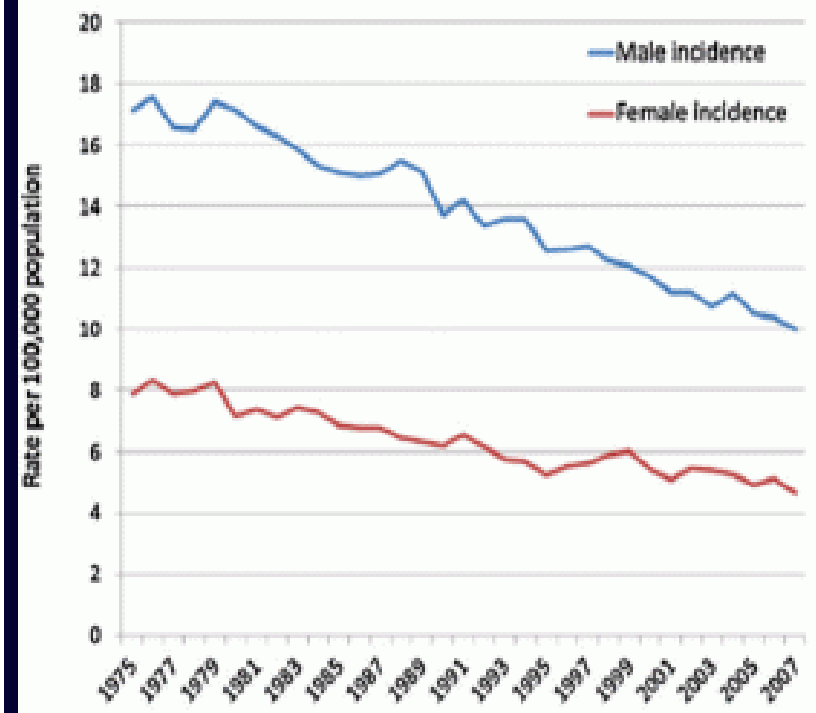
Mide Kanseri İnsidans ve Mortalite

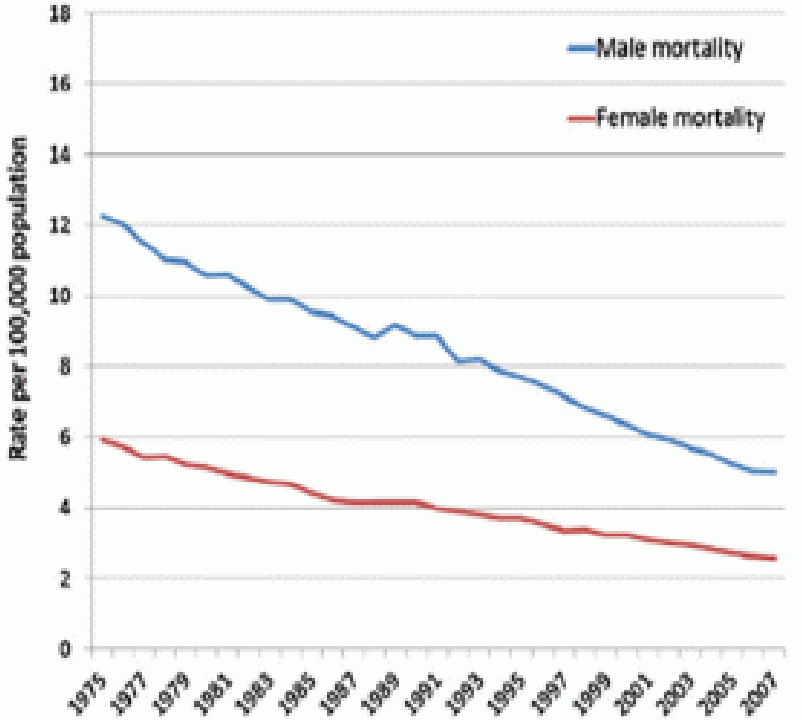
Epidemiyoloji GLOBOCAN 2012-Türkiye-Kad



Mide Kanseri İnsidans ve Mortalite

Guggenheim and Shah





Medinfographics 2012

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

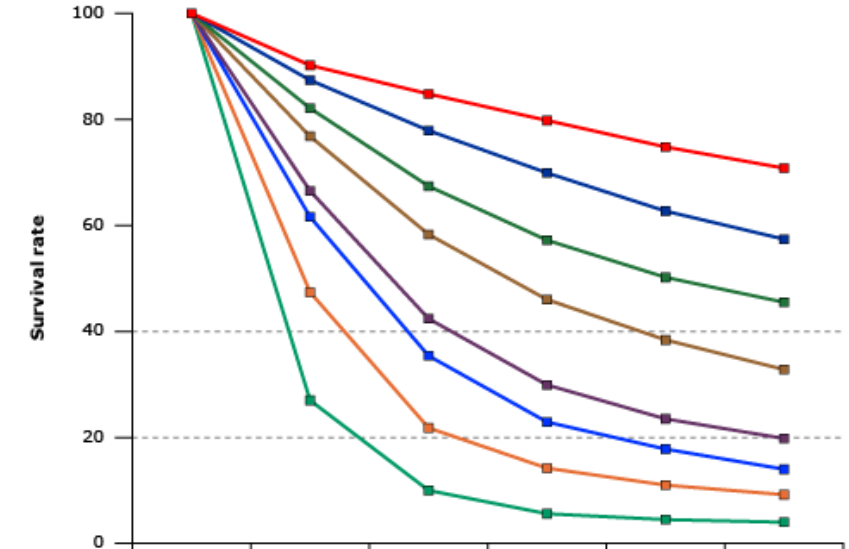
- PET-CT, BT Göre %10(≥T3, N+ daha fazla uzak metastaz tespiti ve tedavi değişimi. Diffüz ve müsinöz gastrik kanserlerde FDG tutulumu oranı düşük. Periton metastaz saptama oranı %50.

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

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

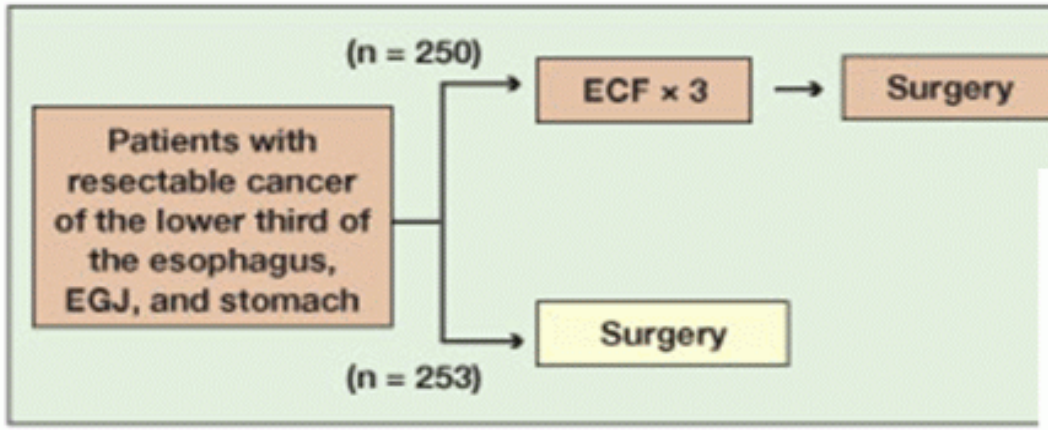
The NEW ENGLAND JOURNAL of MEDICINE

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

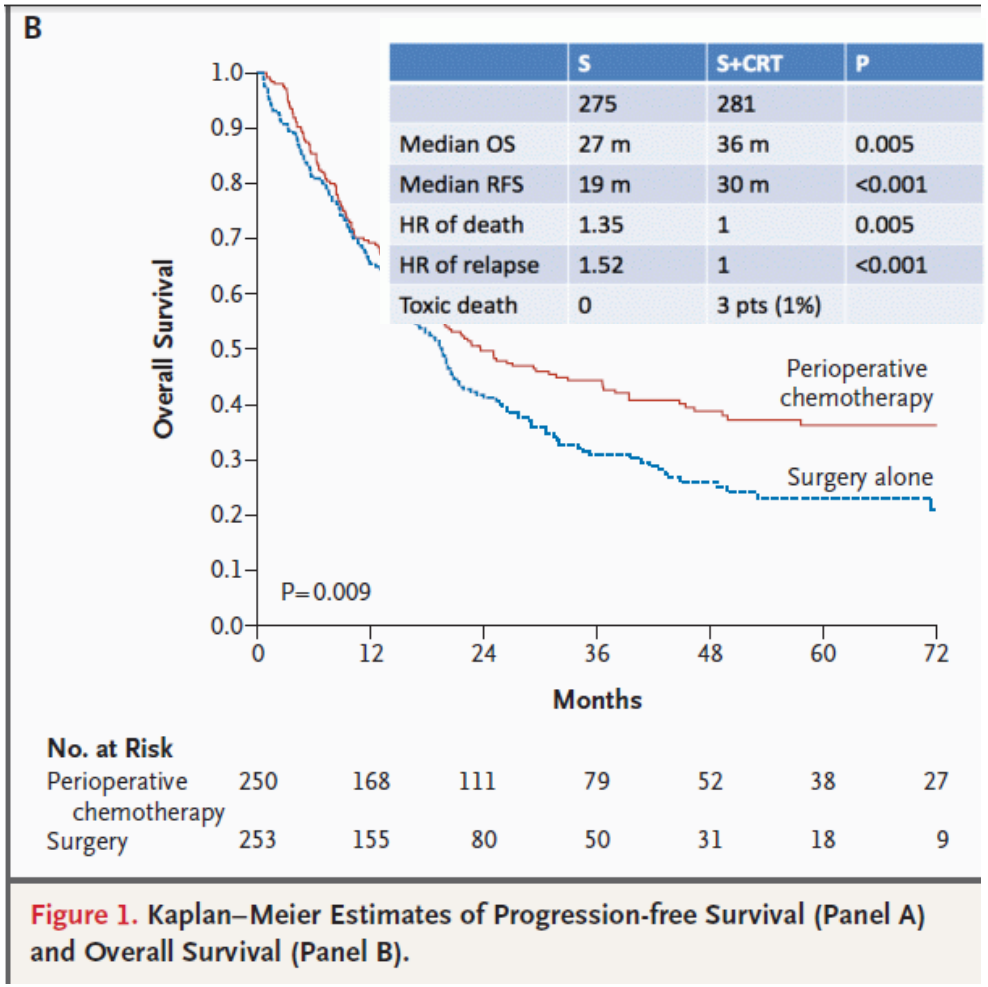


Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

Mide Kanseri Tedavi
Kemoterapi Sonrası Cerrahi

Variable	Perioperative Chemotherapy (no. of deaths/total no.)	Surgery Alone (no. of deaths/total no.)	Hazard Ratio
Age			P for trend=0.43
<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			P for interaction=0.50
Male	126/205	127/191	
Female	23/45	43/62	
Total	149/250	170/253	
WHO performance status			P for interaction=0.63
0	93/169	112/173	
1	56/81	58/80	
Total	149/250	170/253	
Site of primary tumor			P for interaction=0.25
Lower esophagus	23/37	25/36	
Esophagogastric junction	13/28	23/30	
Stomach	113/185	122/187	
Total	149/250	170/253	

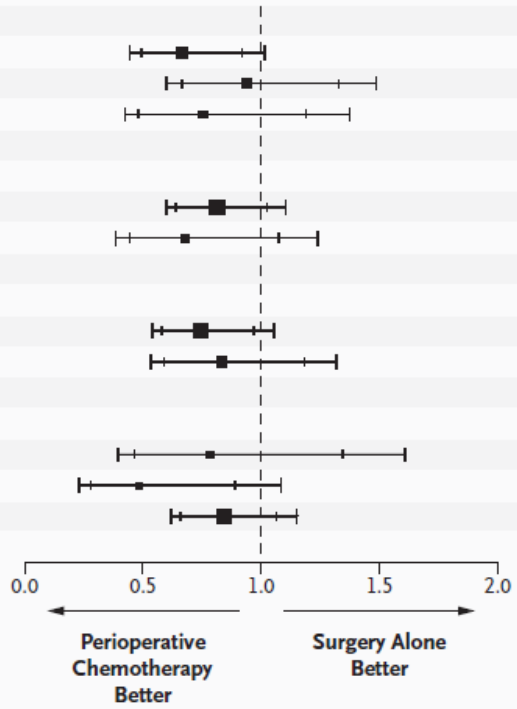
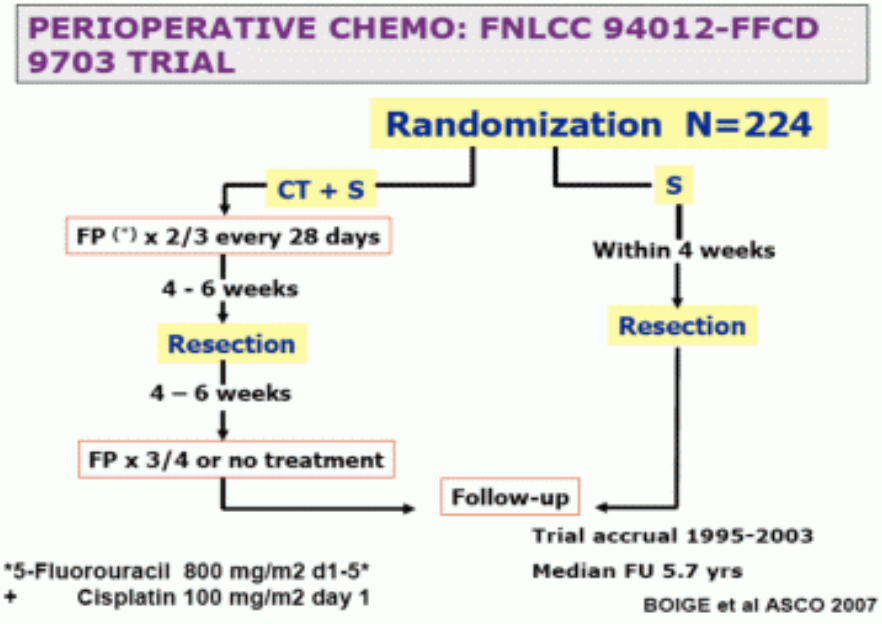


Figure 2. Tests for Heterogeneity of Treatment Effect According to the Baseline Characteristics of the Patients.
The hazard ratios show 95 percent (inner tick marks) and 99 percent (outer tick marks) confidence intervals.

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



Mide Kanseri Tedavi
Kemoterapi Sonrası Cerrahide Kanseri Tedavi

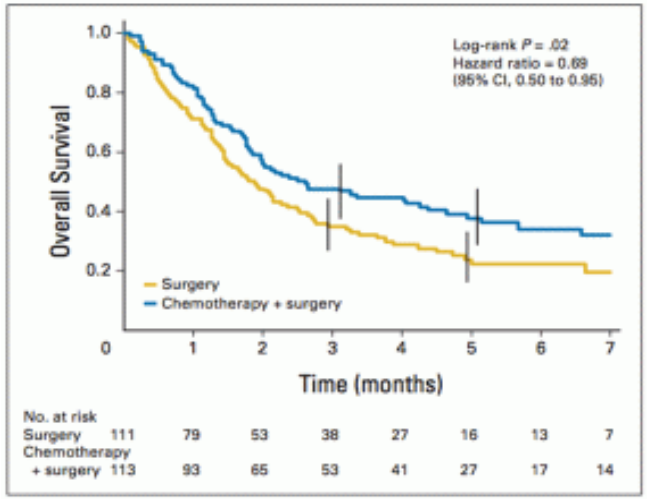


Fig 2. Kaplan-Meier curve showing overall survival from date of random assignment.

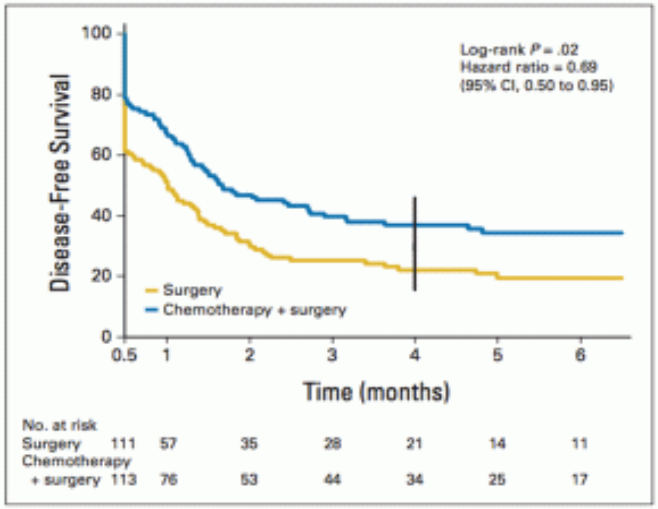


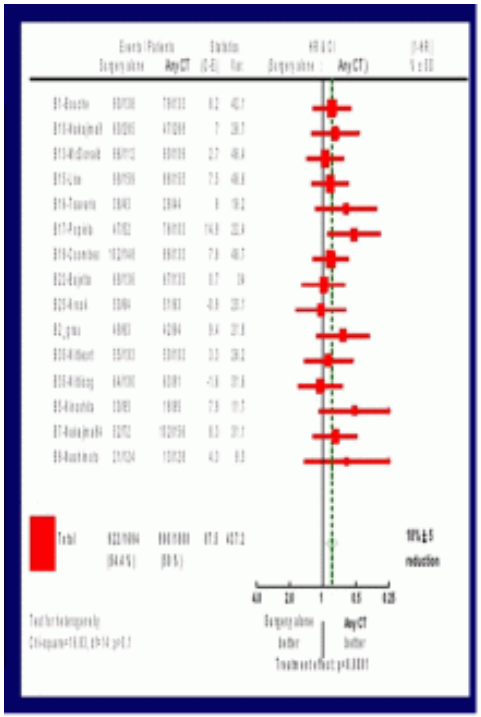
Fig 3. Kaplan-Meier curve showing disease-free survival from landmark time of 6 months after the date of random assignment.

Mide Kanseri Tedavi
Kemoterapi Sonrası Cerrahi

SUMMARY OF TRIALS OF PERIOPERATIVE CHEMOTHERAPY FOR LOCALIZED GASTRIC CANCER

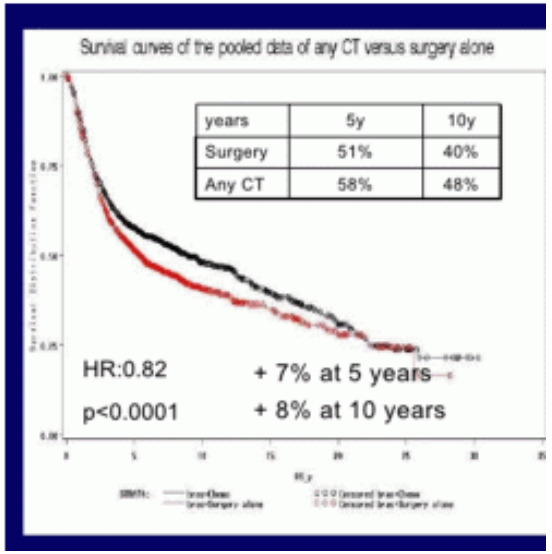
Trial	CT	Nr. Pts Control	Nr. Pts CT	5-year Survival Control	5-year Survival CT	HR (CI at 95%)
Cunningham NEJM 2006	ECF	253 No CT	250	23%	36 %	0.75 0.60-0.93 p=.009
Boige ASCO 2007	CDDP 5-FU	111 No CT	113	24%	38%	0.69 0.50-0.95 p=.021

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

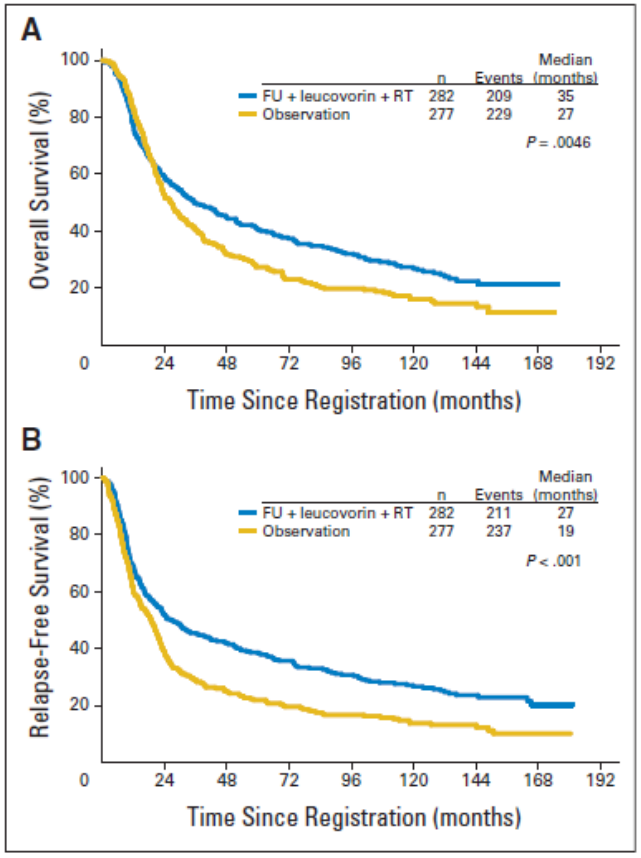
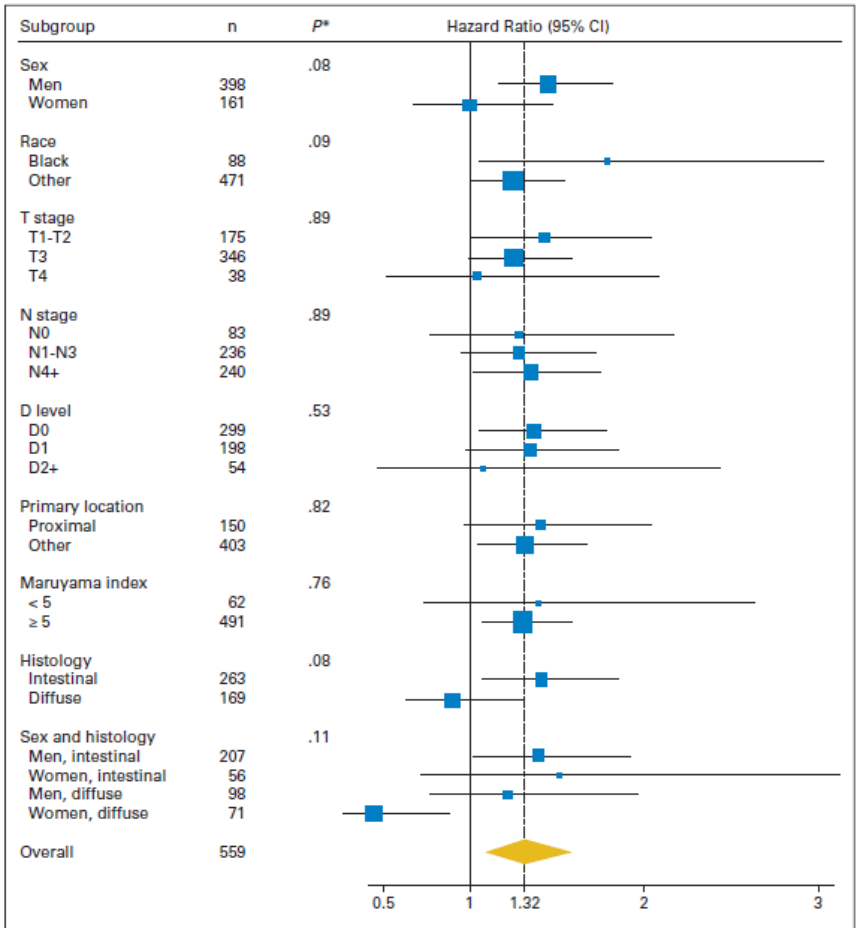


Fig 2. (A) Overall survival by arm; (B) relapse-free survival by arm. FU, fluorouracil; RT, radiotherapy.



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.

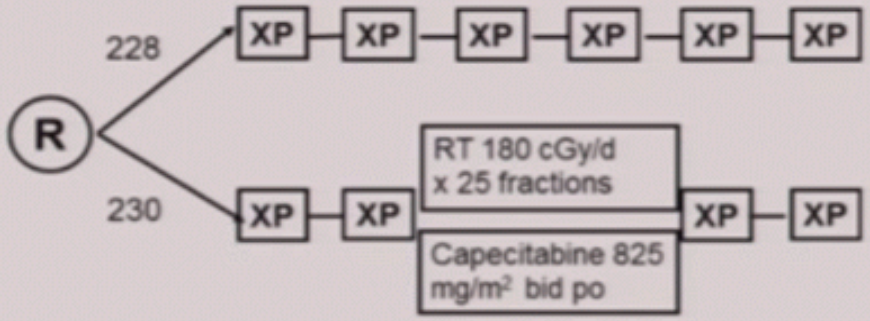
Conclusion
In D2-resected GC, both adjuvant chemotherapy and chemoradiotherapy are tolerated and equally beneficial in preventing relapse. Because results suggest a significant DFS effect of chemoradiotherapy in subsets of patients, the ARTIST 2 trial evaluating adjuvant chemotherapy and chemoradiotherapy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

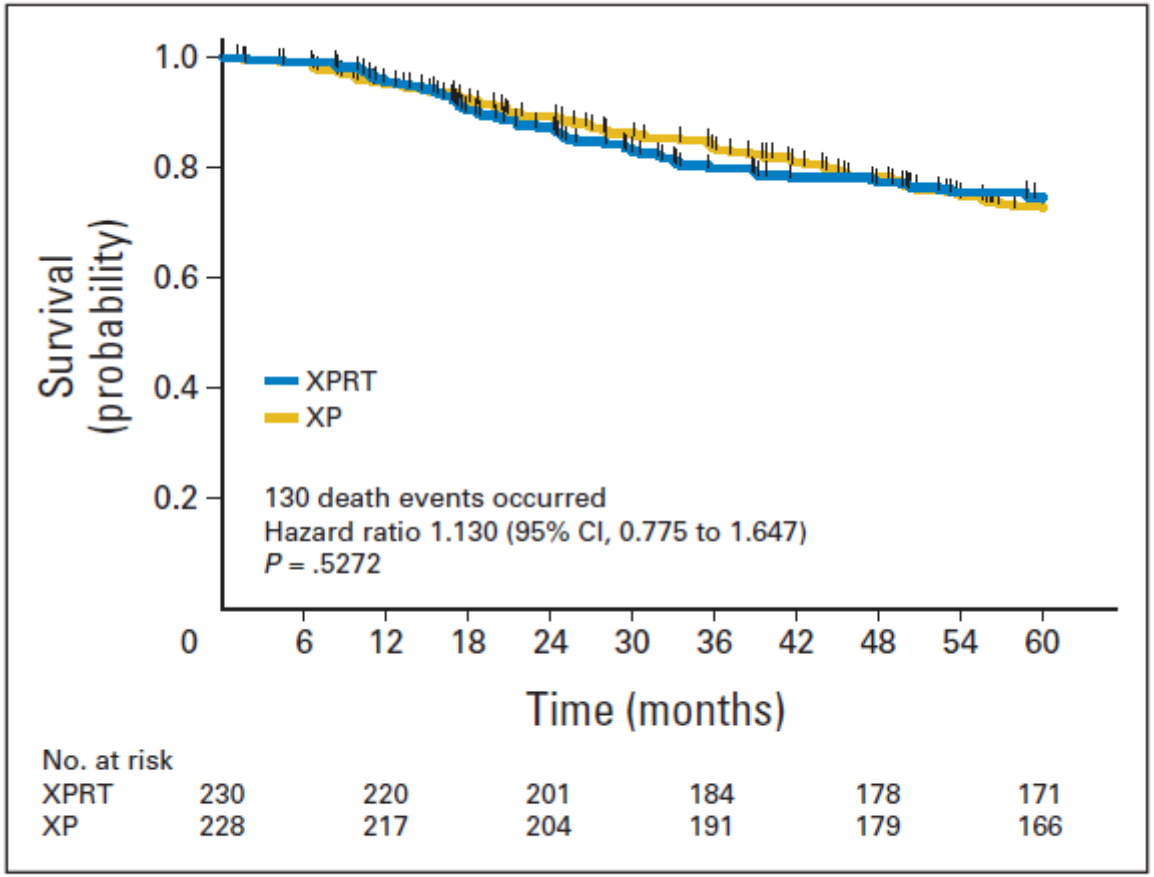


Fig 3. Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Mide Kanseri Tedavi
Cerrahi Sonrası Adjuvan KT? KRT?

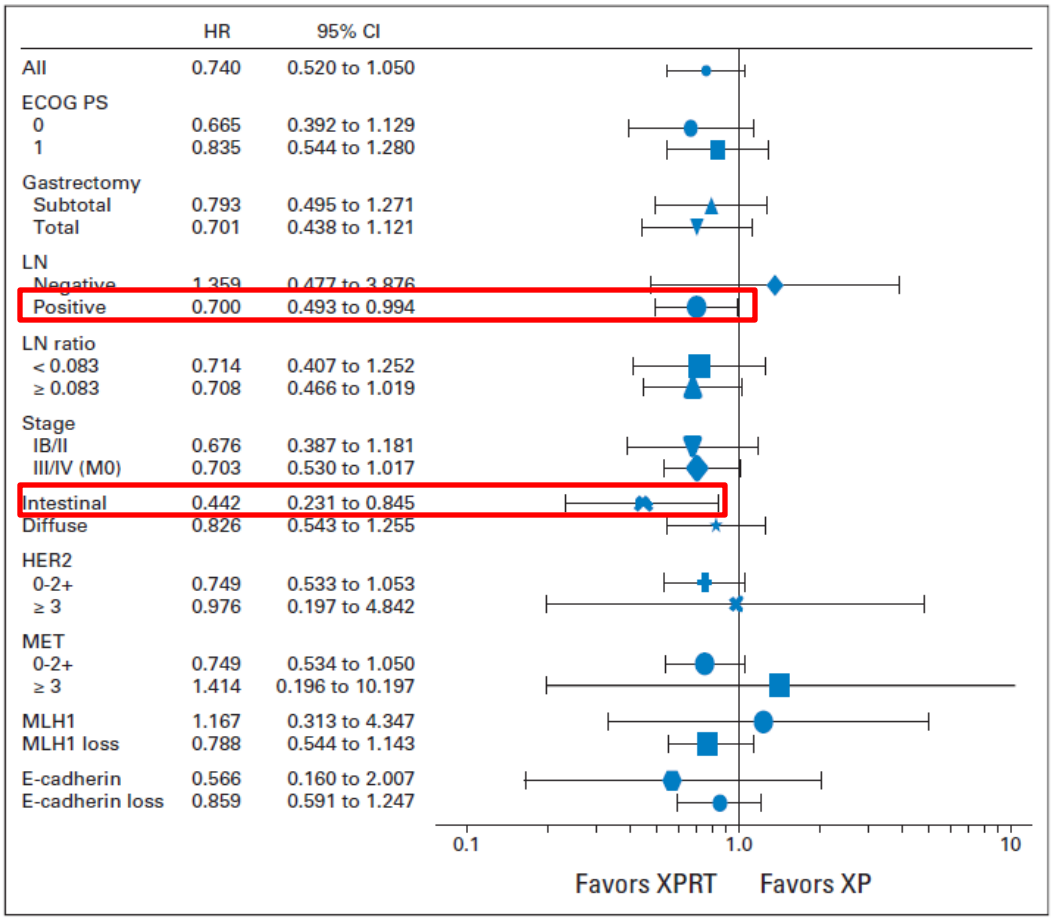


Fig 4. Forest plot of hazard ratios (HRs) and 95% CIs for disease-free survival. ECOG PS, Eastern Cooperative Oncology group performance status; HER2, human epidermal growth factor receptor 2; LN, lymph node; XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

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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, Kaun-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

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See Comment page 291

*Both authors contributed equally

†CLASSIC trial investigators listed at the end of Article

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	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[73] 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**

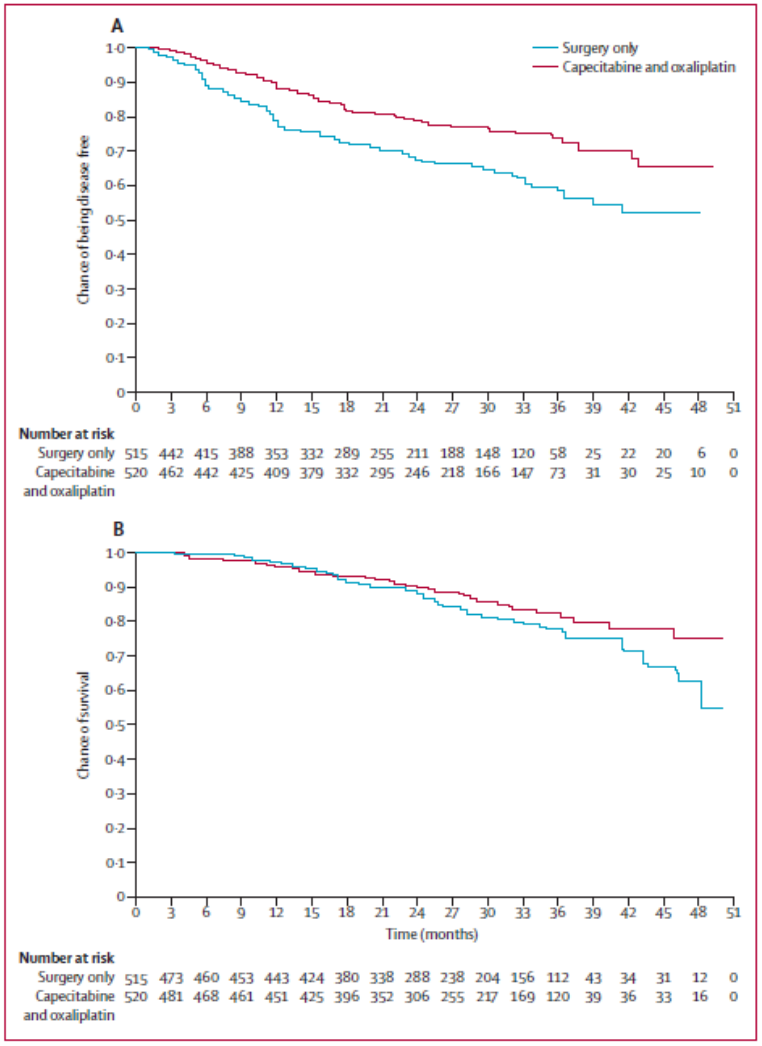

Figure 2: **3 year disease-free survival (A) and preliminary overall survival (B) in the intention-to-treat population**

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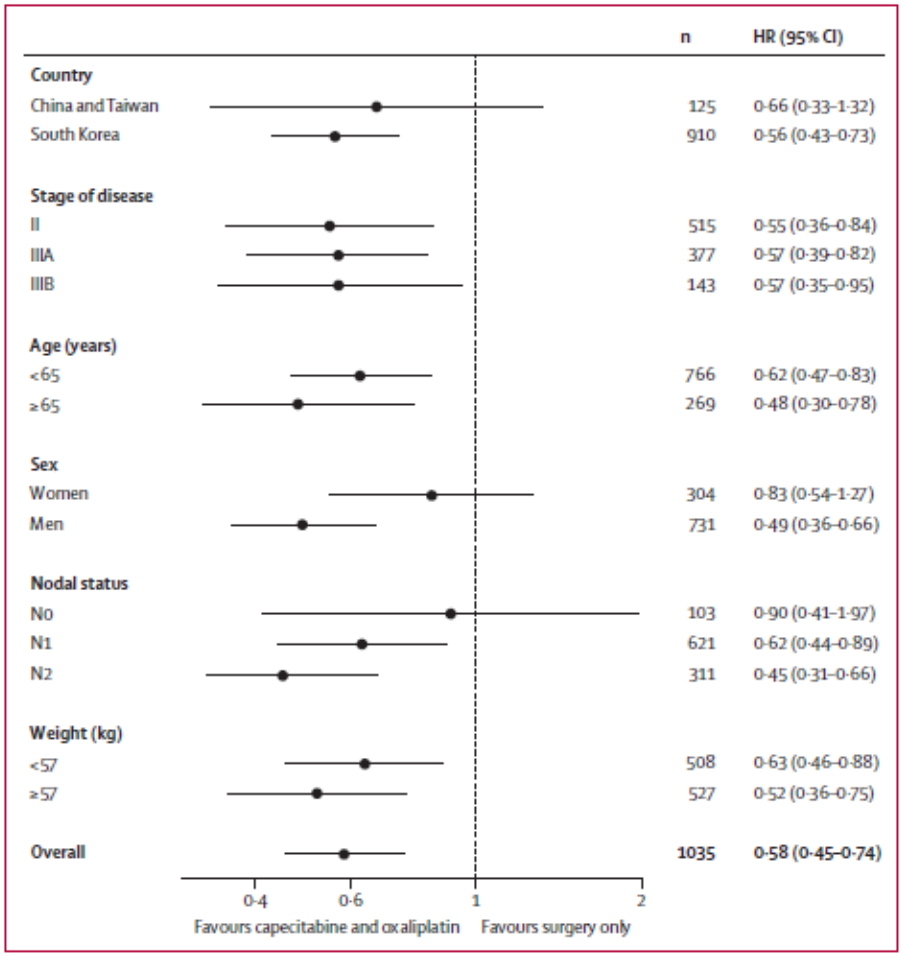

Figure 3: 3 year disease-free survival by stratification and prognostic factors in the intention-to-treat population

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	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	

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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%

Aşağıdakilerden hangisi doğrudur

A- Mide kanserinde genetik sendromlar hastalığın %30 'dan sorumludur

B-Mide kanserinde PET-CT evelemede her zaman daha doğru bilgi verir.

C-Lokal ileri mide kanserinin tedavisinde neoadjuvan Kemoterapi tek seçenektir.

D-Mide kanseri insidansı azalmak ile beraber mortalite oranı yüksektir.

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EPİDEMİYOLOJİ

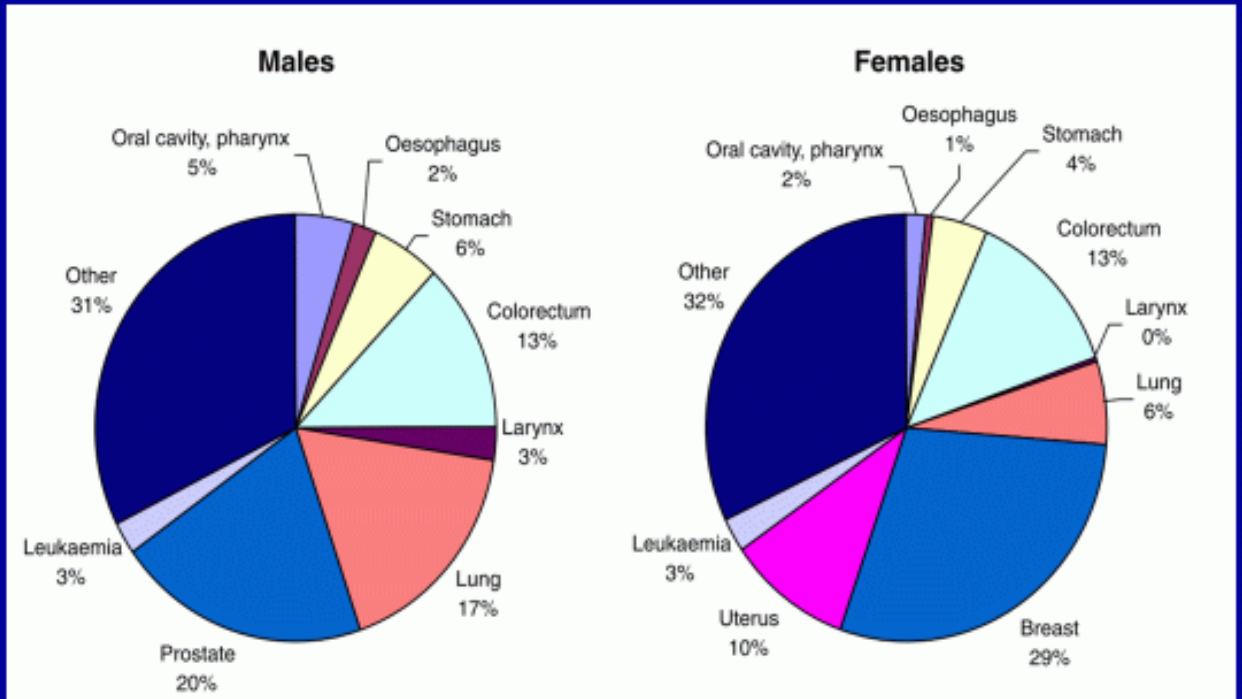

Fig. 1 – Distribution of new cancer cases in Europe by gender, 2006 Source: Ferlay et al.[2]

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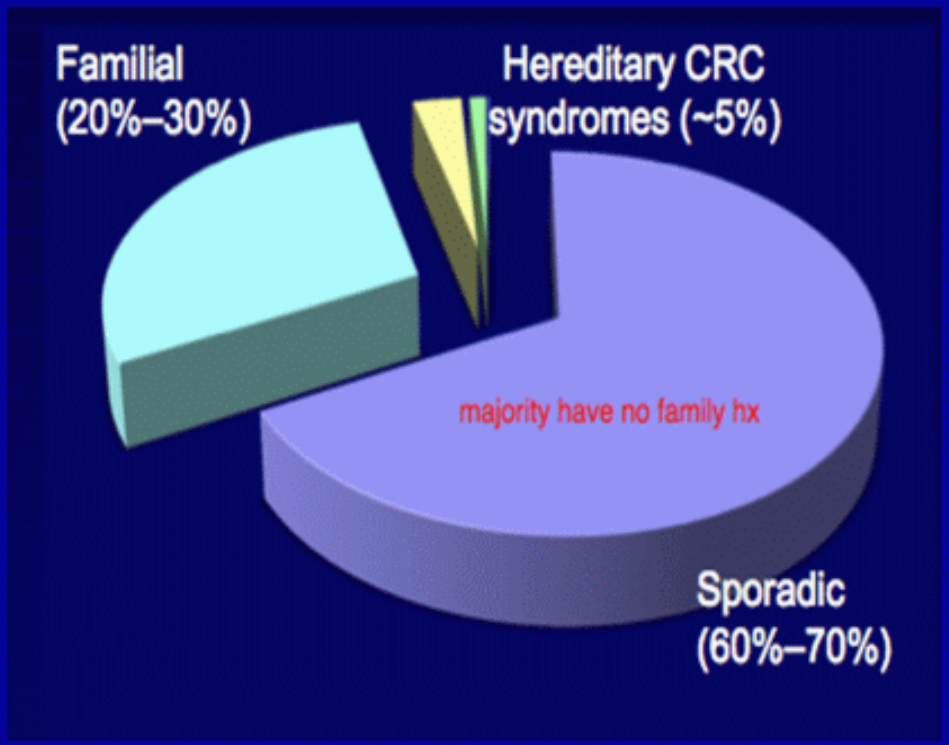
Genetik ve Risk Faktörleri

Herediter KRK Sendromlar



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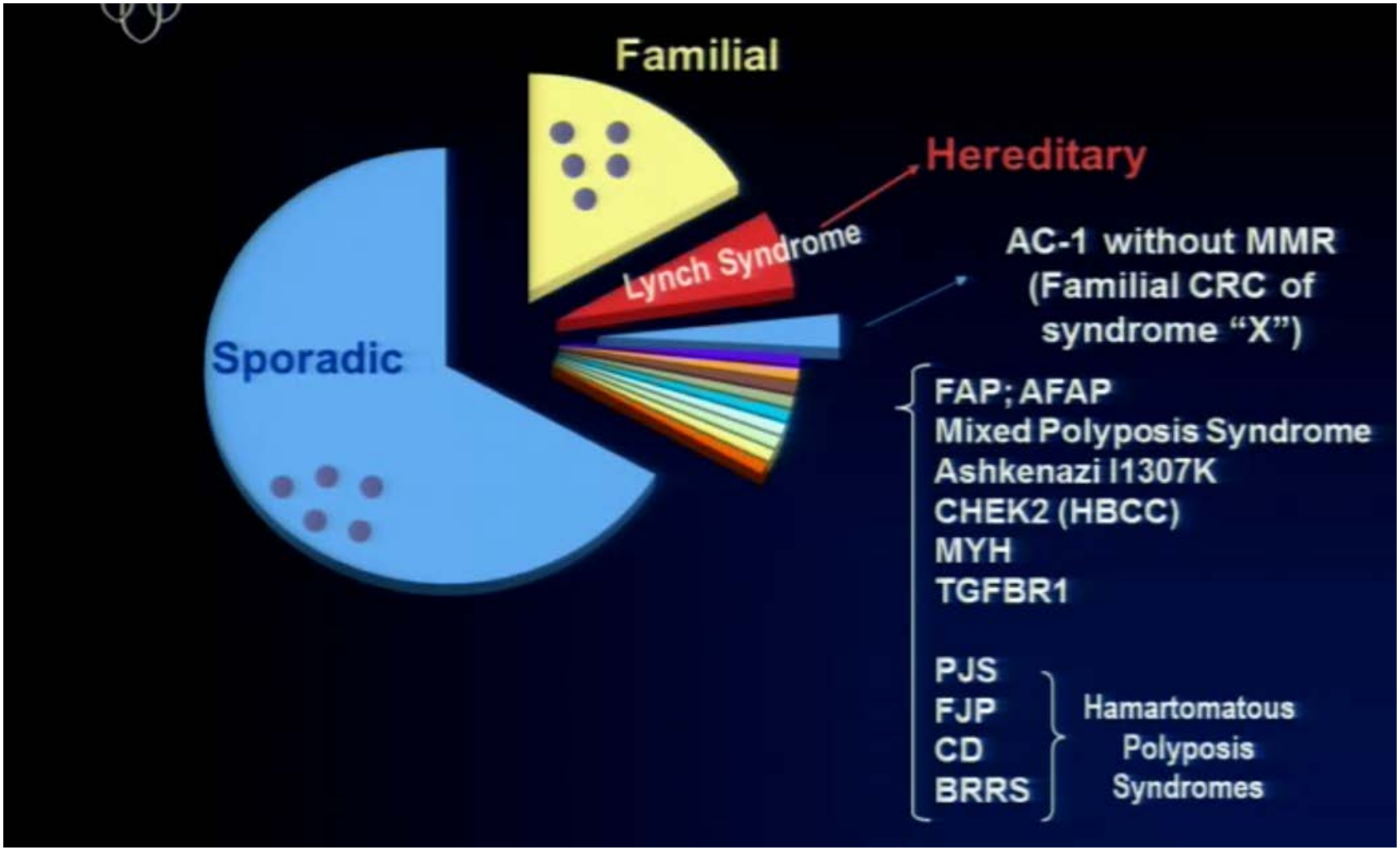
Genetik ve Risk Faktörleri



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Genetik ve Risk Faktörleri

Annual worldwide incidence of CRC is 1,023,152*:

- Lynch syndrome (LS) accounts for ≈ 2-5% (20,460-51,160 cases).
- < 1% (10,230 cases) constitute FAP.
- ≈ 20% (204,630 cases) are familial (2 or more first-degree relatives with CRC.

*International Agency for Research on Cancer. Globocan 2002. Available at: http://www-dep.iarc.fr/.

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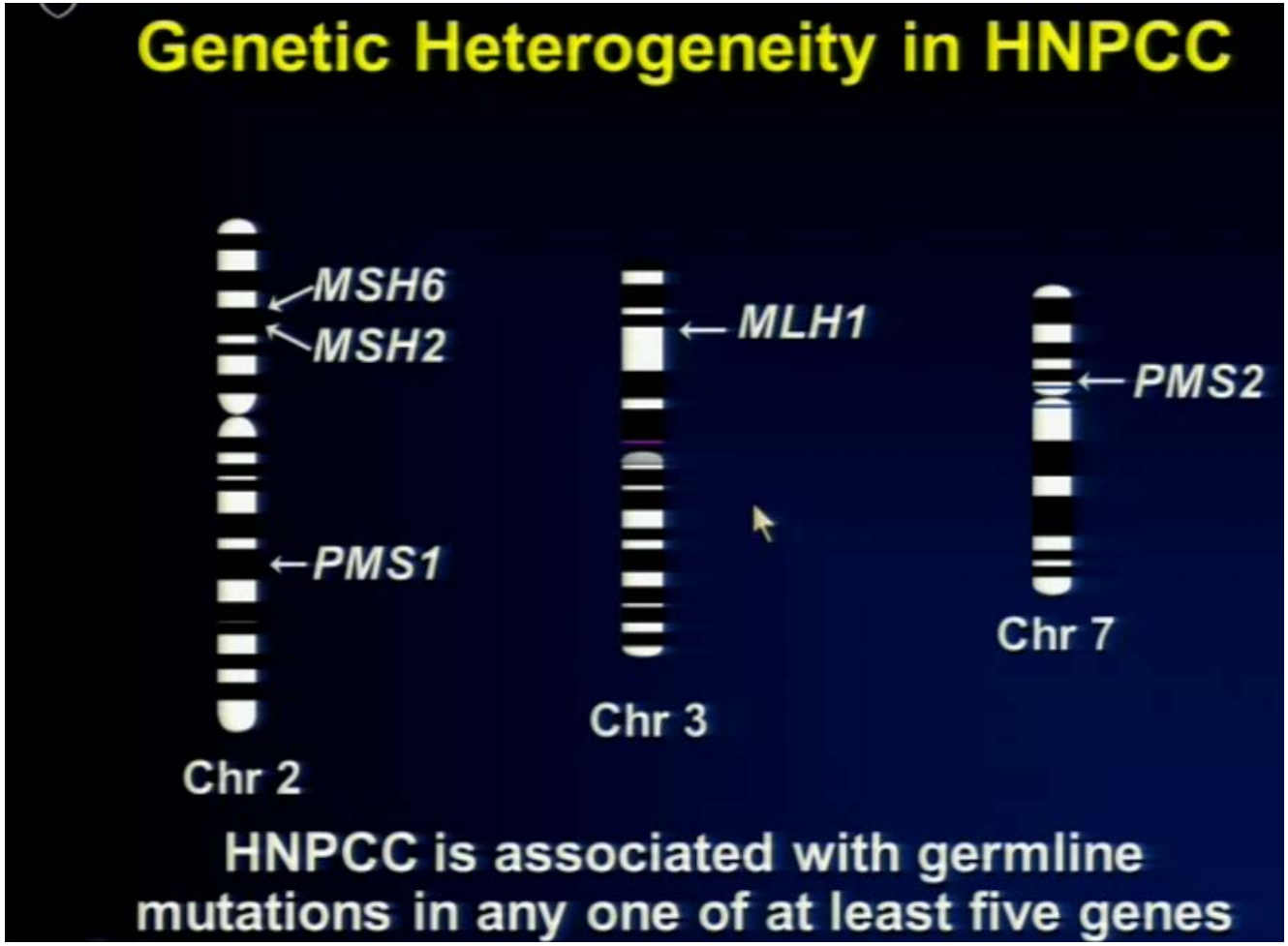
Genetik ve Risk Faktörleri



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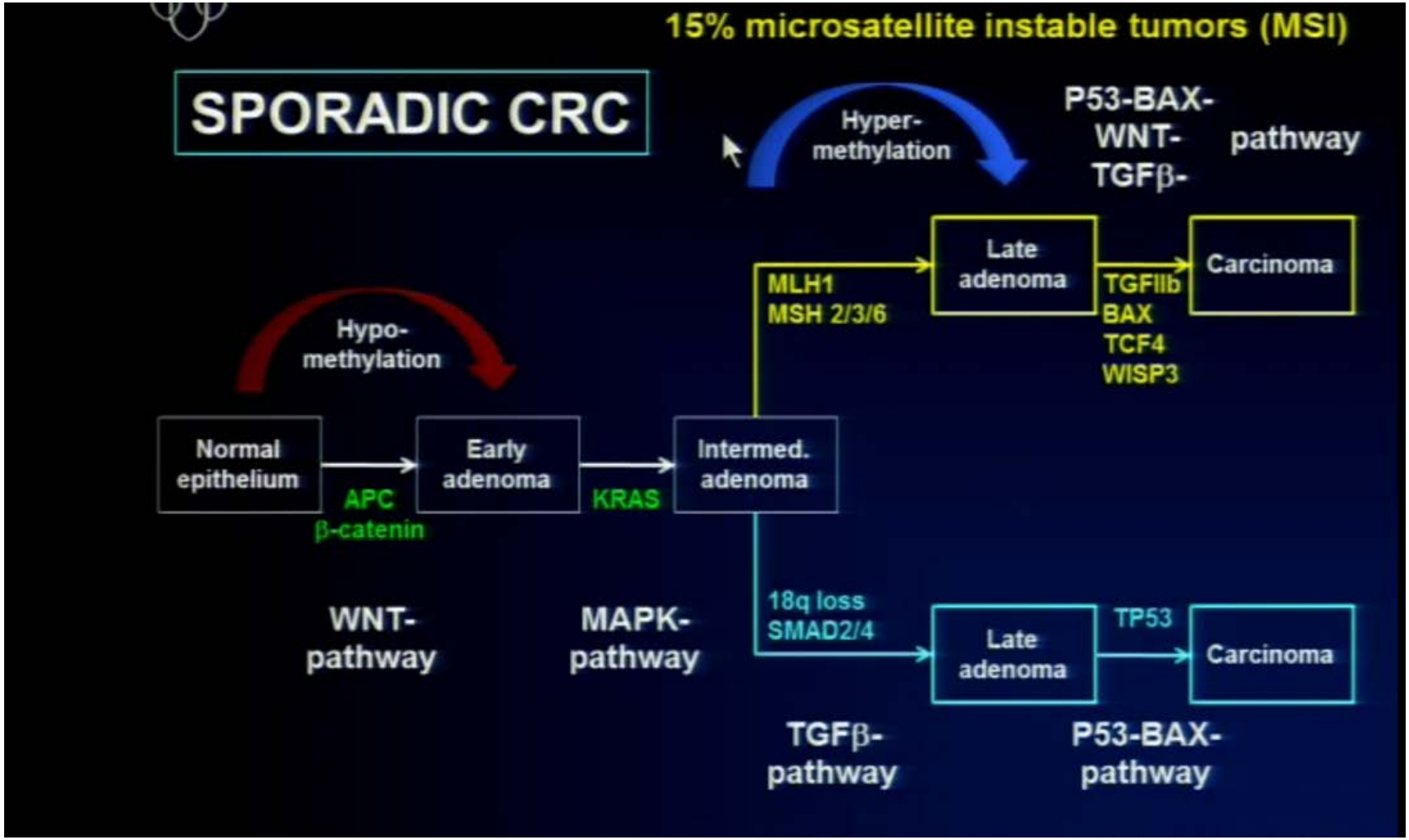
Genetik ve Risk Faktörleri



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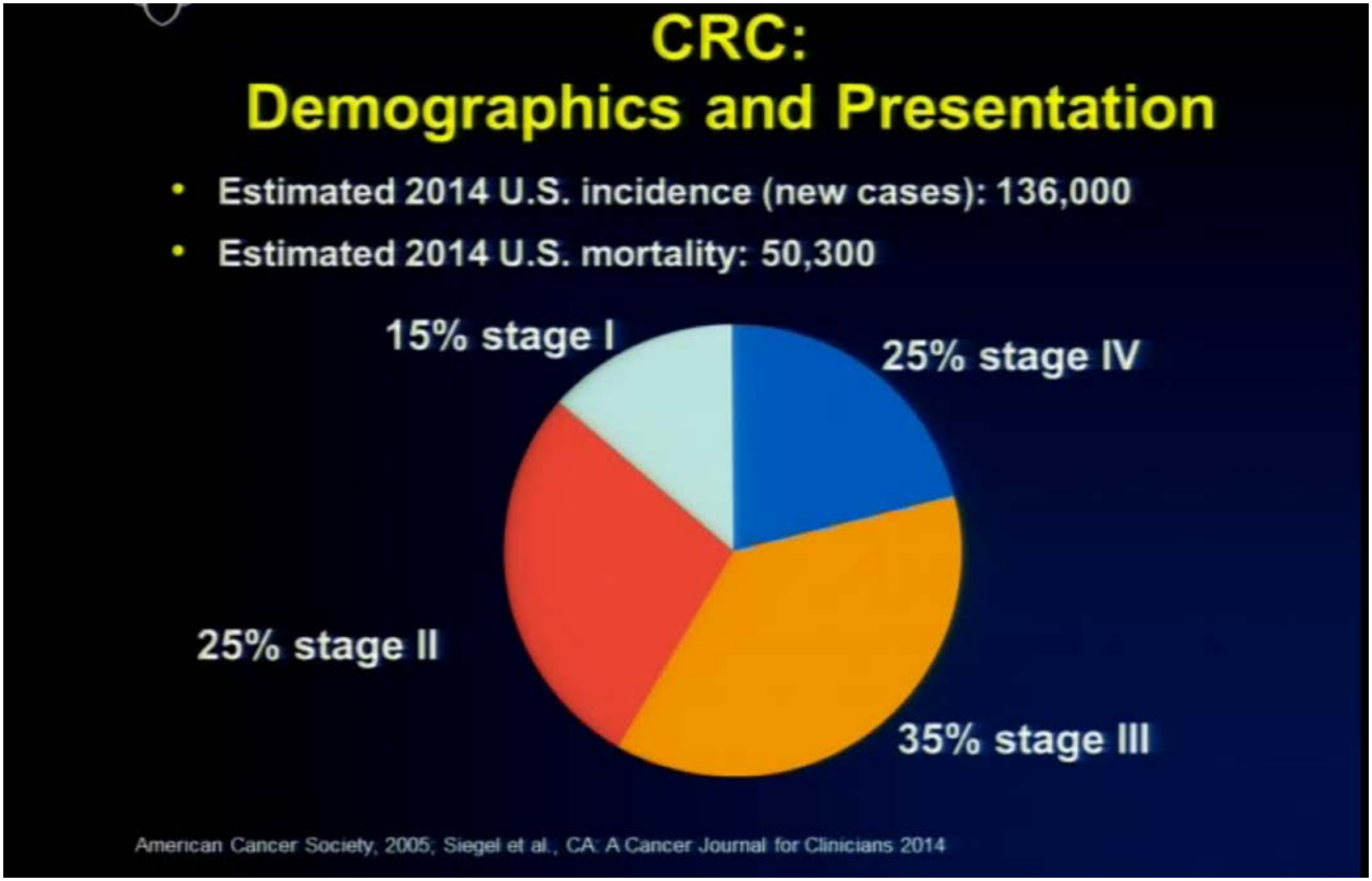

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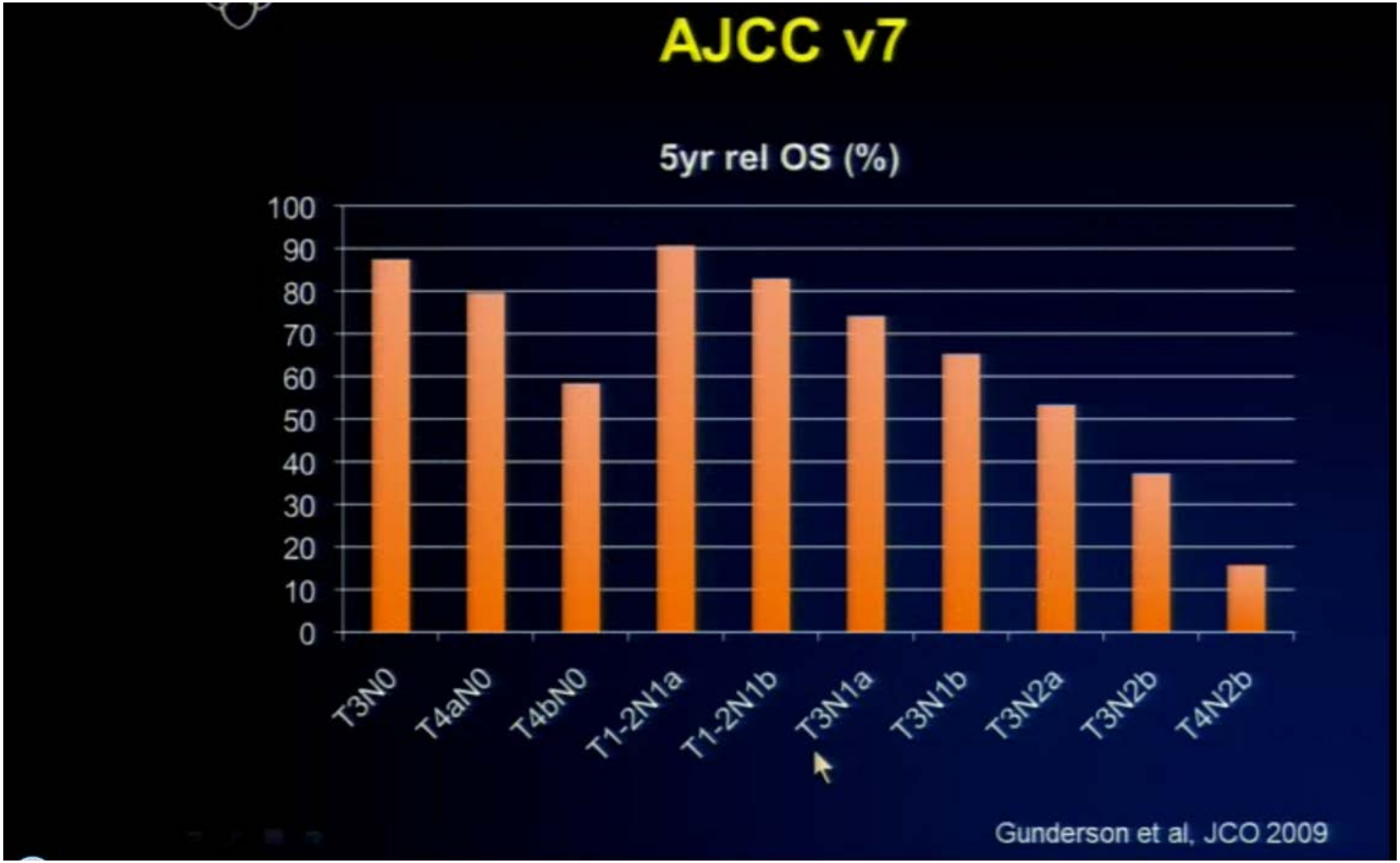

Kolon Kanseri Evreleme

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016 Staging Colon Cancer

NCCN Guidelines Index
Colon Cancer Table of Contents
Discussion

Table 1. Definitions for T, N, M

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria[a]
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum[b]
T4b	Tumor directly invades or is adherent to other organs or structures[b,c]

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Table 2. Anatomic Stage/Prognostic Groups

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (eg, ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

*Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

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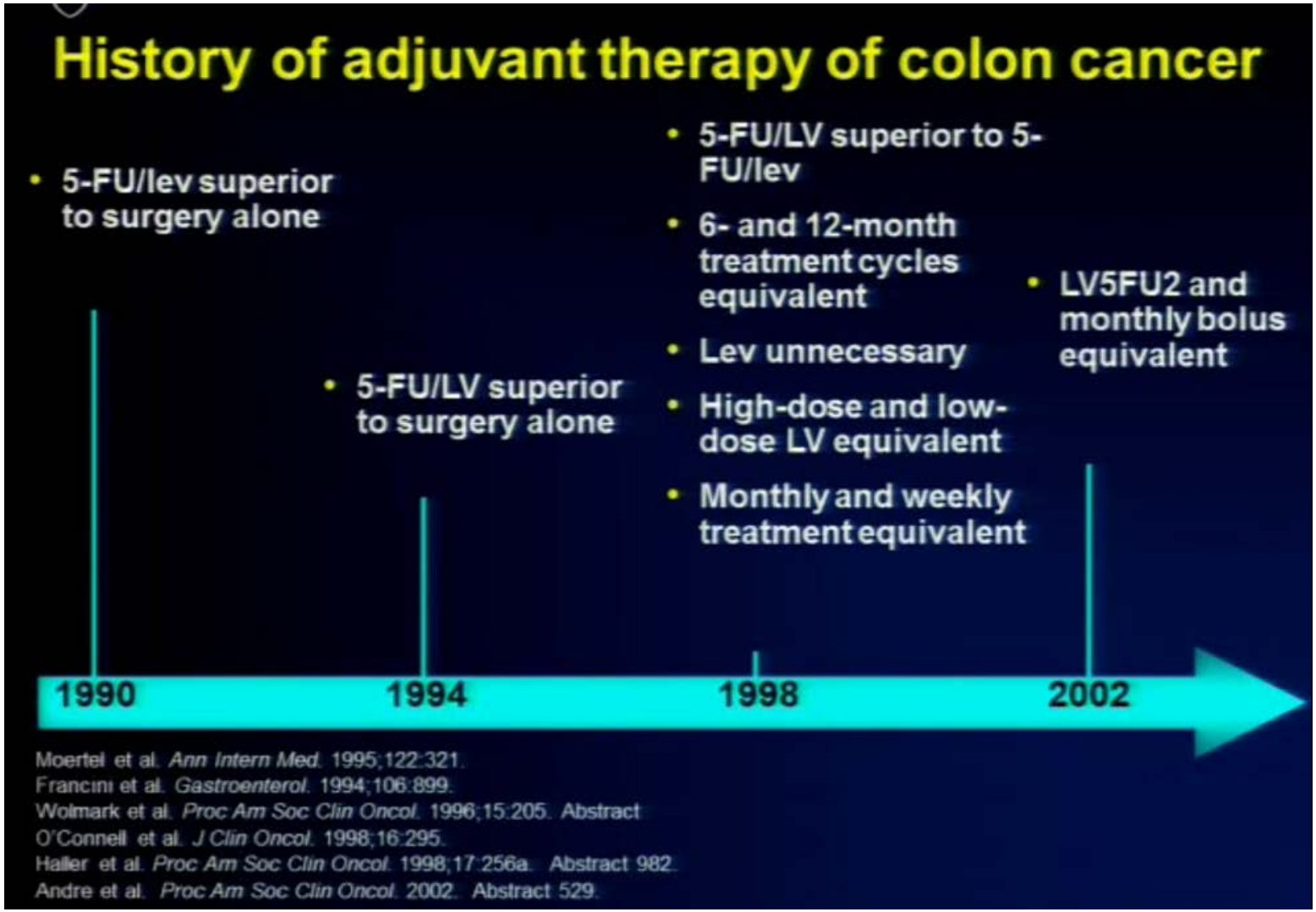

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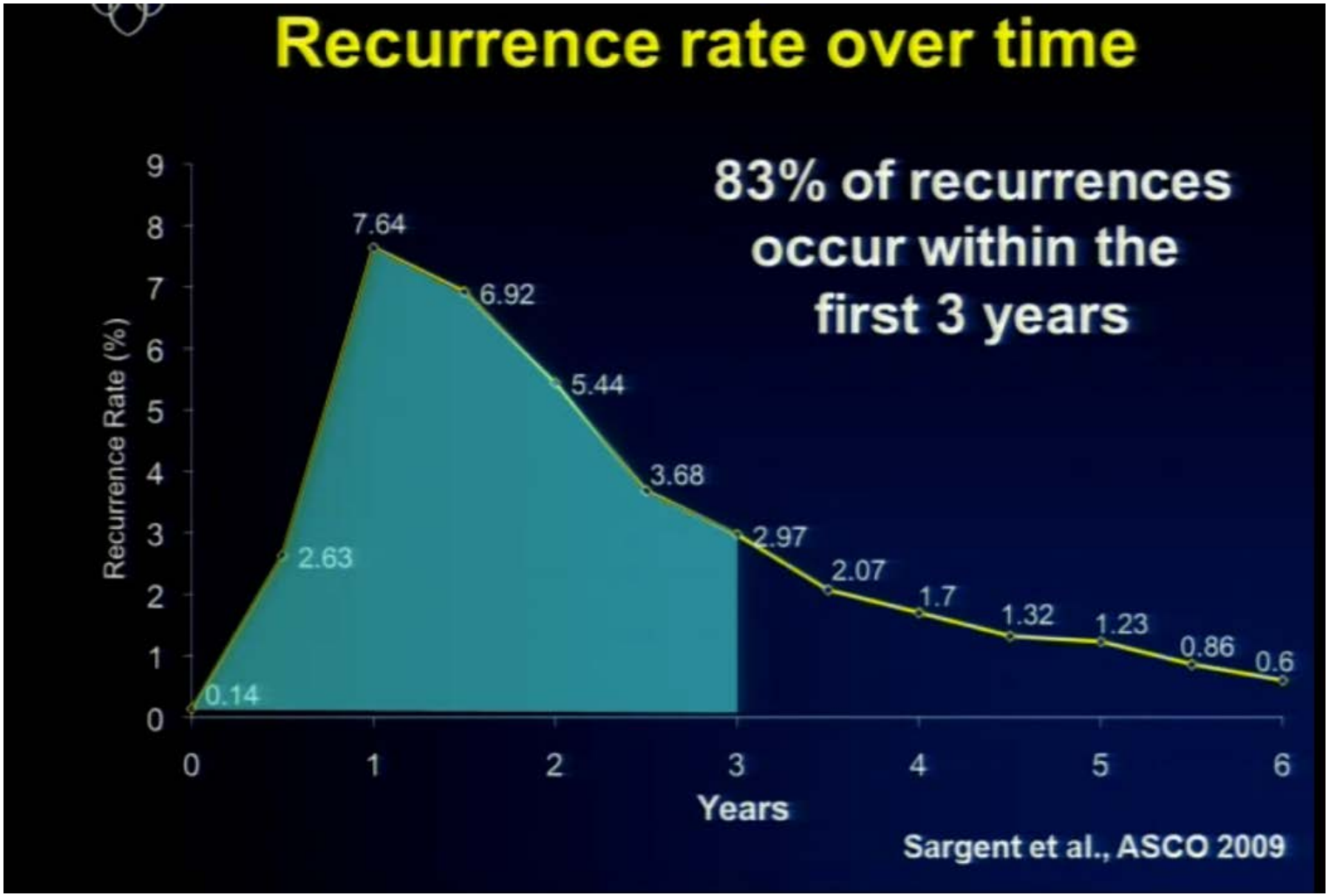

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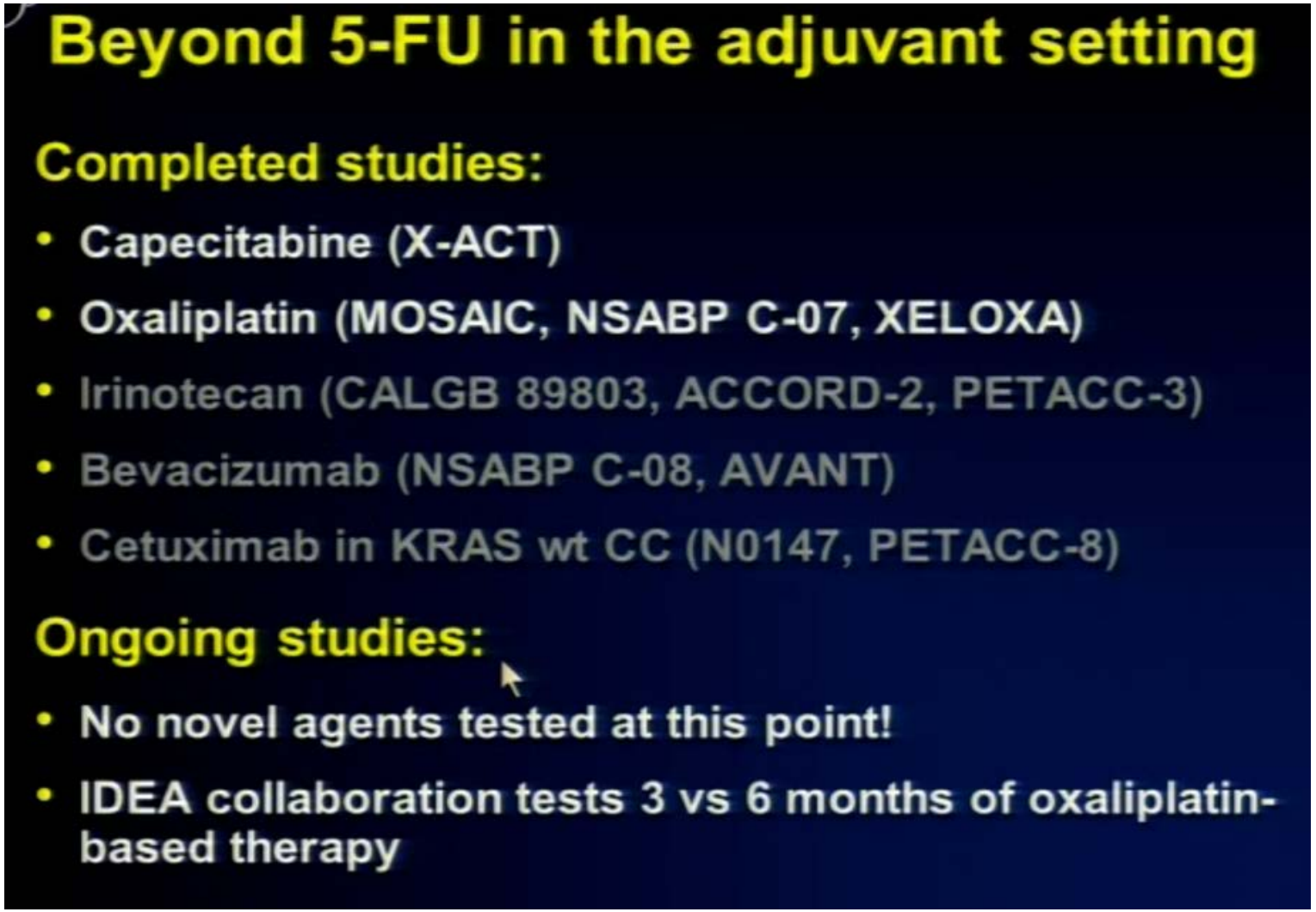

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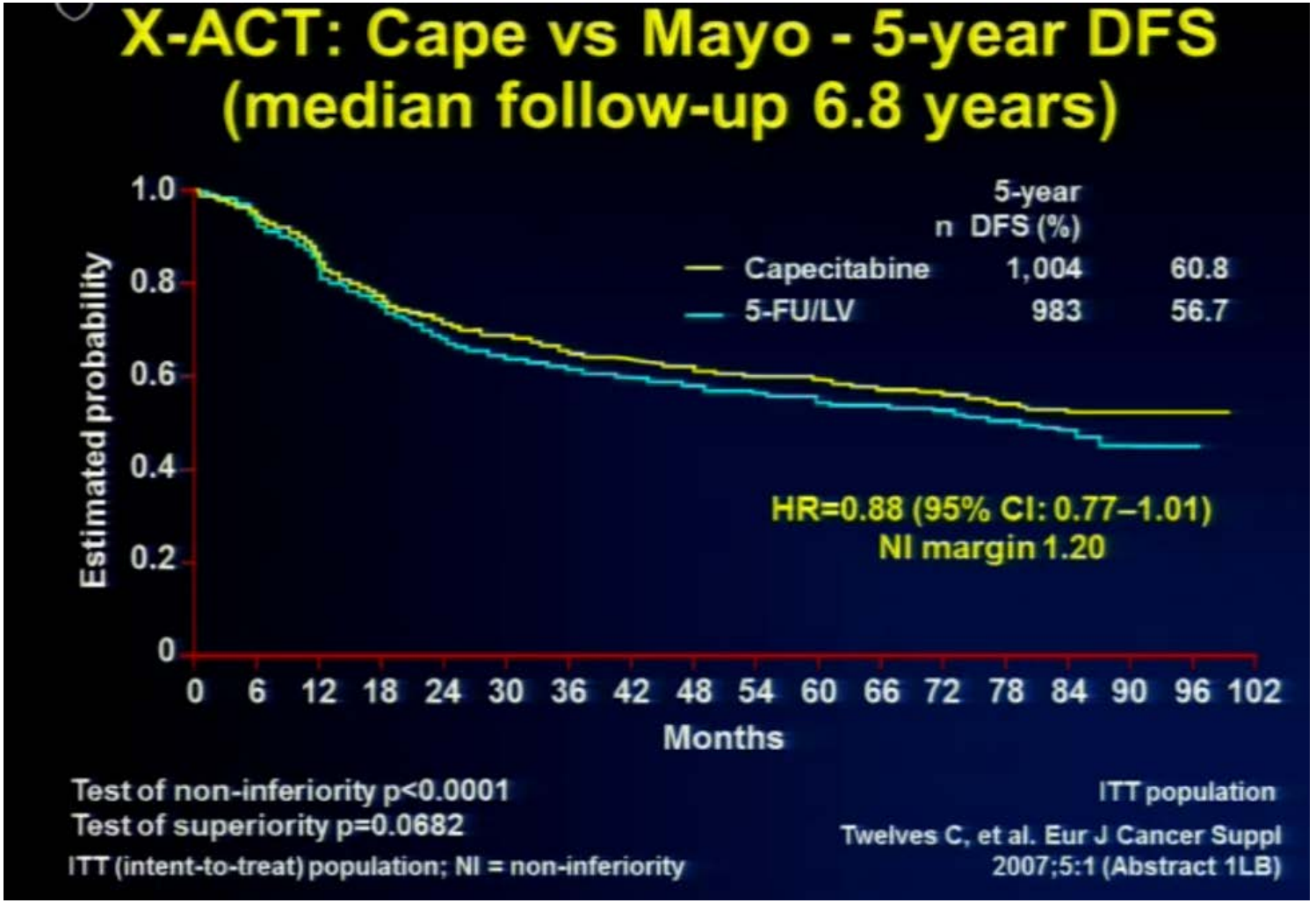

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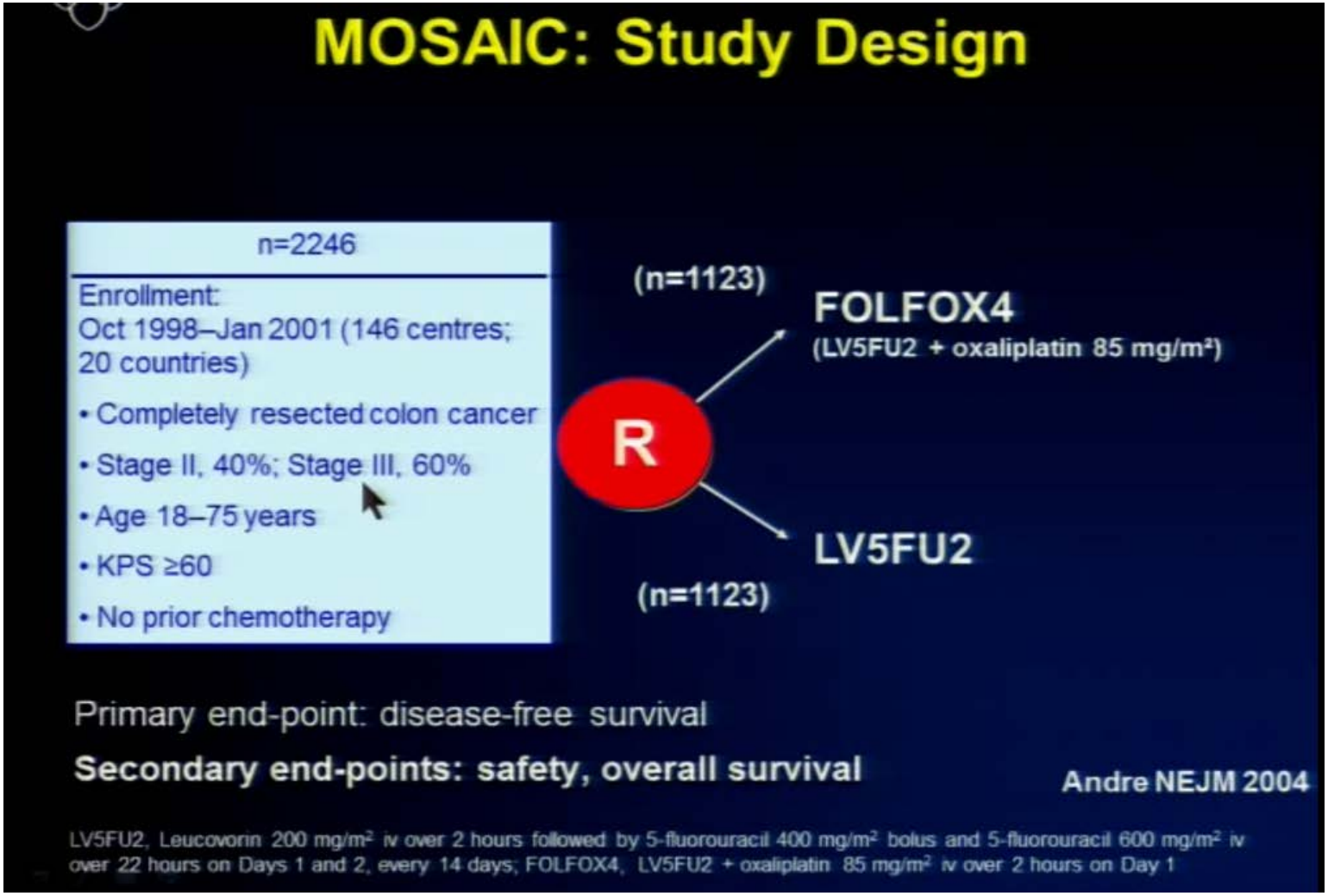

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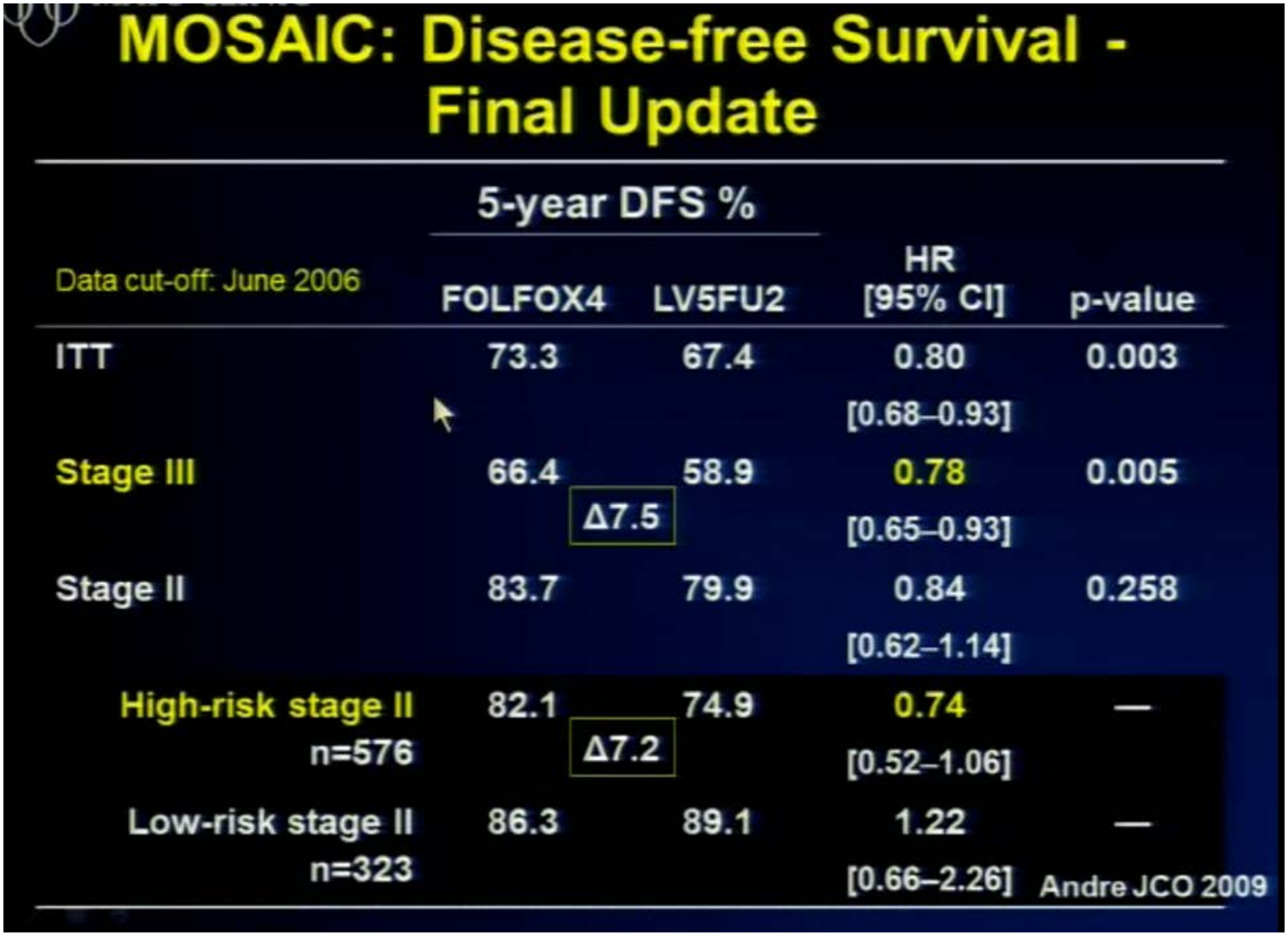

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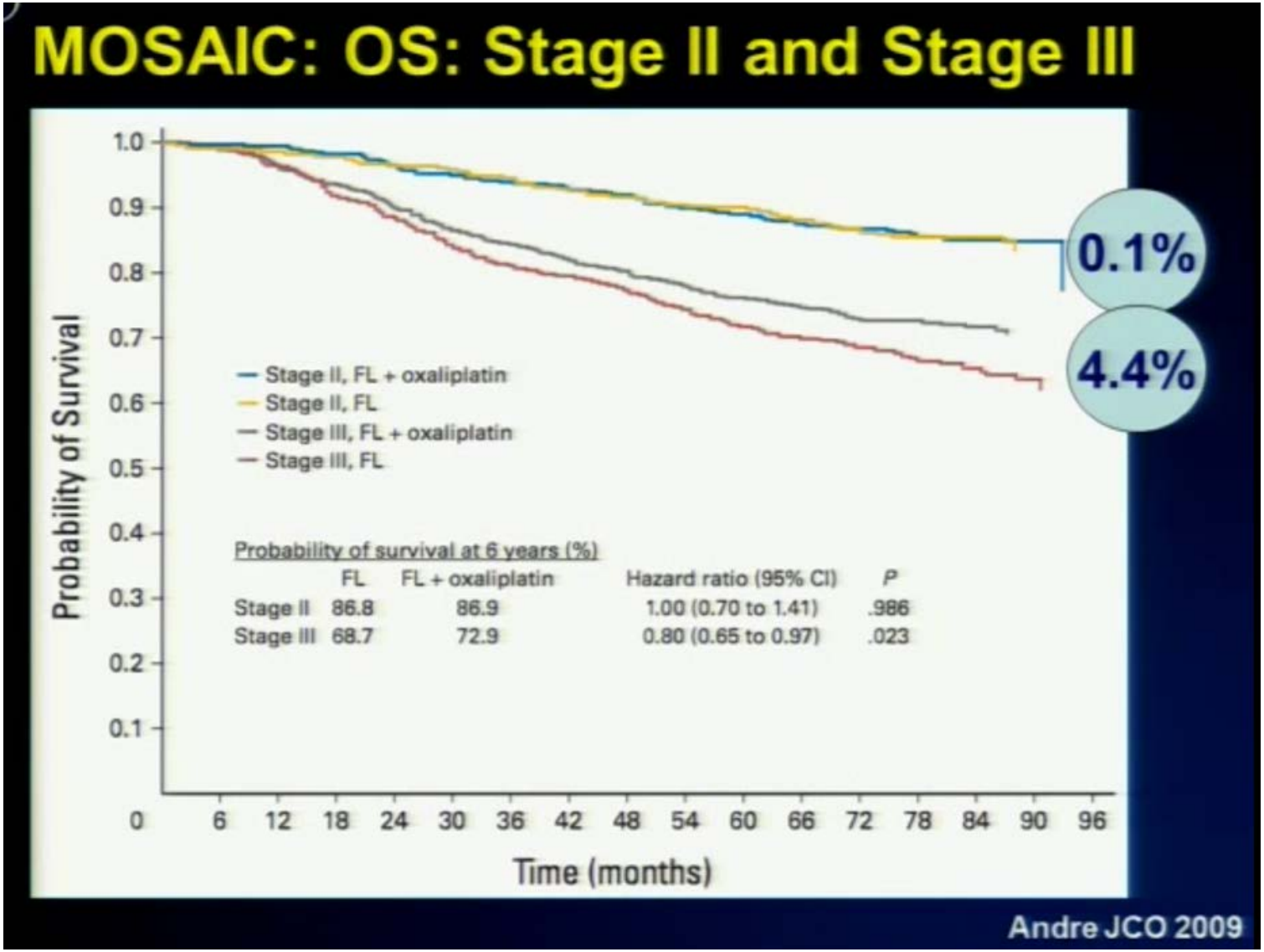

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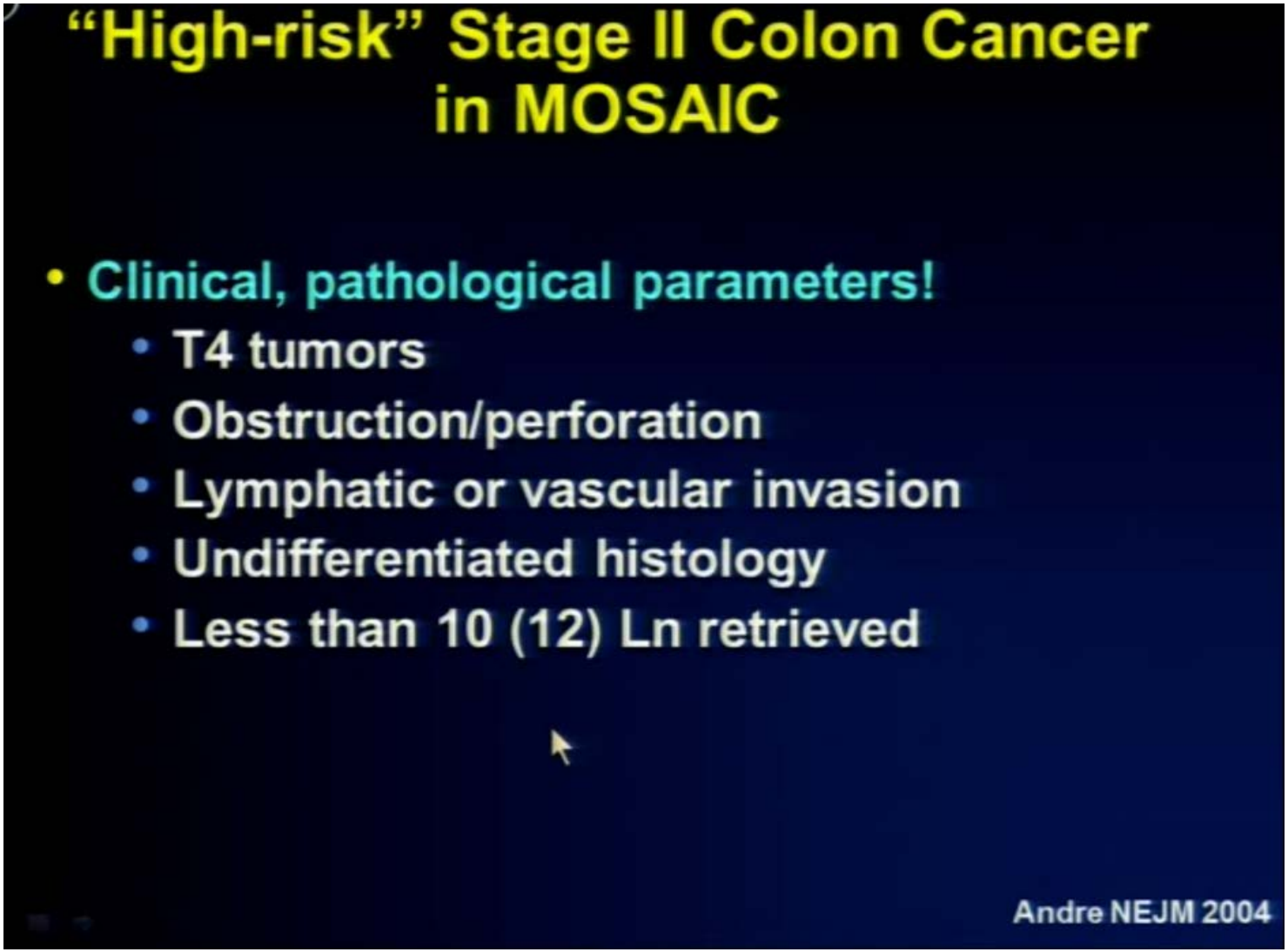

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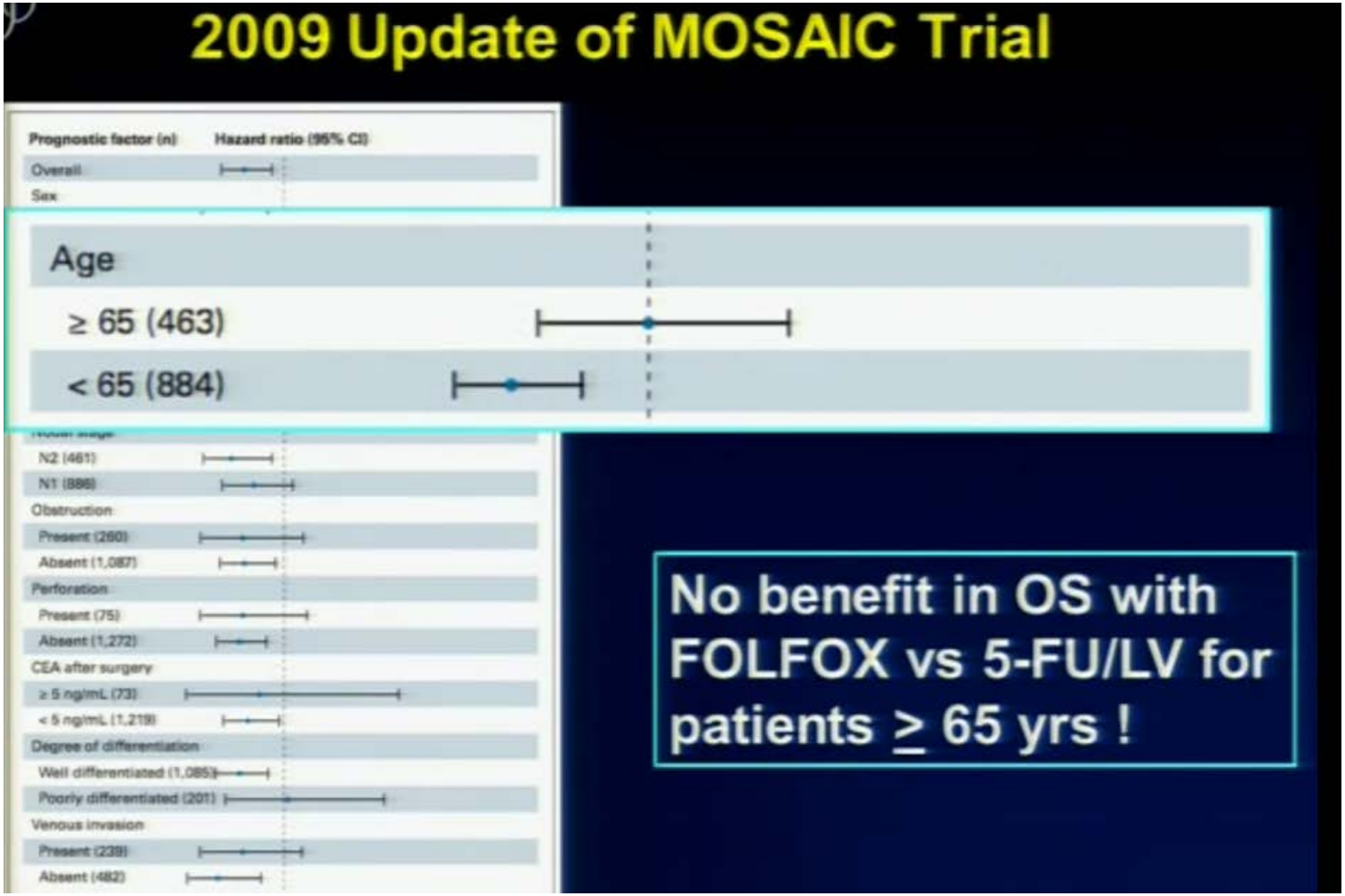

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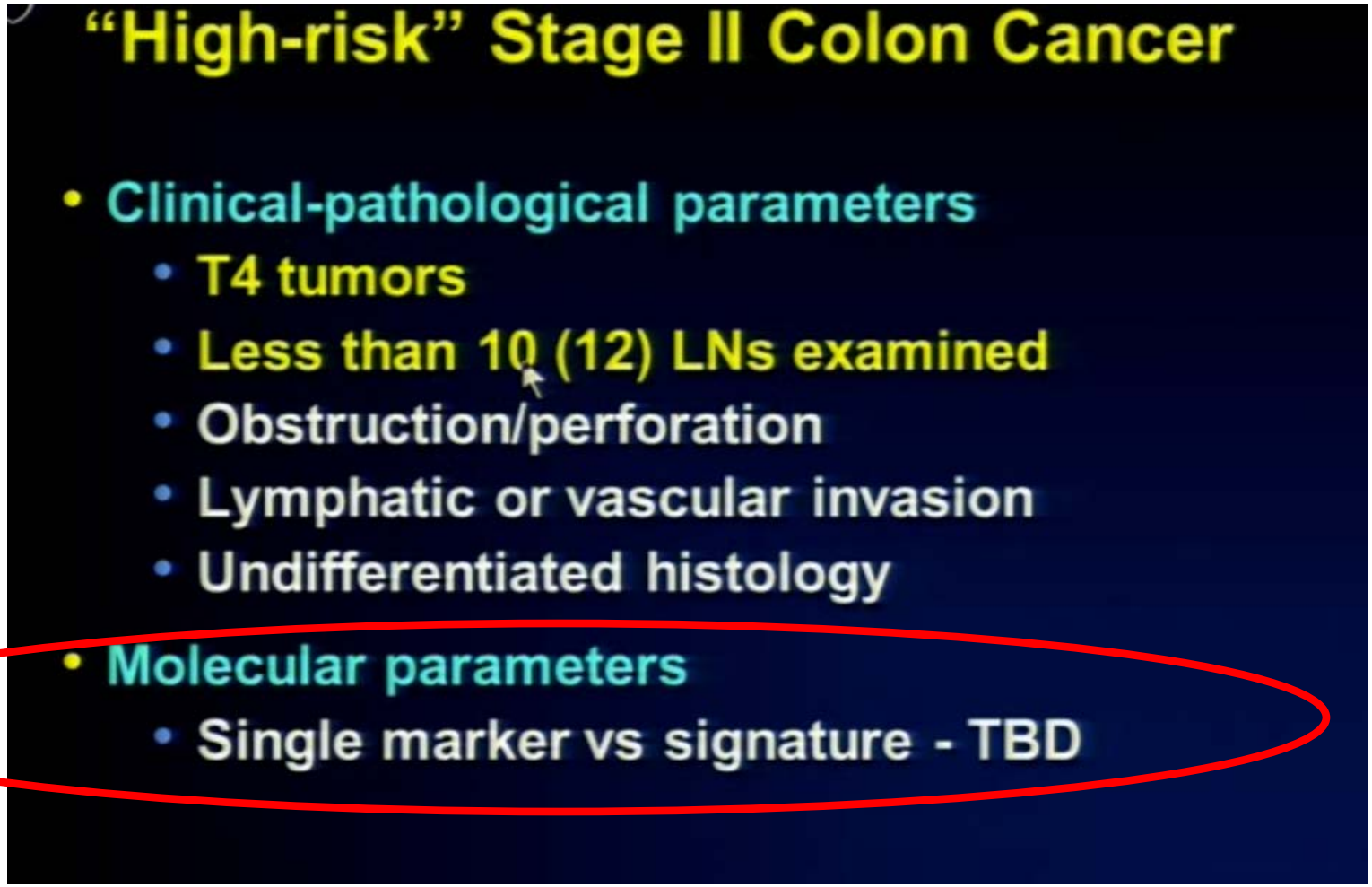

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Defective MMR - Colon cancer

- Characterized by presence of MSI & loss of MLH1, MSH2, MSH6 or PMS2 expression
- ~15% of Sporadic CC, >90% loss of MLH1
- Clinical Correlations: Right sided, Female, Early stage, Better prognosis
- Tumors: Poorly differentiated, Signet-ring-cell, Lymphocytic infiltration, near diploid
- MMR-D cells resistant to 5-FU[1,2]

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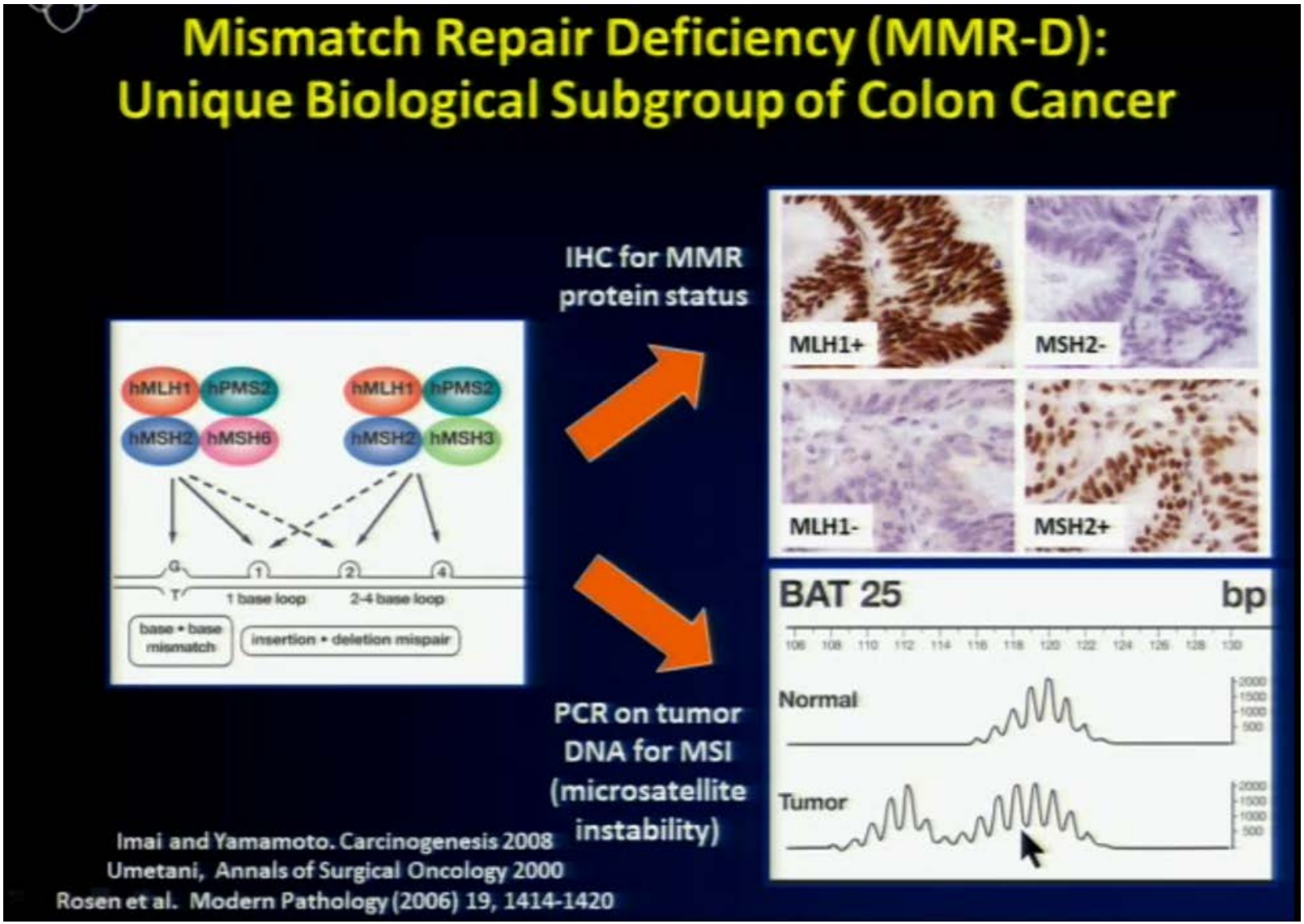

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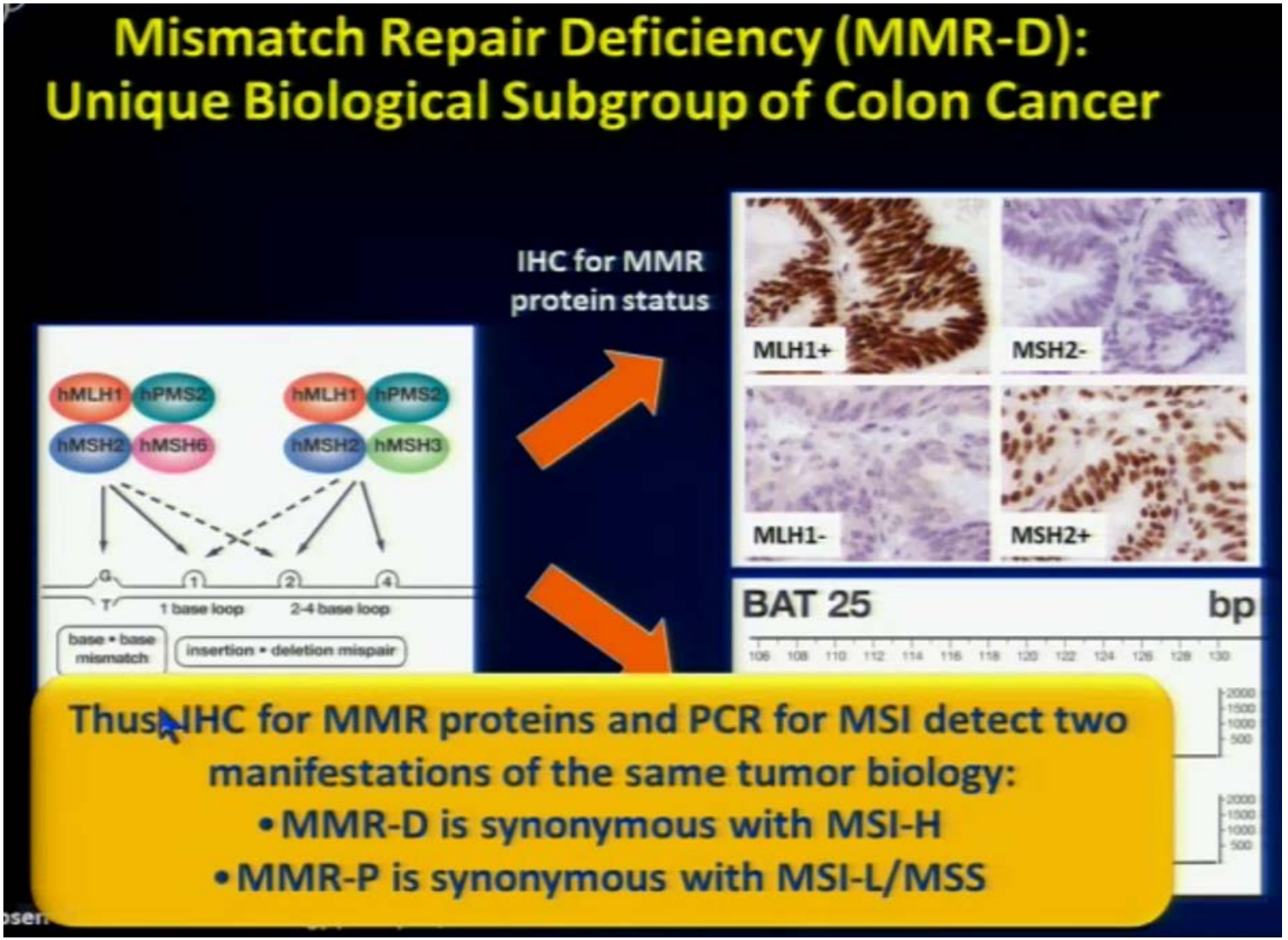

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prognostic Role of *KRAS* and *BRAF* in Stage II and III Resected Colon Cancer: Results of the Translational Study on the PETACC-3, EORTC 40993, SAKK 60-00 Trial

Arnaud D. Roth, Sabine Tejpar, Mauro Delorenzi, Pu Yan, Roberto Fiocca, Dirk Klingbiel, Daniel Dietrich, Bart Biesmans, György Bodoky, Carlo Barone, Enrique Aranda, Bernard Nordlinger, Laura Cisar, Roberto Labianca, David Cunningham, Eric Van Cutsem, and Fred Bosman

From Oncosurgery, Geneva University Hospital, Geneva; National Center of Competence in Research Molecular Oncology, Swiss Institute of Bioinformatics, Lausanne; Swiss Group for Clinical Cancer Research, Bern; Department of Pathology, Lausanne University, Lausanne, Switzerland; Digestive Oncology Unit, University Hospital Gasthuisberg; Center For Human Genetics, Katholieke Universiteit Leuven, Leuven, Belgium; Department of Surgical and Morphological Sciences, University of Genova, Genova; Medical Oncology, Catholic University of Sacred Heart, Roma; Unit of Medical Oncology, Ospedali Riuniti, Bergamo, Italy; Szt László Hospital, Budapest, Hungary; Medical Oncology Service, Hospital Universitario Reina Sofia, Cordoba, Spain; Hôpital Ambroise Paré, CHU Paris Ouest, Boulogne, France; Pfizer, NY; and Medical Oncology, The Royal Marsden Hospital, Sutton, United Kingdom.

Submitted April 6, 2009; accepted October 1, 2009; published online ahead of print at www.jco.org on December 14, 2009.

Supported by Pfizer.

S.T. and E.V.C. are Senior Clinical

A B S T R A C T

Purpose
Mutations within the *KRAS* proto-oncogene have predictive value but are of uncertain prognostic value in the treatment of advanced colorectal cancer. We took advantage of PETACC-3, an adjuvant trial with 3,278 patients with stage II to III colon cancer, to evaluate the prognostic value of *KRAS* and *BRAF* tumor mutation status in this setting.

Patients and Methods
Formalin-fixed paraffin-embedded tissue blocks (n = 1,564) were prospectively collected and DNA was extracted from tissue sections from 1,404 cases. Planned analysis of *KRAS* exon 2 and *BRAF* exon 15 mutations was performed by allele-specific real-time polymerase chain reaction. Survival analyses were based on univariate and multivariate proportional hazard regression models.

Results
KRAS and *BRAF* tumor mutation rates were 37.0% and 7.9%, respectively, and were not significantly different according to tumor stage. In a multivariate analysis containing stage, tumor site, nodal status, sex, age, grade, and microsatellite instability (MSI) status, *KRAS* mutation was associated with grade ($P = .0016$), while *BRAF* mutation was significantly associated with female sex ($P = .017$), and highly significantly associated with right-sided tumors, older age, high grade, and MSI-high tumors (all $P < 10^{-4}$). In univariate and multivariate analysis, *KRAS* mutations did not have a major prognostic value regarding relapse-free survival (RFS) or overall survival (OS). *BRAF* mutation was not prognostic for RFS, but was for OS, particularly in patients with MSI-low (MSI-L) and stable (MSI-S) tumors (hazard ratio, 2.2; 95% CI, 1.4 to 3.4; $P = .0003$).

Conclusion
In stage II-III colon cancer, the *KRAS* mutation status does not have major prognostic value. *BRAF* is prognostic for OS in MS-L/S tumors.

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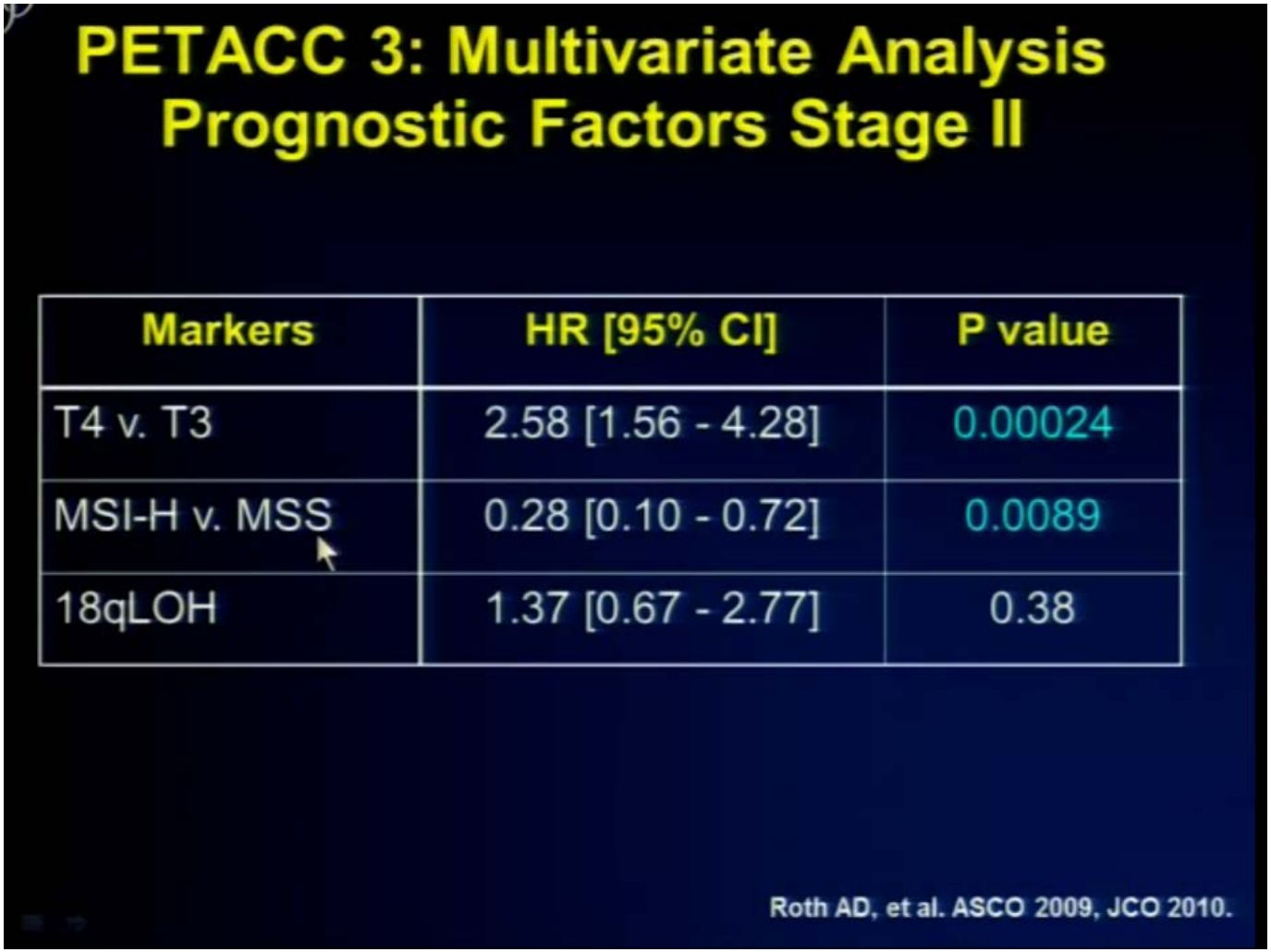


Kolon Kanseri Tedavi

Tumor Microsatellite-Instability Status as a Predictor of Benefit from Fluorouracil-Based Adjuvant Chemotherapy for Colon Cancer

Christine M. Ribic, M.Sc., Daniel J. Sargent, Ph.D., Malcolm J. Moore, M.D., Stephen N. Thibodeau, Ph.D., Amy J. French, B.A., Richard M. Goldberg, M.D., Stanley R. Hamilton, M.D., Pierre Laurent-Puig, M.D., Ph.D., Robert Gryfe, M.D., Ph.D., Lois E. Shepherd, M.D., Dongsheng Tu, Ph.D., Mark Redston, M.D., and Steven Gallinger, M.D.

ABSTRACT

BACKGROUND

Colon cancers with high-frequency microsatellite instability have clinical and pathological features that distinguish them from microsatellite-stable tumors. We investigated the usefulness of microsatellite-instability status as a predictor of the benefit of adjuvant chemotherapy with fluorouracil in stage II and stage III colon cancer.

METHODS

Tumor specimens were collected from patients with colon cancer who were enrolled in randomized trials of fluorouracil-based adjuvant chemotherapy. Microsatellite instability was assessed with the use of mononucleotide and dinucleotide markers.

RESULTS

Of 570 tissue specimens, 95 (16.7 percent) exhibited high-frequency microsatellite instability. Among 287 patients who did not receive adjuvant therapy, those with tumors displaying high-frequency microsatellite instability had a better five-year rate of overall survival than patients with tumors exhibiting microsatellite stability or low-frequency instability (hazard ratio for death, 0.31 [95 percent confidence interval, 0.14 to 0.72]; P=0.004). Among patients who received adjuvant chemotherapy, high-frequency microsatellite instability was not correlated with increased overall survival (hazard ratio for death, 1.07 [95 percent confidence interval, 0.62 to 1.86]; P=0.80). The benefit of treatment differed significantly according to the microsatellite-instability status (P=0.01). Adjuvant chemotherapy improved overall survival among patients with microsatellite-stable tumors or tumors exhibiting low-frequency microsatellite instability, according to a multivariate analysis adjusted for stage and grade (hazard ratio for death, 0.72 [95 percent confidence interval, 0.53 to 0.99]; P=0.04). By contrast, there was no benefit of adjuvant chemotherapy in the group with high-frequency microsatellite instability.

Kolon Kanseri Tedavi

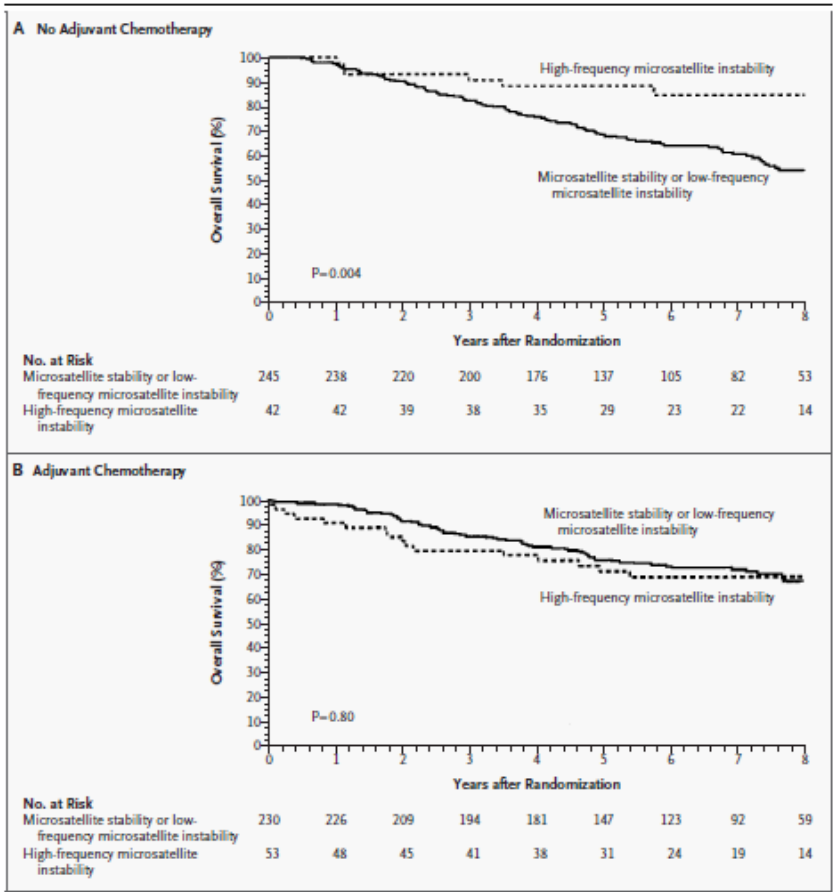


Figure 1. Kaplan–Meier Estimates of Overall Survival among Patients with Stage II or Stage III Colon Cancer According to the Microsatellite-Instability Status of the Tumor.

In the absence of adjuvant chemotherapy, the patients with tumors displaying high-frequency microsatellite instability had significantly longer overall survival than patients with tumors exhibiting microsatellite stability or low-frequency microsatellite instability (hazard ratio for death, 0.31 [95 percent confidence interval, 0.14 to 0.72]; P=0.004) (Panel A). When the analysis was limited to the group receiving adjuvant chemotherapy, patients with tumors exhibiting high-frequency microsatellite instability did not have a significant increase in overall survival as compared with patients with tumors exhibiting microsatellite stability or low-frequency microsatellite instability (hazard ratio for death, 1.07 [95 percent confidence interval, 0.62 to 1.86]; P=0.80) (Panel B). The analysis included data for eight years from the date of randomization.

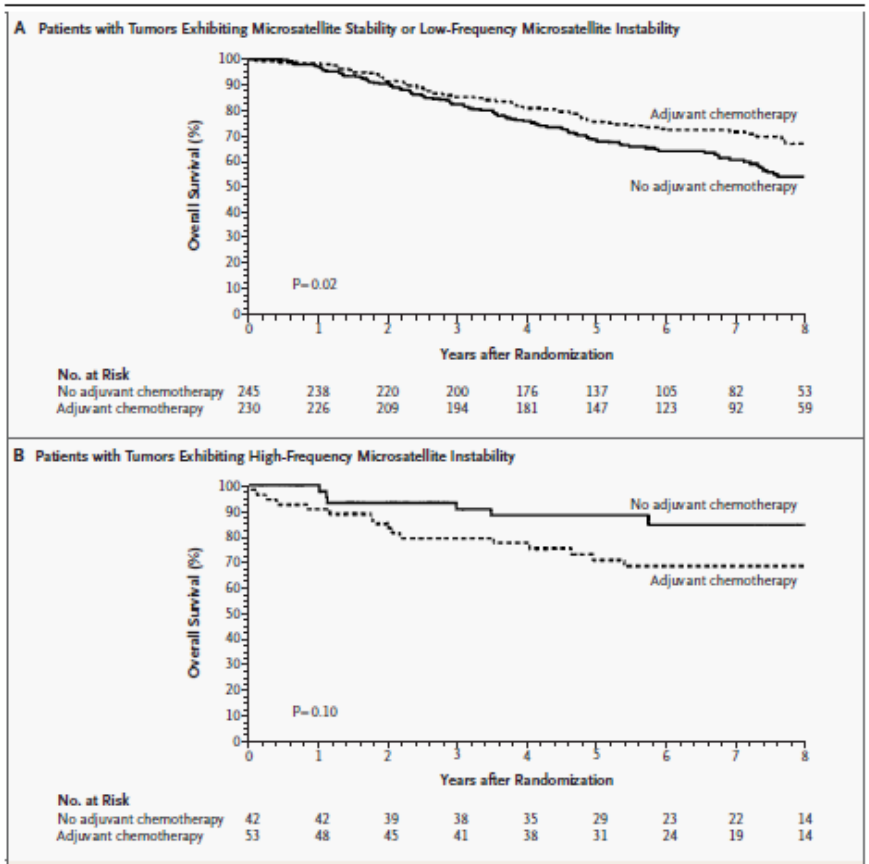
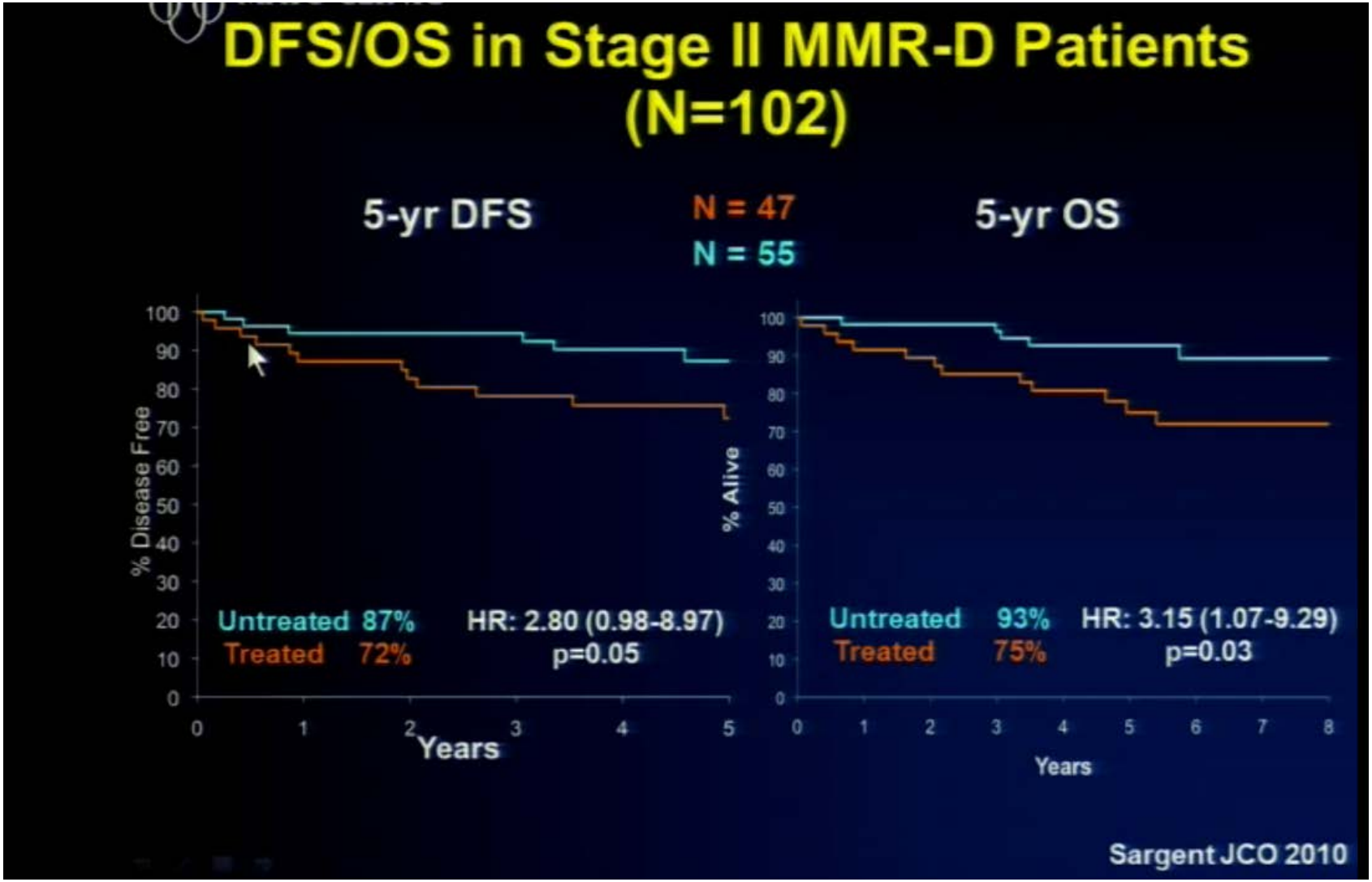


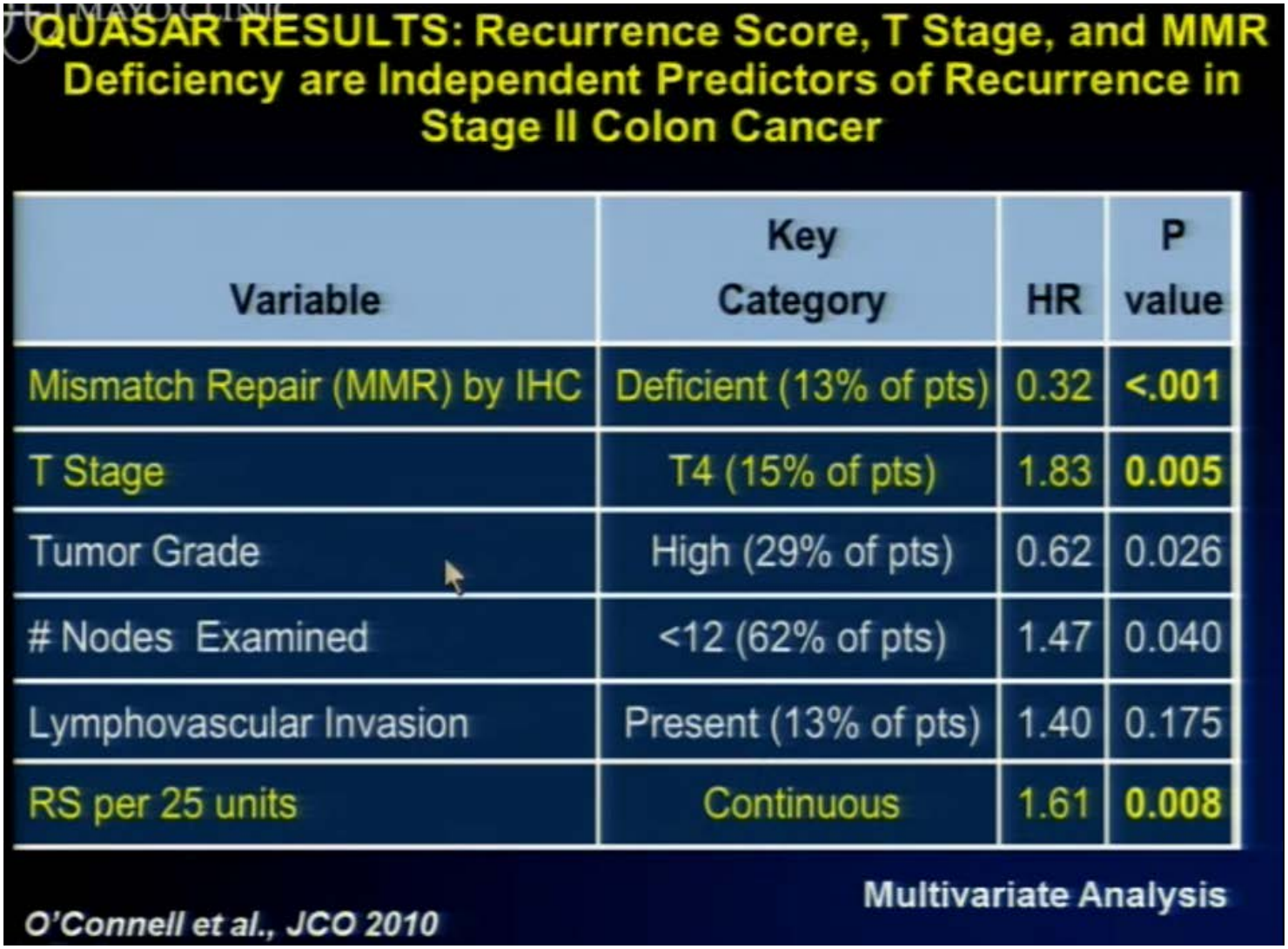
Figure 2. Kaplan–Meier Estimates of Overall Survival among Patients with Stage II or Stage III Colon Cancer According to Treatment Status.

Patients with tumors exhibiting microsatellite stability or low-frequency microsatellite instability who received adjuvant chemotherapy had a significant increase in overall survival as compared with patients who received no adjuvant chemotherapy (hazard ratio for death, 0.69 [95 percent confidence interval, 0.50 to 0.94]; P=0.02) (Panel A). Among patients with tumors exhibiting high-frequency microsatellite instability, there was no significant difference in the duration of overall survival between patients who received adjuvant chemotherapy and those who did not (hazard ratio for death, 2.17 [95 percent confidence interval, 0.84 to 5.55]; P=0.10) (Panel B). The analysis included data for eight years from the date of randomization.

Kolon Kanseri Tedavi



Kolon Kanseri Tedavi



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PATHOLOGIC STAGE[e]	ADJUVANT THERAPY[n,o]	SURVEILLANCE[u]
Tis; T1, N0, M0	None	Colonoscopy at 1 y ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[v] repeat in 3 y, then every 5 y[w]
T2, N0, M0	None	
T3, N0, M0[k,l] (MSI-H)	None	• History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[x] every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • Chest/abdominal/pelvic CT[h] every 6-12 mo (category 2B for frequency <12 mo) for up to 5 y for patients at high risk for recurrence[y] • Colonoscopy[b] in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[v] repeat in 3 y, then every 5 y[w] • PET-CT scan is not routinely recommended • See Principles of Survivorship (COL-G)
T3, N0, M0[k,l] (MSI-L or MSS and no high-risk features)	Clinical trial or Observation or Consider capecitabine[p] or 5-FU/leucovorin[p]	
T3, N0, M0 at high risk for systemic recurrence[k,l,m] or T4, N0, M0	Capecitabine[p,q] or 5-FU/leucovorin[p,q] or FOLFOX[o,p,q,r] or CapeOx[p,q,r,s] or FLOX[p,q,r,s,t] or Clinical trial or Observation	
Node-positive disease, see COL-4		

If Recurrence, See Workup (COL-9)

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PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES (2 of 2)

mFOLFOX 6
Oxaliplatin 85 mg/m² IV, day 1*
Leucovorin 400 mg/m² IV, day 1**
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion.
Repeat every 2 weeks.[1,2,3]

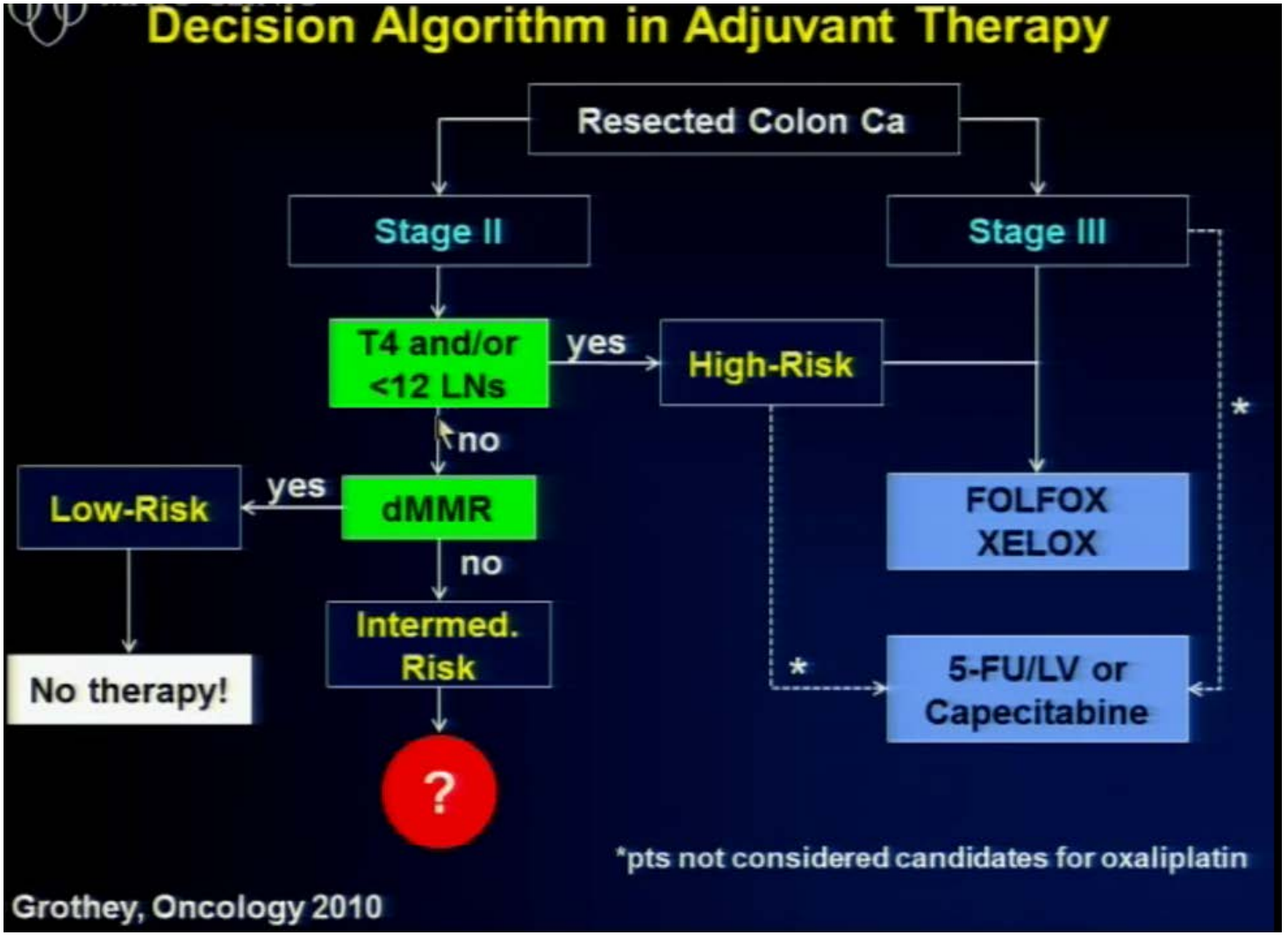
FLOX[4]
5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8-week cycle x 3 with oxaliplatin 85 mg/m² IV administered on weeks 1, 3, and 5 of each 8-week cycle x 3.

Capecitabine[5]
Capecitabine 1250 mg/m² twice daily days 1–14 every 3 wks x 24 wks.

CapeOx[6]
Oxaliplatin 130 mg/m² over 2 hours, day 1
Capecitabine 1000 mg/m² twice daily days 1–14 every 3 weeks x 24 weeks.

5-FU/leucovorin
- Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.[7]
- Simplified biweekly infusional 5-FU/LV (sLV5FU2)[8]
  Leucovorin 400** mg/m² IV day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours)† continuous infusion. Repeat every 2 weeks.

Kolon Kanseri Tedavi



Aşağıdakilerden hangisi doğrudur

A-MSI olanlarda 5-fu tedavisine direnç vardır

B-MSI kötü prognoz ile ilişkilidir

C-Yüksek MSI kolon kanserlerinin %10 oluşturur

D-MSI kromozom instabilitesinden meydana gelir

Rektum Kanseri

EVRELEME

- BT
- MR
- REUS
- PET-CT

Rektum Ca

Klinik T evre

- MR muskularis propriya invaziyonunu %94 sensitive de belirliyor
- Fakat REUS spesifite daha yüksek(%86 vs. %68)

Klinik N evre

- BT sensitive ve spesifite (%50–74)
- REUS sensitive ve spesifite (%67 –78)
- MR sensitive ve spesifite (%66 –76)

Circumferential Resection Margin

- Operasyon öncesi yüksek rezülasyonlu MR ile CRM (≥ 1mm)belirlemek prognoz hakında doğru bilgi verir.

- PET-CT rutin kulanımı yok, soliter metastazlarda metastektomi planlanıyorsa istenir.

Bipat et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology 2004 . Taylor et al. **Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol 2014**

Rektum ca Evreleme

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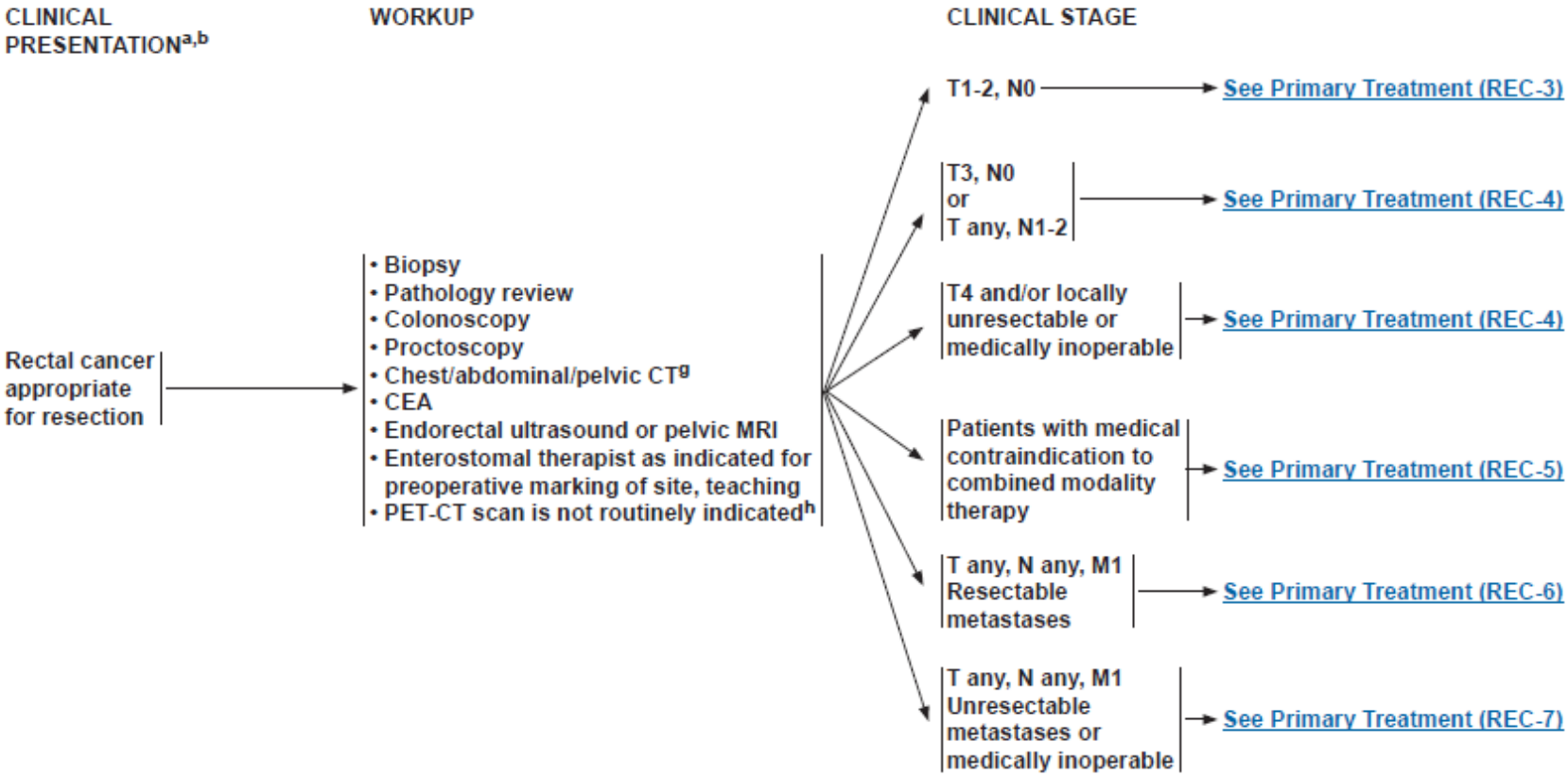

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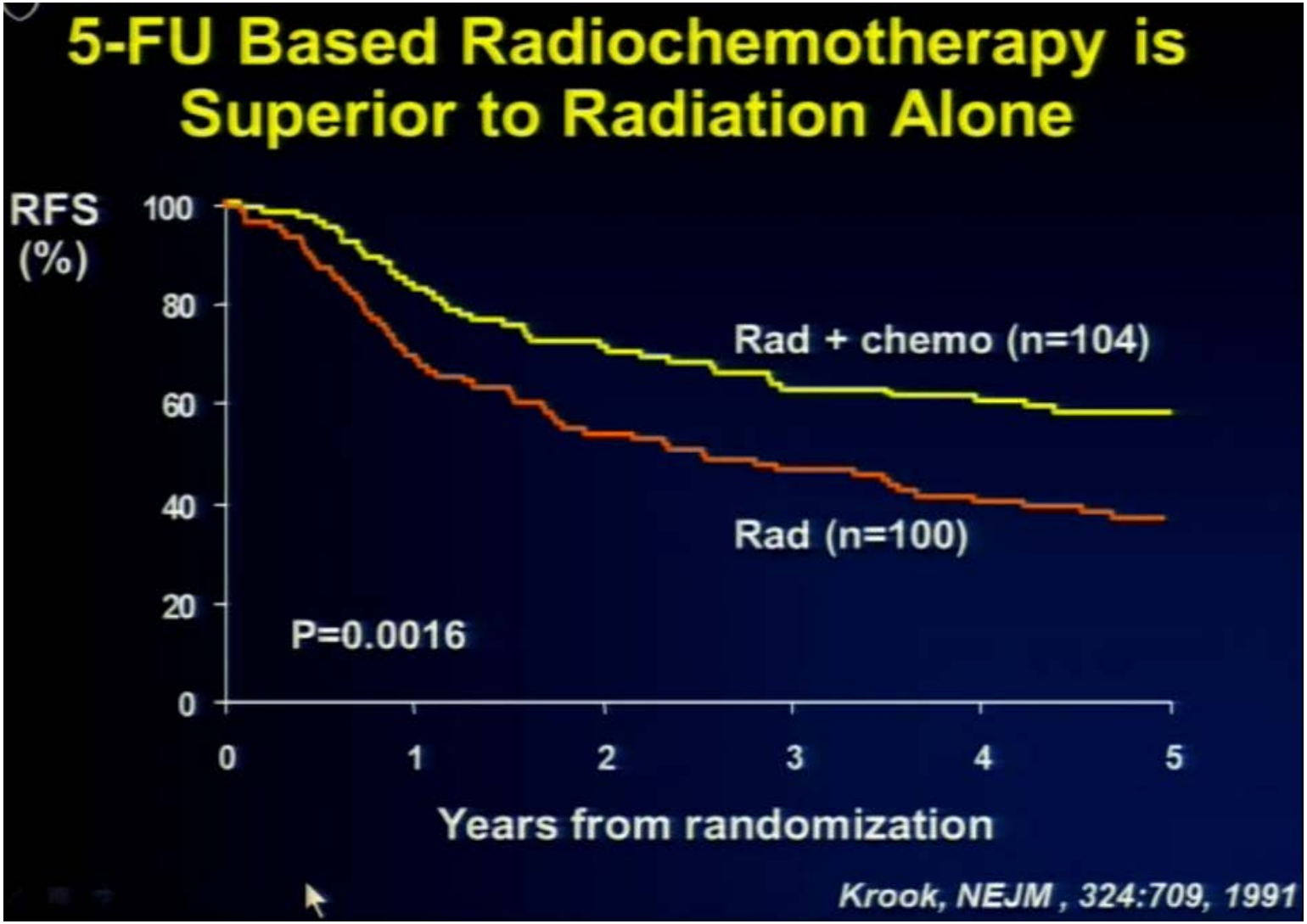
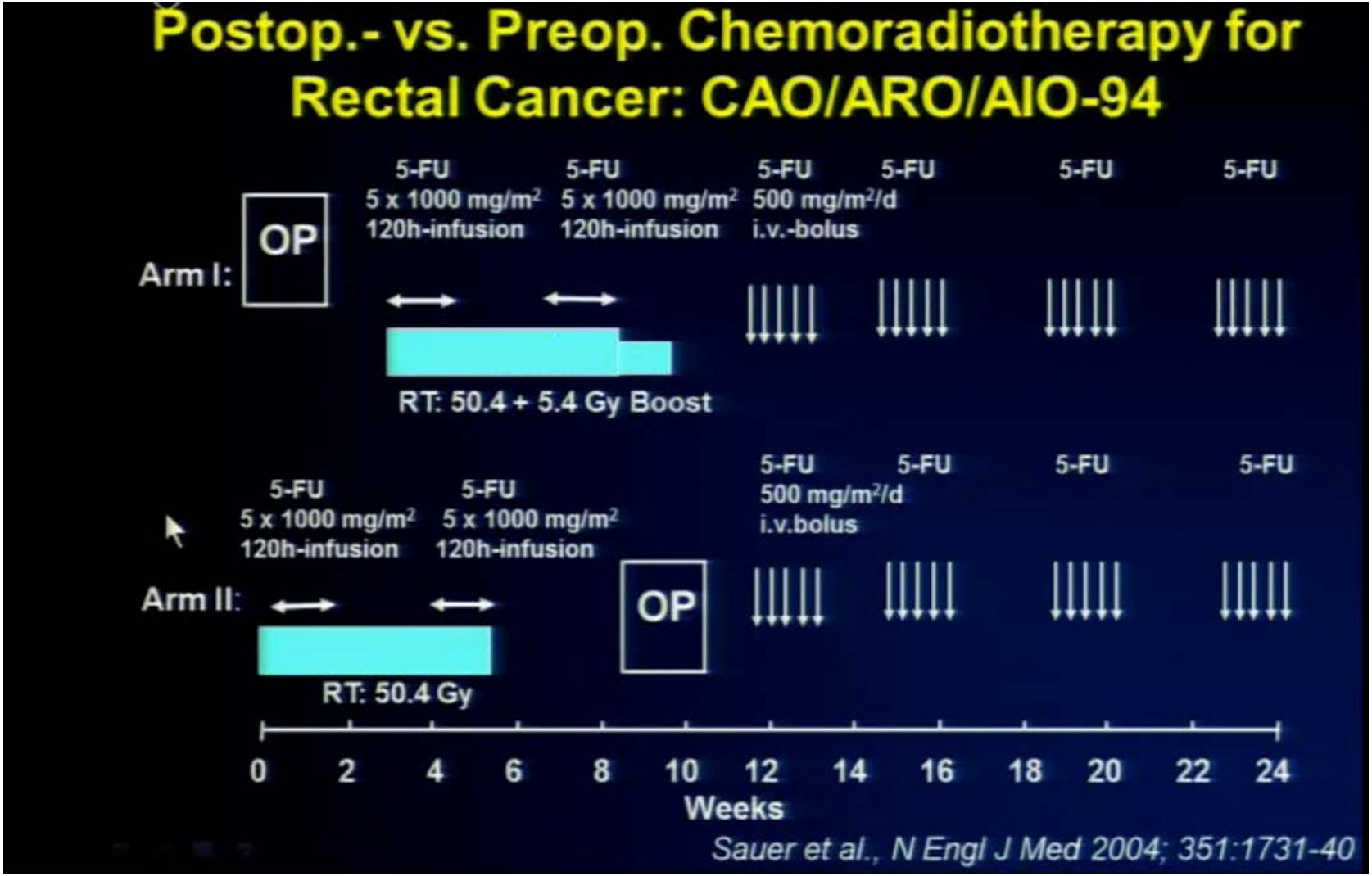


Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT

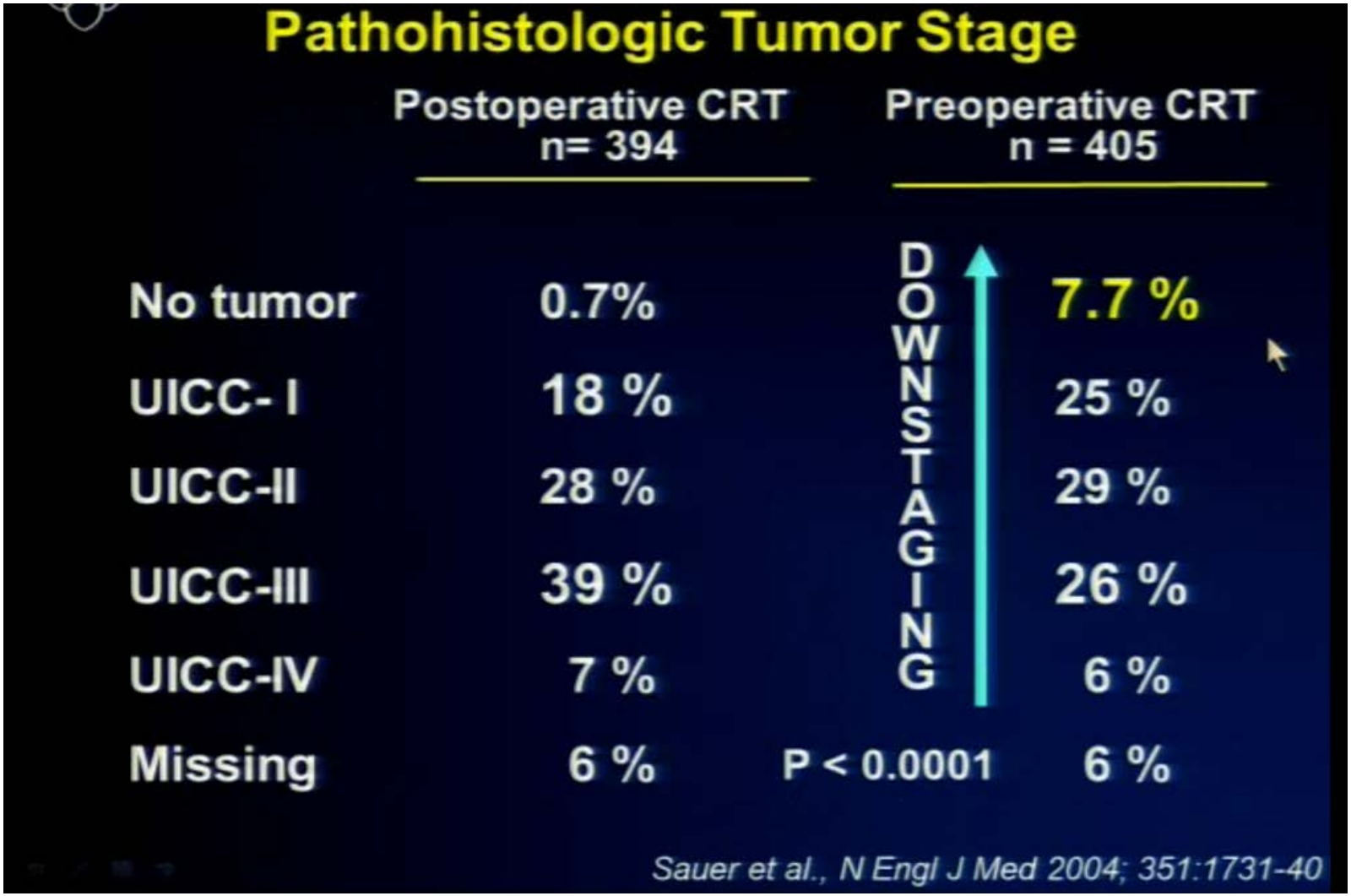
Table 1. Baseline Characteristics of the 799 Eligible Patients, According to Randomly Assigned Treatment Group.*

Characteristic	Preoperative Chemoradiotherapy (N=405)	Postoperative Chemoradiotherapy (N=394)	P Value
Age — yr			0.35
Median	62	62	
Range	30–76	33–76	
Sex — no. (%)			0.21
Male	286 (71)	262 (66)	
Female	119 (29)	132 (34)	
Clinical tumor category — no. (%)			0.16
T1 or T2	19 (5)	18 (5)	
T3	277 (68)	262 (66)	
T4	23 (6)	10 (3)	
Unknown	86 (21)	104 (26)	
Clinical nodal category — no. (%)			0.88
Node-negative	168 (41)	153 (39)	
Node-positive	217 (54)	202 (51)	
Unknown	20 (5)	39 (10)	
Distance of tumor from anal verge — no. (%)			0.008
<5 cm	157 (39)	117 (30)	
5–10 cm	166 (41)	168 (43)	
>10 cm	47 (12)	69 (18)	
Unknown	35 (9)	40 (10)	

Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT



Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT



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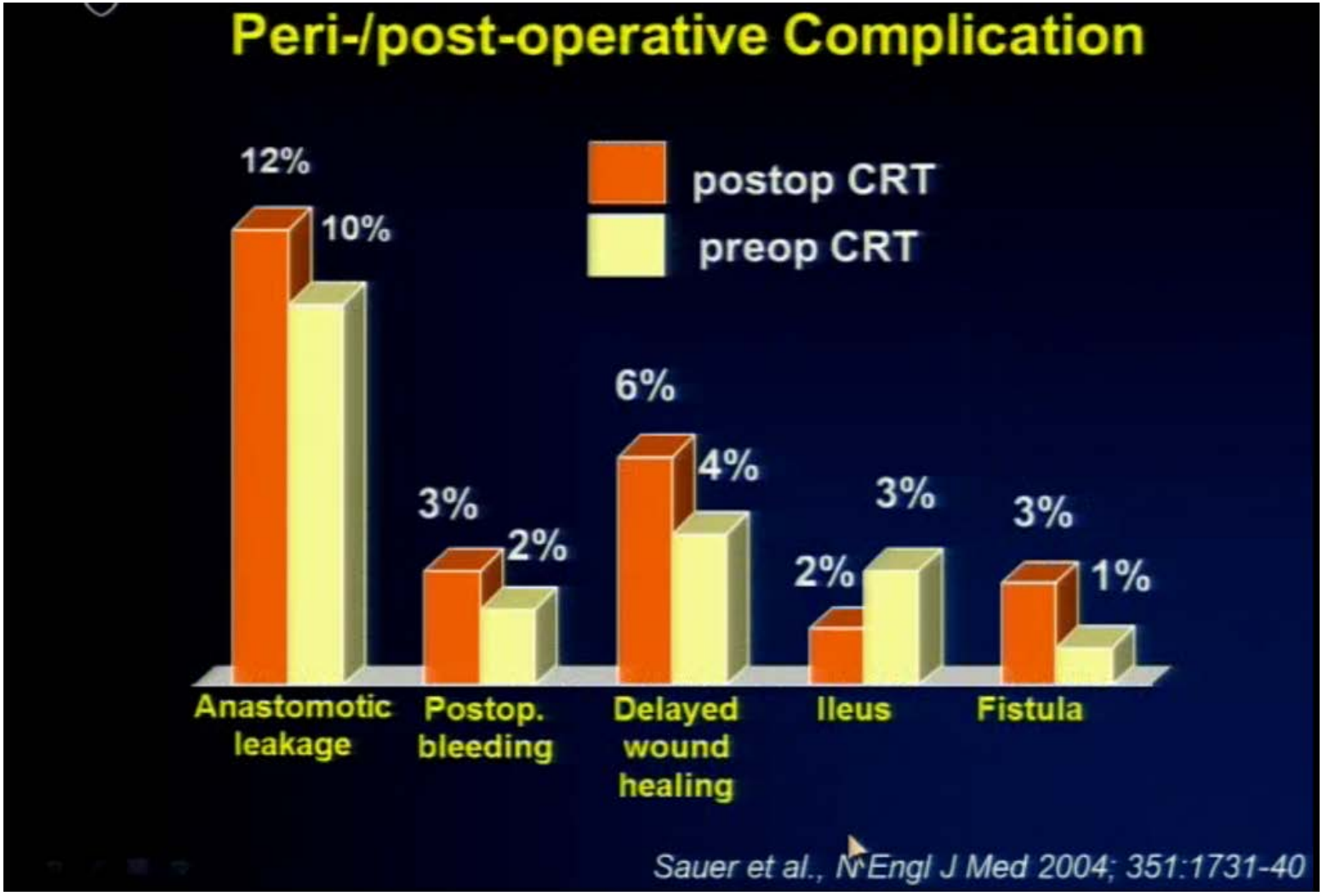

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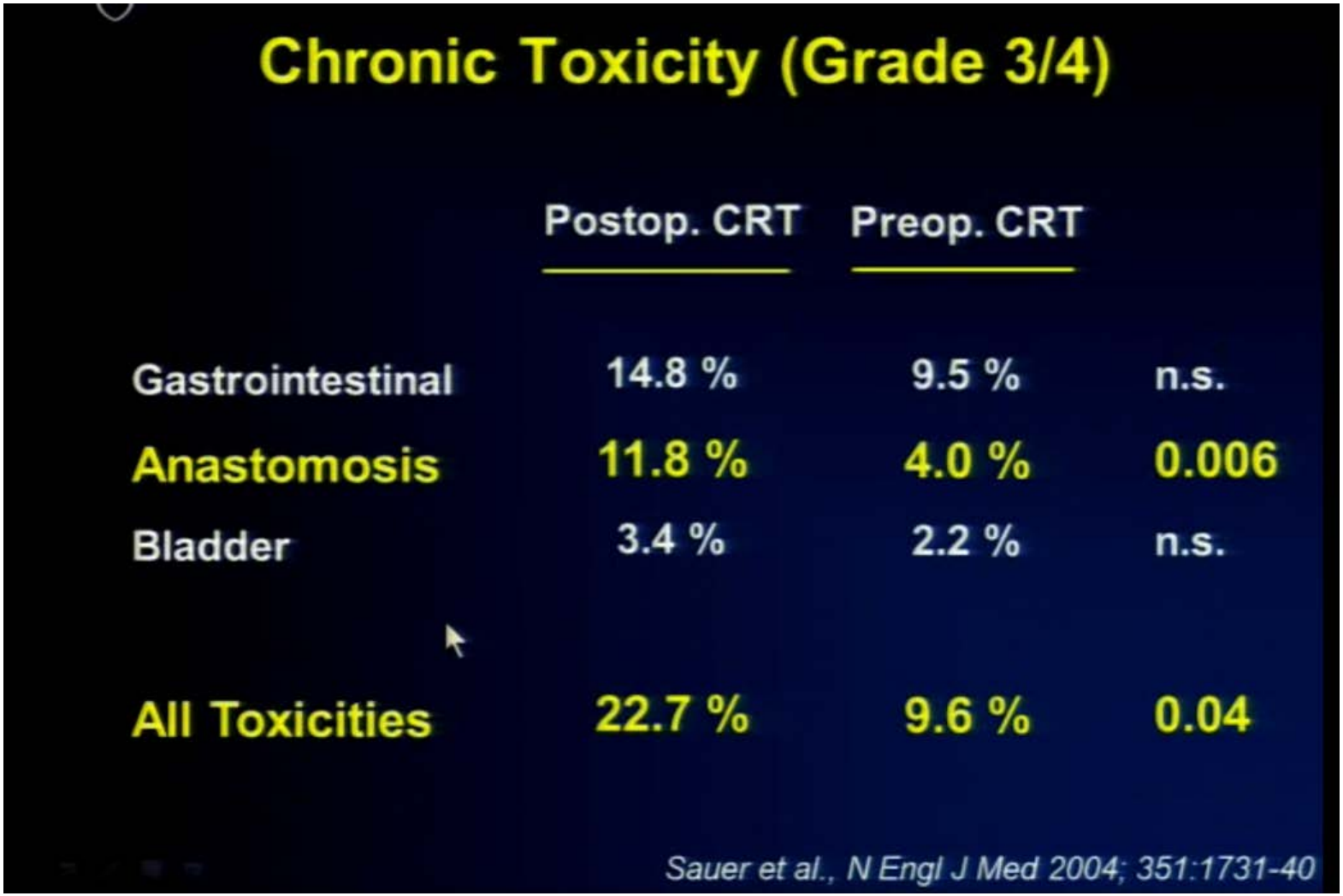

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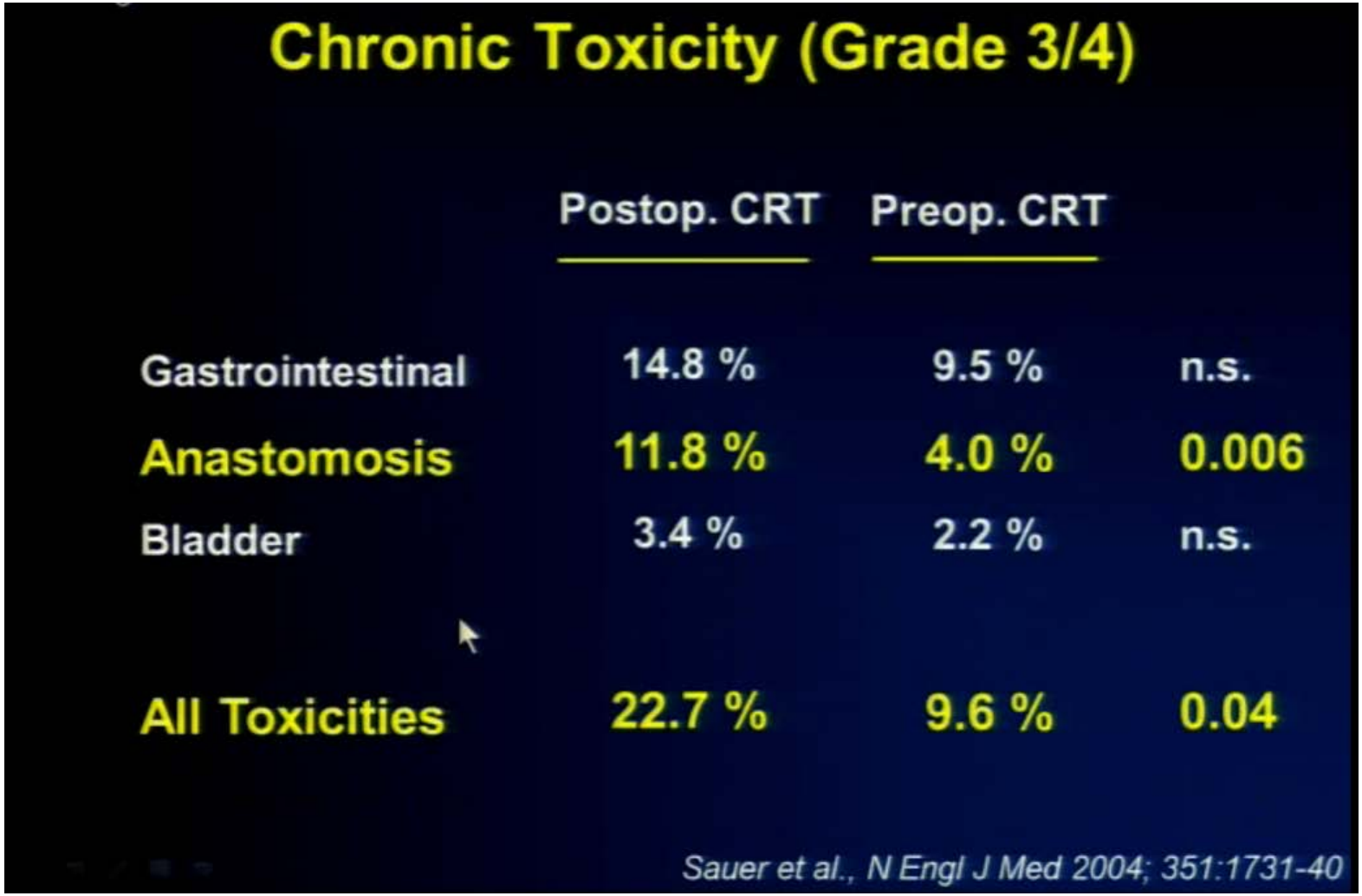

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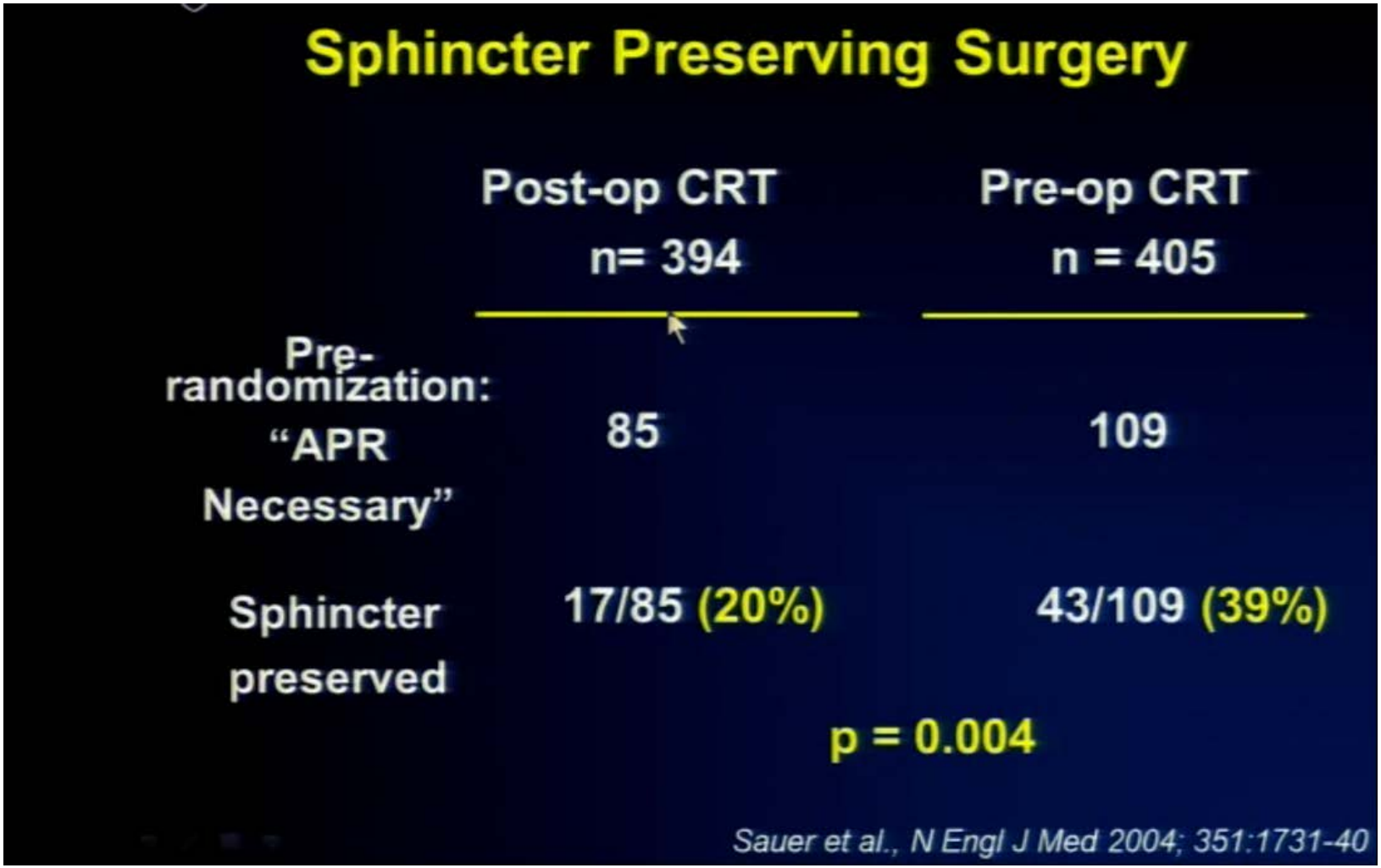

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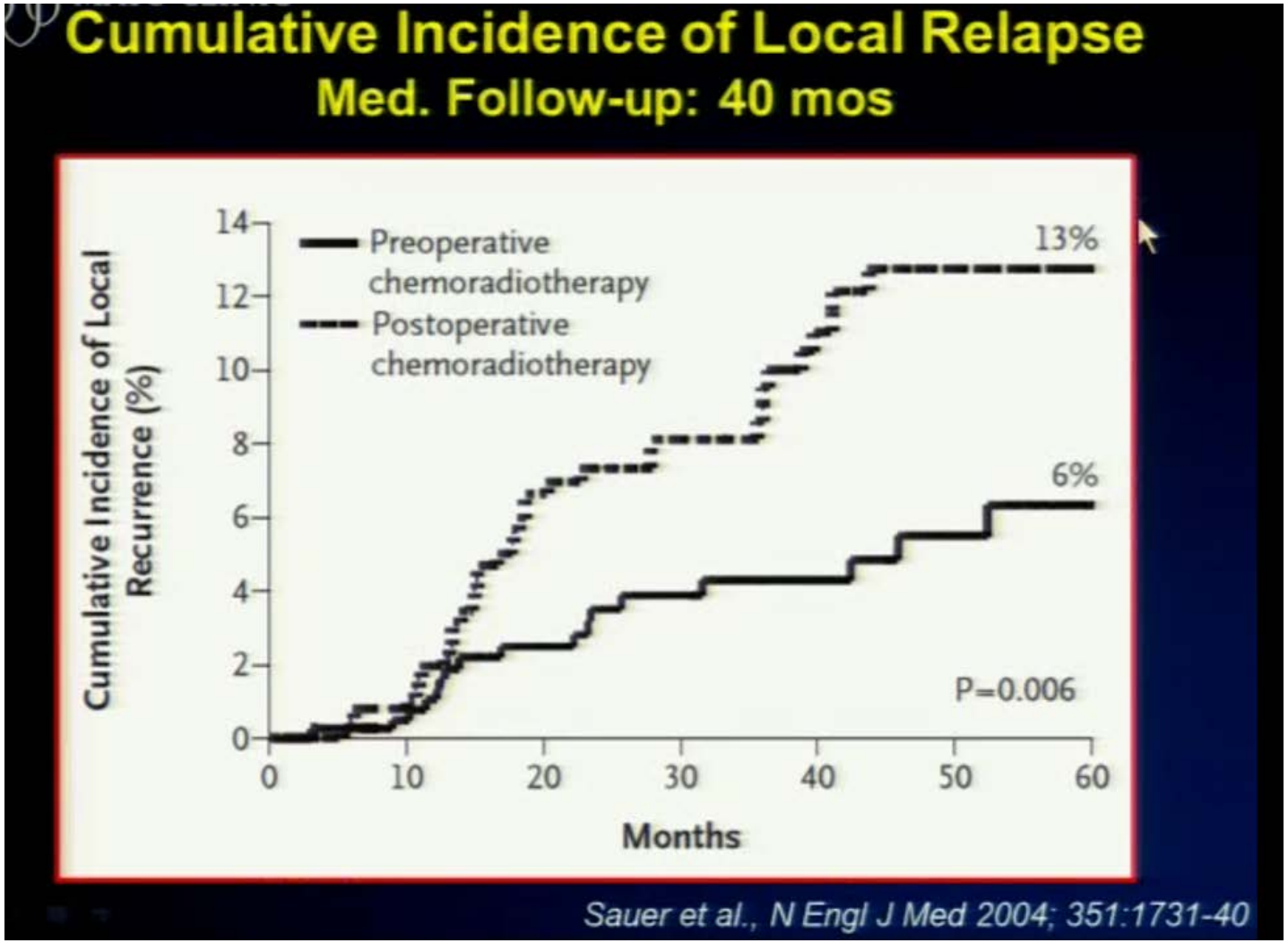

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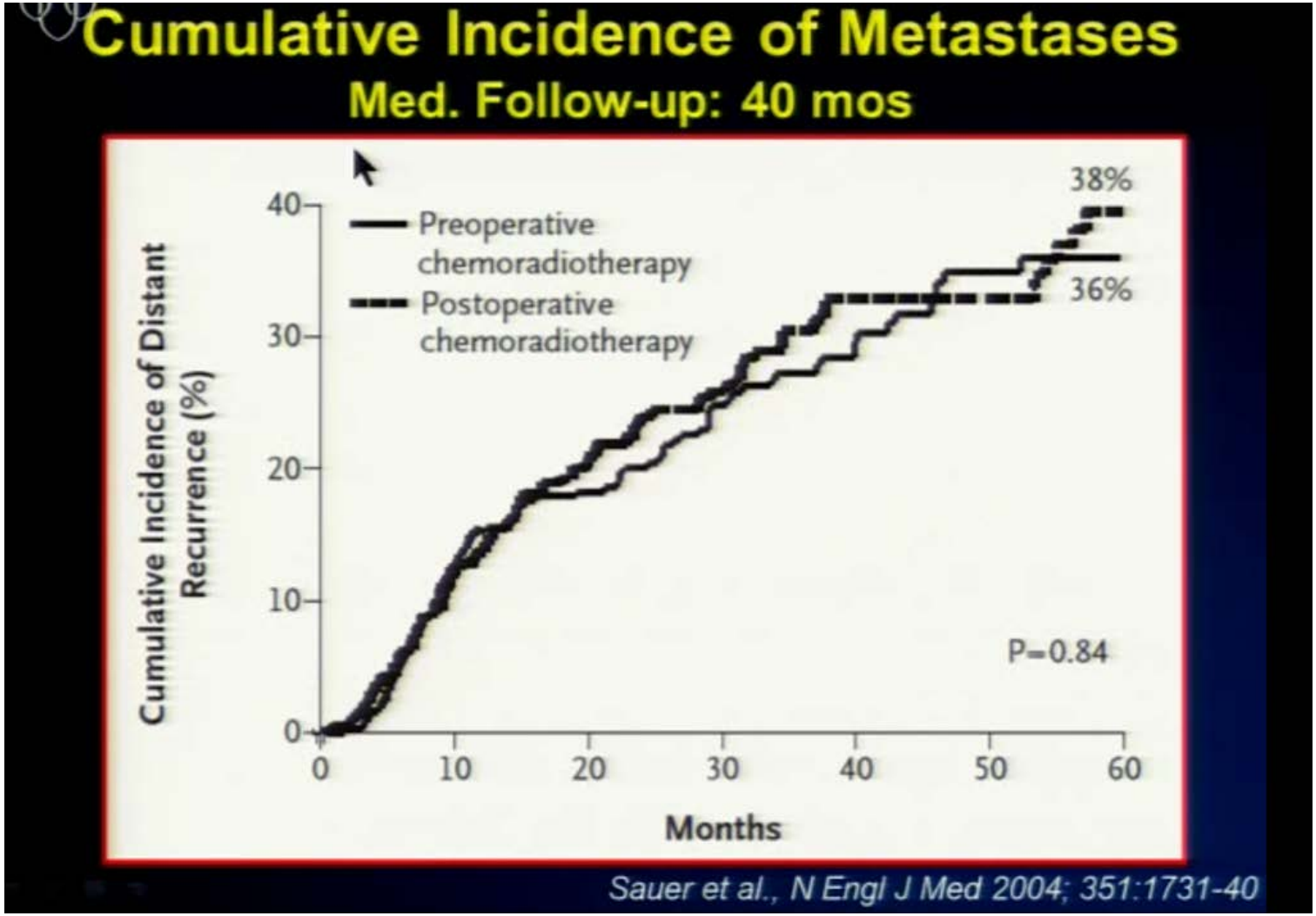

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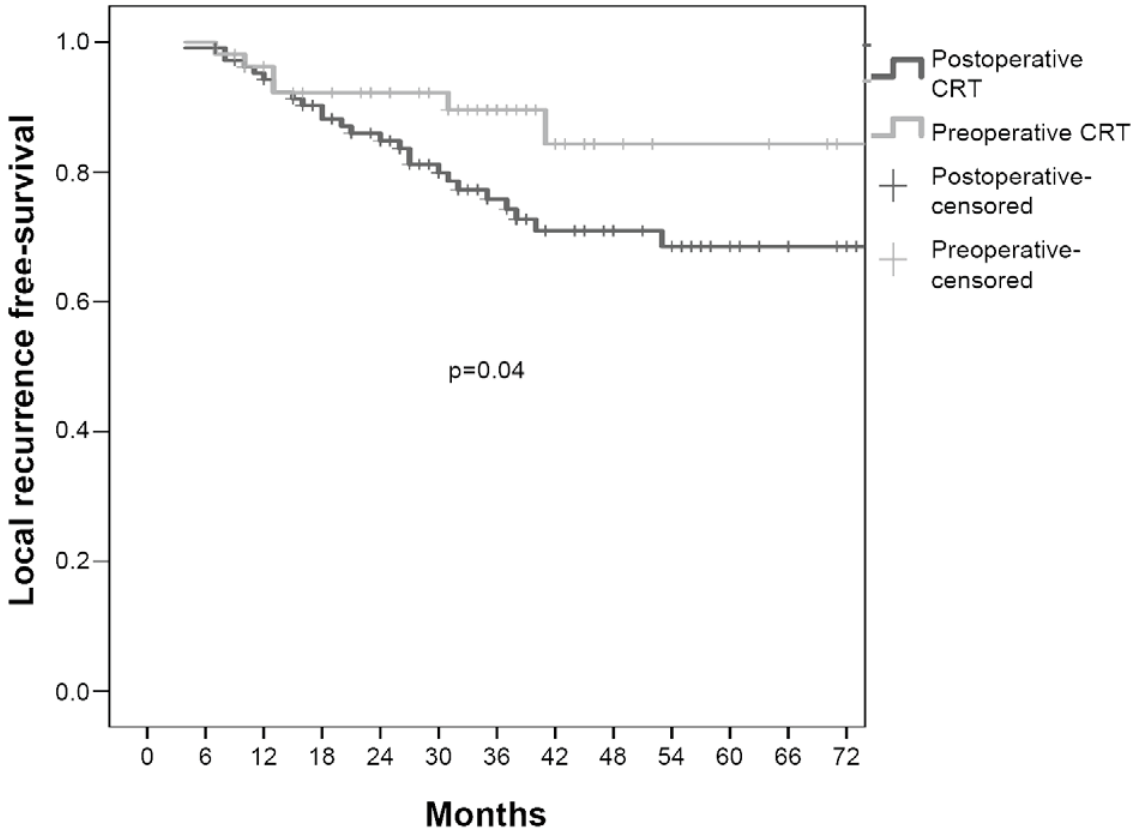
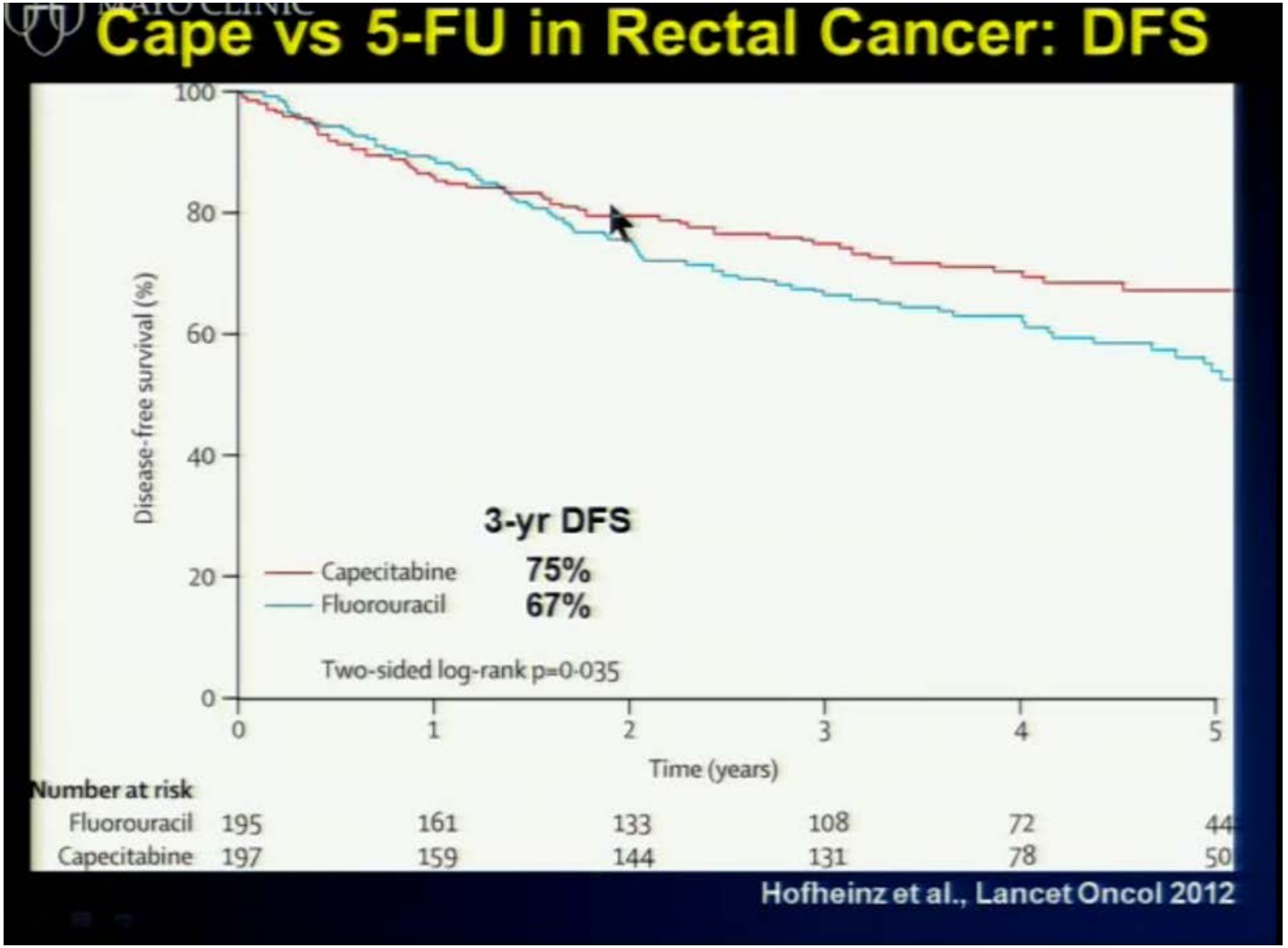
Cerrahi Öncesi KRT



Tural D et al. Preoperative chemoradiotherapy improves local recurrence free survival in locally advanced rectal cancer. JBUON 2013

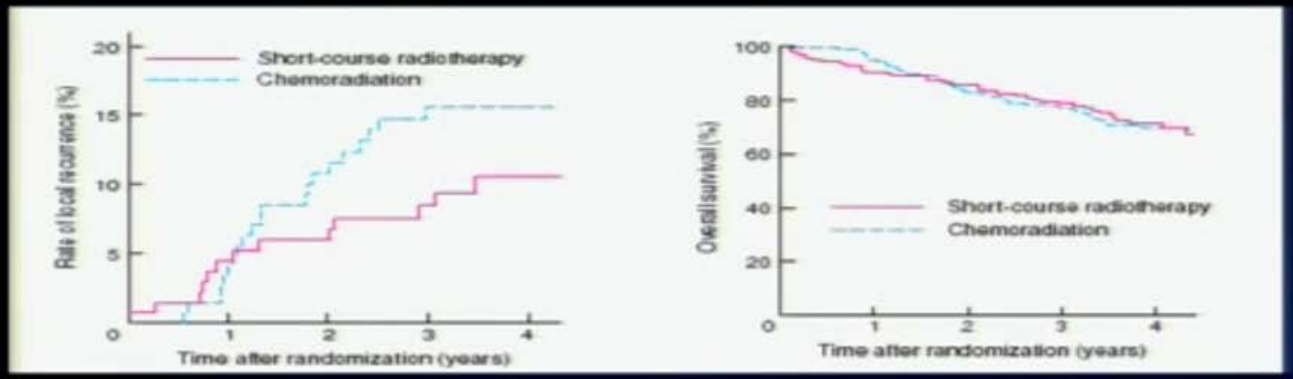
Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT



Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT vs. 5X5 RT

5 x 5 Gy versus 5-FU CRT ?

POLISH



Bujko et al., Br J Surg 2006

AUSTRALIA

T3NxM0	5 x 5 Gy	5-FU CRT	P
Number of pts.	163	163	
3-year LR rates	7.5%	4.4%	0.24
5-year M1	27%	30%	0.92
5-year OS	74%	70%	0.62

Ngan et al., JCO 2012

Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT Dezavantajları

Overtreatment

- Alman çalışmasında cT3,T4 yada cN+ kabul edilen ve cerrahi sonrası KRT kolundaki hastaların %18 patolojik Evre I

Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT cT3 N0?

VOLUME 26 · NUMBER 3 · JANUARY 20 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

- The accuracy of preoperative ERUS/MRI for staging mid to distal cT3N0 rectal cancer is limited because 22% of patients have undetected mesorectal LN involvement despite combined-modality therapy

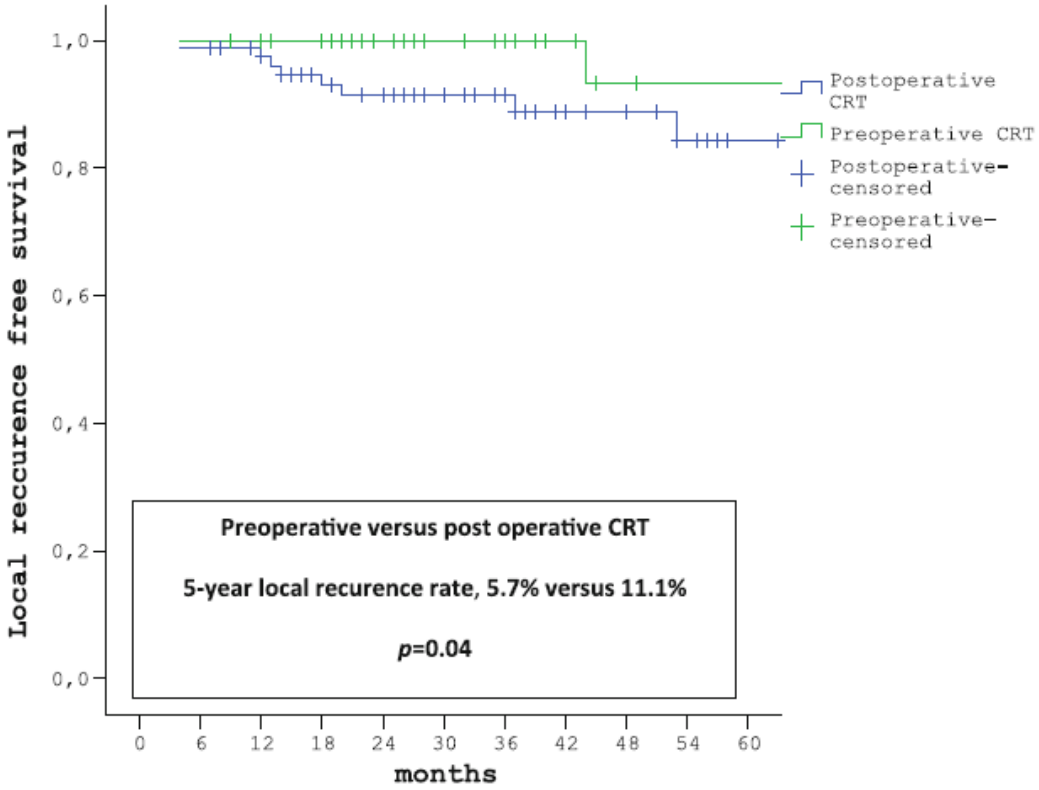
DOI: 10.1200/JCO.2007.13.5434

J Clin Oncol 26:368-373. © 2008 by American Society of Clinical Oncology

Rektum Kanserinde Tedavi
Cerrahi Öncesi KRT cT3 N0?

Int J Clin Oncol

Fig. 1 Local recurrence-free survival in patients with preoperative chemoradiation vs. postoperative chemoradiation in stage T3, N0, M0 rectal adenocarcinoma



Tural D et al. Preoperative versus postoperative chemoradiotherapy in stage T3, N0 rectal cancer. Int J Clin Oncol

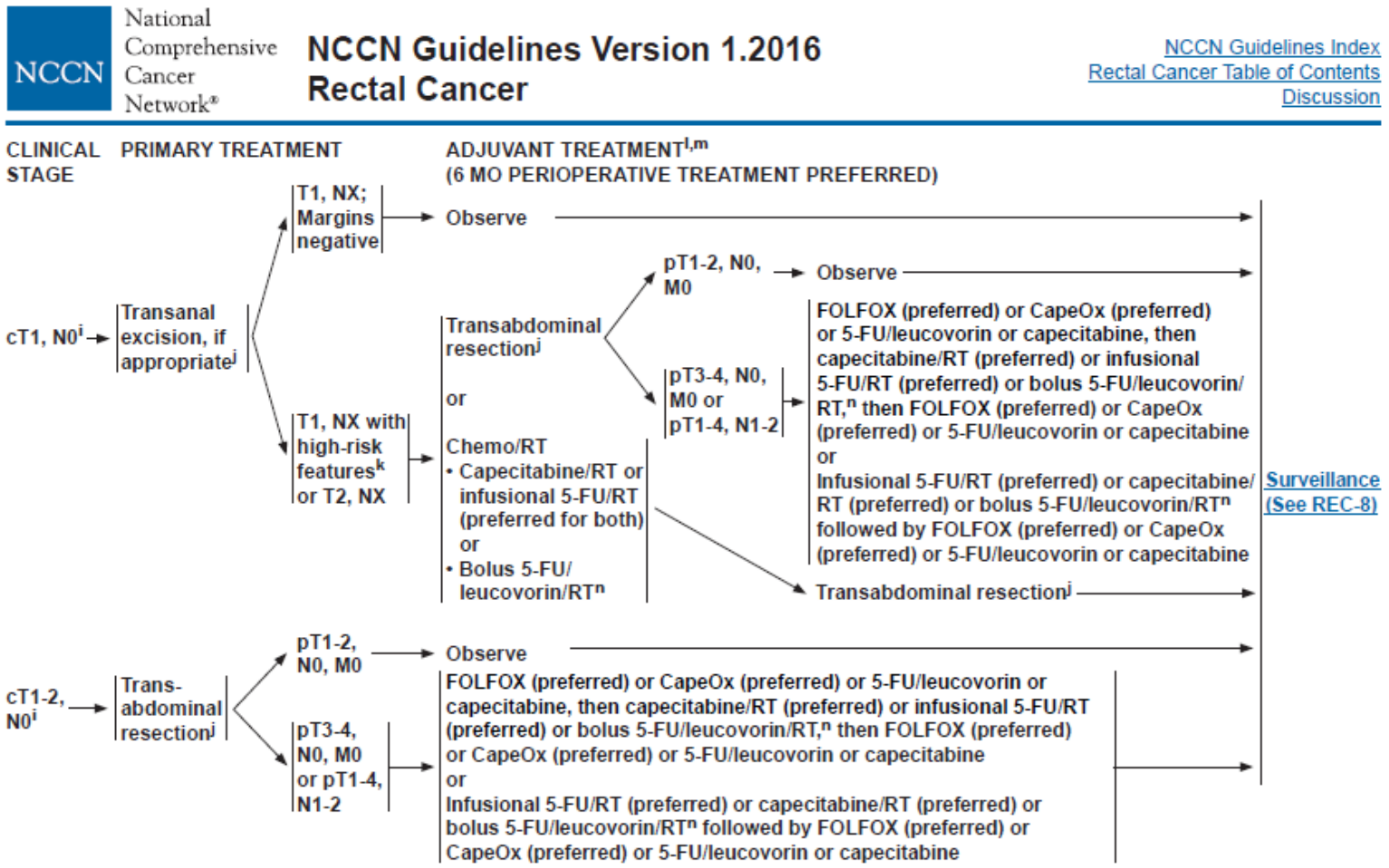
Proksimal Rektum pT3 N0 Kanserinde Tedavi Cerrahi Sonrası KRT? KT?

- The rectal cancers were stratified as upper rectal if located within 10 to 15 cm from the anal verge

- Local recurrence rates at 5 years were 7.5% in the upper rectal group compared with 21.5% in the lower rectal group

- For carefully selected patients with upper T3N0 lesions it may be appropriate to omit pelvic radiation if careful pathology evaluation suggests a low risk of local recurrence (minimal perirectal fat invasion, negative circumferential margins, adequate node dissection) after a confirmed TME by an experienced surgeon.

Rektum Kanserinde Tedavi



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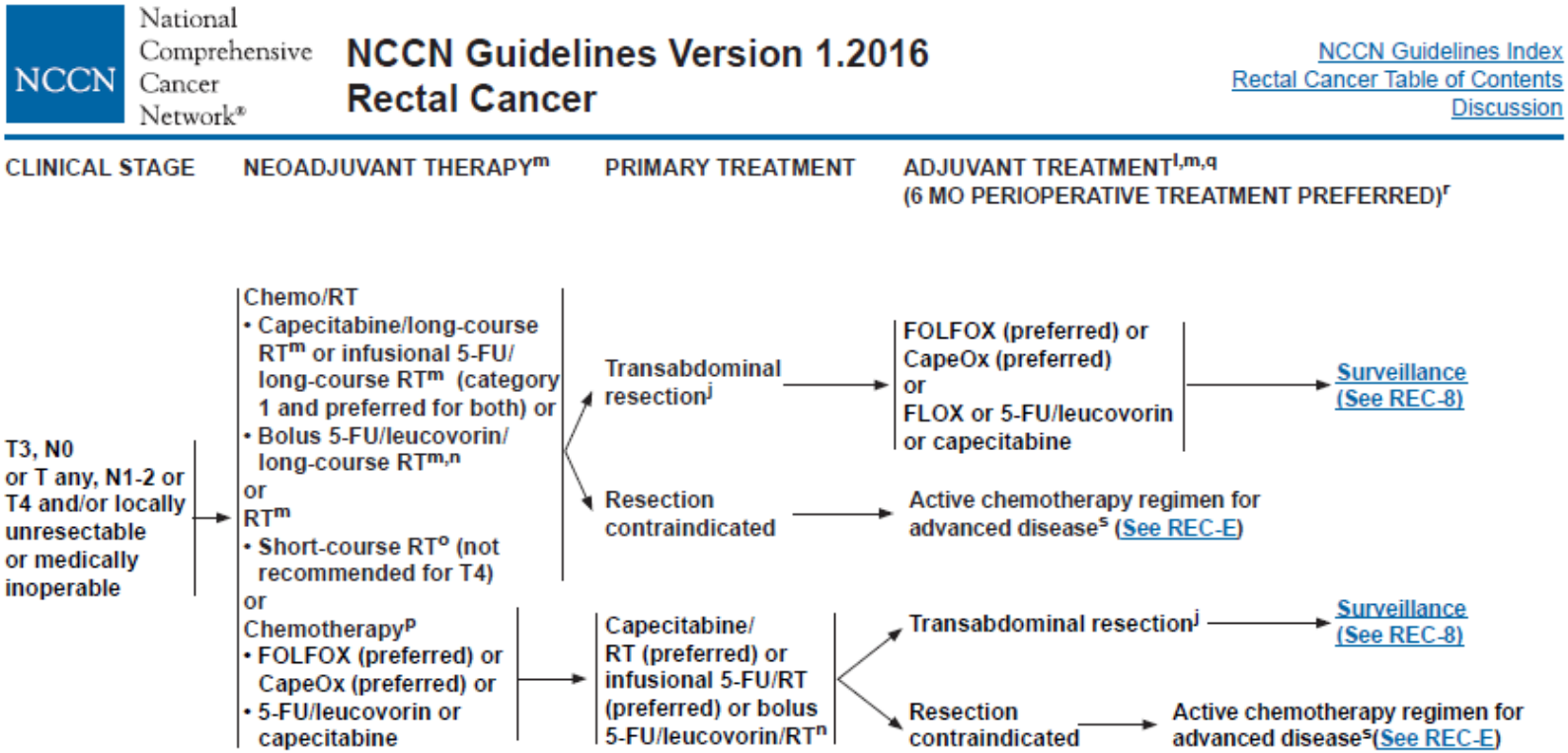

52 yaşında E , rektal kanamayla başvuruyor. Kolonoskopide rektum 6 cm kitle saptanıyor. Kolonoskopik bx; adeno ca olarak geliyor. Rektal EUS T3 N1 ile uyumlu ve BT'de uzak metastaz yok. Aşağıdaki tedavilerin hangisini önerirsiniz?

A- Abdominoperitoneal rezeksiyon sonrası adjuvan kemoradiyoterapi

B- Abdominoperitoneal rezeksiyon sonrası adjuvan kemoterapi

C-Neoadjuvan 5-FU eş zamanlı radyoterapi sonrası Abdominoperitoneal rezeksiyon sonrası adjuvan kemoterapi

D-Hepsi