

# **Gastric Cancer: Burning Issues**

#### Shailesh V. Shrikhande

MS, MD, FRCS (Hon)

Deputy Director, Tata Memorial Hospital Chief, GI and HPB Surgery HOD & Professor, Surgical Oncology Tata Memorial Centre Mumbai, India





# Early Gastric Cancer (EGC): Definition and treatment

- Defined as cancer which is confined to the mucosa and submucosa regardless of lymph nodes status. (T1, any N)
- Treatment :
  - endoscopic resection,
  - surgery (gastrectomy),
  - antibiotic treatment for eradication of *Helicobacter pylori*, and adjuvant therapies





# **Endoscopic Diagnosis**



White light endoscopy

Chromoendoscopy

Narrow band imaging (NBI)



## **NBI vs WLE vs Chromoendoscopy**

- NBI superior to chromoendoscopy & conventional endoscopy
- Accuracy

 WLE
 68.9%

 Chromoendoscopy
 91 %

 NBI
 93.6 %

J. Zhang et al. BMC Gastroenterology, Vol. 11, 2011, pp. 135-141.



# **Endoscopic Ultrasonography (EUS)**

#### **Diagnosing invasion depth**



Preoperatively to assess the submucosal vasculature in order to predict intraoperative bleeding



# EMR vs ESD

Meta-analysis comparing outcomes of EMR and ESD

9 nonrandomized studies; 2410 patients and 4237 treated lesions

En-bloc resection rate was 94.3% with ESD vs 53.8% with EMR

**Complete resection rates were 92.6 and 37.5%** 

5-year recurrence-free rate was 100 versus 82.5%.

For tumors < 5mm in size, there was no difference in complete or en-bloc resection rates between the two techniques

Cao Y, Liao C, Tan A, et al. Endoscopy 2009



# **Strip Biopsy**



**Identification of lesion** 



Margin: chromoendoscopy



Injection of physiological solution







Grasping of lesion with forcep

Cutting





**Disadvantage:** 

Large tumors (>1.5cm) cannot be resected en bloc

**Piecemeal resection: difficult to assess completion/ curability** 

**Increased incidence of residual tumor: 2.3 - 35 %** 





#### Dissecting along the submucosal layer directly with a high-frequency knife

**Indications:** 

Differentiated intramucosal cancers without ulcer findings, irrespective of size

**Differentiated intramucosal cancers < 3 cm in size with ulcer** 

Differentiated minute invasive submucosal SM1 (< 500 μm below the muscularis mucosa) cancers < 3 cm

Undifferentiated intramucosal cancers < 2 cm in size without ulcer



# **ESD- procedure**



Figure Method of endoscopic submucosal dissection. (A-B) Marking under chromoendoscoy; (C) solution injection outside marking; (D) circumferential mucosal incision; (E) solution injection beneath the lesion; (F-G) submucosal dissection; (H) retrieval of resected specimen



# Post-Endoscopic Resection: Management, Surveillance

**EMR:** 

Annual endoscopic surveillance to ensure early detection of metachronous cancer (5.9%)

#### ESD:

Annual endoscopic surveillance + half-yearly abdominal CT or EUS, for at least 3 years in order to detect lymph node or distant metastasis



# **Surgery for EGC**

For those not meeting the criteria for EMR / ESD

- Gastrectomy
- Local resection
- Laparoscopic resections

NCCN recommends observation without adjuvant therapy for patients with Tis or T1, N0 disease who have uninvolved resection margins.



Is Gastrectomy a major procedure?

ACS NSQIP database: Gastrectomy for Cancer 2005 to 2010 N=2,580

Total Gastrectomy vs. Partial gastrectomy Morbidity- 29.3 vs. 19.9 % (p < 0.001) Mortality- 5.4 vs. 3.4 % (p < 0.015)

Gastrectomy for cancer as currently practiced carries significant morbidity and mortality

Papenfuss WA et al. Ann Surg Oncol. 2014



## **Levels Of LN Dissection**

- D1 : Stations 1- 6
- D2 : D1 + stations 7-11
- D3 : D2 + stations 12-14
- D4 : D3 + stations 15-16

#### Anything less than D1 is termed as D0 dissection













# **Bursectomy**

**Meta-analysis** 

- 2 RCT's; 3 Retrospective studies
- No superiority to non-bursectomy (OS)
- Subgroup analyses:
  - ?May improve survival in serosa-positive patients

Wei-Song Shen et al. World J Gastroenterol 2014

Bursectomy is not recommended as a routine procedure Well designed large scale studies necessary?













Shrikhande SV et al. Recent Advances in Surgery, Jaypee, India 2006



Surgical treatment of gastric cancer: 15-year follow-up  $\rightarrow \mathscr{D}$ 

#### Median follow-up of 15 years

D2 lymphadenectomy: Lower locoregional recurrence and gastric-cancer-related death rates than D1.

D2 arm: Significantly higher postoperative mortality, morbidity, and reoperation rates.

Because a safer, spleen-preserving D2 resection technique is currently available in highvolume centres, D2 lymphadenectomy is the recommended surgical approach for patients with resectable (curable) gastric cancer.



# **Learning Curve**

#### Mortality and morbidity rates in RCTs

	MRC trial	Dutch trial	Our Centre
Morbidity	46%	43%	4.4-15.5%
Mortality	13%	10%	0-1.6%

#### Attributed to learning curve effect Distal Pancreato-splenectomy

Cusheri et al. Lancet et al.1996;347:995-9 Bonenkamp JJ. Lancet.1995;345:745-8





#### Learning curve in D2 gastrectomy

## Prospective audit on a single surgeon trained in D2 18-24 months / 15-25 cases before plateau

D2 gastrectomy only in centres with adequate supervision

Parikh D et al. Br J Surg. 1996;83:1595-9

# **Gastric Cancer**

**Digestive** 



Original Paper

Dig Surg 2006;23:192–197 DOI: <u>10.1159/000094537</u>

Received: December 12, 2005 Accepted: April 10, 2006 Published online: July 12, 2006

#### D2 Lymphadenectomy for Gastric Cancer in Tata Memorial Hospital: Indian Data Can Now Be Incorporated in Future International Trials

Shailesh V. Shrikhande<sup>a</sup> Parul J. Shukla<sup>a</sup> Sajid Qureshi<sup>a</sup> Ravichand Siddachari<sup>a</sup> Vivek Upasani<sup>a</sup> Mukta Ramadwar<sup>b</sup> Anagha C. Kakade<sup>c</sup> Rohini Hawaldar<sup>c</sup>

Morbidity (4.4%) Mortality (1.25%) Consultants n=84 Residents n=75

#### No difference in outcomes!

Dig Surg 2006



## **IMPORTANCE OF FROZEN SECTION**

**390 patients** 

22% margins positive

**Clear resection margins significantly** 

improved survival

Resection line disease in stomach cancer British Stomach Cancer Group Br Med J (Clin Res Ed). 1984;289(6445):601-3

Practical Approach Aim for a 5 cm margin Intra-operative analysis is standard



# Gastric Cancer (>T2N+)



ECF x 3 -> Surgery -> ECF x 3 Epirubicin (50mg/m2) D1 Cisplatin (60mg/m2) D1 Fluorouracil (200mg/m<sup>2</sup>) IV D1-21 (TMH- 750 mg/m<sup>2</sup> 5 days) Cycles q3weeks



#### Perioperative Chemotherapy is routinely used at TMH



Epirubicin, oxaliplatin, and capectabine is just as "MAGIC"al as epirubicin, cisplatin, and fluorouracil perioperative chemotherapy for resectable locally advanced gastro-oesophageal cancer

	EOX		ECF
Chen et al. (2014)	Kalachand et al. (2013)	Our series (2014)	Cunningham et al. (2006)
26	52	99	250
55	62 (35-79)	51 (30-77)	62 (29-85)
73%	79%	75%	82%
n.a.	90%	93%	86%
0%	2%	1%	1%
85%	67%	80%	n.a.
n.a.	48%	60%	42%
11.5%	6%	76%	n.a.
11.5-19.2%	17%	1-14%	0.5-27.8%
	Chen <i>et al.</i> (2014) 26 55 73% n.a. 0% 85% n.a. 11.5% 11.5-19.2%	EOX           Chen et al. (2014)         Kalachand et al. (2013)           26         52           55         62 (35-79)           73%         79%           n.a.         90%           0%         2%           85%         67%           n.a.         48%           11.5%         6%           11.5-19.2%         17%	EOX           Chen et al. (2014)         Kalachand et al. (2013)         Our series (2014)           26         52         99           55         62 (35-79)         51 (30-77)           73%         79%         75%           n.a.         90%         93%           0%         2%         1%           85%         67%         80%           n.a.         48%         60%           11.5%         6%         76%           11.5-19.2%         17%         1-14%

Table 3: Comparison of compliance, toxicity and efficacy profile of EOX in published literature

NA = Not available. EOX = Epirubicin. oxaliplatin. capecitabine. ECF = Epirubicin. cisplatin. and fluorouracil

#### 99 patients; 94 taken up for surgery; 85 resected 64% compliance to 6# Comparable grade III/IV toxicities



## Can Chemotherapy replace the need for D2 Lymphadenectomy

Shrikhande *et al. World Journal of Surgical Oncology* 2013, **11**:31 http://www.wjso.com/content/11/1/31



RESEARCH

**Open Access** 

## D2 lymphadenectomy is not only safe but necessary in the era of neoadjuvant chemotherapy

Shailesh V Shrikhande<sup>1\*†</sup>, Savio G Barreto<sup>1†</sup>, Sanjay D Talole<sup>2</sup>, Kumar Vinchurkar<sup>1</sup>, Somashekar Annaiah<sup>1</sup>, Kunal Suradkar<sup>1</sup>, Shaesta Mehta<sup>3</sup> and Mahesh Goel<sup>1</sup>

#### No difference in LN harvested

LN metastases present even in those with major pathological response to NACT

World J Surg Oncol 2013

ORIGINAL ARTICLE





# Proximal gastrectomy versus total gastrectomy for proximal third gastric cancer: total gastrectomy is not always necessary

Pavan Sugoor<sup>1</sup> • Sanket Shah<sup>1</sup> • Rohit Dusane<sup>1</sup> • Ashwin Desouza<sup>1</sup> • Mahesh Goel<sup>1</sup> • Shailesh V. Shrikhande<sup>1</sup>

*Conclusions* The extent of resection for proximal third gastric cancer does not influence the clinical outcome. PG and TG have similar survival rates. Both procedures can be accomplished safely. Therefore, PG should be an alternative to TG, even in locally advanced proximal gastric cancers treated by NACT, provided that the tumor size and location permit preservation of adequate remnant of stomach without compromising oncological resection margins. Future QOL studies would further lend credence to the concept of PG for proximal third gastric cancer.



# Radical Gastrectomy: Trends over time

Period	A (2002 - 2005)	B (2006 - 2009)	C (2010 - 2014)	D (2015 – 2019)	Total	
Ν	220	227	542	785	1774	
Total	33 (15%)	18 (4.9%)	94 (17.3%)	214 (27.26%)	359 (20.23%)	
Proximal Gastrectomy	38 (17.3%)	23 (6.3%)	76 (14%)	54 (6.87%)	182 (10.25%)	
Subtotal Gastrectomy	140 (63.6%)	167 (45.9%)	313 (57.7%)	423 (53.88%)	795 (44.81%)	
Extended	5 (2.3%)	2 (0.5%)	30 (5.5%)	39 (4.96%)	55 (3.1%)	
Wedge/Sleeve	4 (1.8%)	17 (4.7%)	29 (5.4%)	35 (4.45%)	69 (3.9%)	
Leak rate	7 (3.2%)	8 (3.5%)	13 (2.4%)	18 (2.3%)	38 (2.14%)	
Re-exploration rate	5 (2.3%)	4 (1.8%)	28 (5.2%)	19 (2.4%)	42 (2.7%)	
Lymph node yield	15 (2 – 46)	14 (4 - 67)	17 (0 - 76)	19 (1-68)	17 (0 – 76)	
Median Hospital Stay	13 (7 – 52)	12 (3 - 89)	8 (3 - 56)	8 (5-51)	8 (3 – 89)	
Morbidity	14 (6.4%)	55 (24.2%)	118 (21.8%)	99 (12.6%)	222 (12.51%)	
Mortality	2 (0.9%)	1 (0.4%)	12 (2.2%)	9 (1.14%)	21 (1.18%)	

Bhandare M, Shrikhande SV et al. Indian Journal of Cancer 2019 Batra S, Bhandare M, Shrikhande SV et al. Manuscript in Submission 2020







Kitano S, et al. Surg Laparosc Endosc 1994; 4: 146-1148.





#### Major early complications following open, laparoscopic and robotic gastrectomy

K. M. Kim, J. Y. An, H. I. Kim, J. H. Cheong, W. J. Hyung and S. H. Noh

Department of Surgery, Yonsei University College of Medicine, 250 Seongsanno, Seodaemun-gu, Seoul 120-752, Korea Correspondence to: Dr S. H. Noh (e-mail: sunghoonn@yuhs.ac)

#### 5839 patients (4542 open, 861 lap and 436 robotic gastrectomies) Open: Higher Tumour stage / complex resections Minimally invasive: Anastomotic leak commoner

"Laparoscopic and robotic gastrectomy had overall complication and mortality rates similar to open surgery, but anastomotic leaks were more common with the minimally invasive techniques".



Long-term survival after laparoscopic distal gastrectomy is not inferior to open distal gastrectomy in clinical stage I gastric cancer.

Study suggests that the laparoscopic distal gastrectomy is an oncologically acceptable alternative to open distal gastrectomy

Koreans now moving towards Laparoscopic gastrectomy in advanced gastric cancer and robotic gastrectomy



# **Advanced Peritoneal Carcinomatosis (PC)**

- Peritoneal carcinomatosis presents as a significant treatment challenge
- Incidence,
- In GC:

20% at presentation (60% in the natural history of disease)





#### **Peritoneal Cancer Index**





# Extent of CarcinomatosisLow :PCI < 10</td>Moderate :PCI > 10, <20</td>High :PCI > 20

Annals of SURGICALONCOLOGY OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY



ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Improves Survival of Patients with Peritoneal Carcinomatosis from Gastric Cancer: Final Results of a Phase III Randomized Clinical Trial

- Randomized phase III study
- Sixty-eight gastric PC patients were randomized into CRS alone (n = 34) or CRS ? HIPEC (n = 34)
- The median survival was 6.5 months in CRS and 11.0 months in the CRS + HIPEC groups
- Conclusions. For synchronous gastric PC, CRS ? HIPEC with mitomycin C 30 mg and cisplatin 120 mg may improve survival with acceptable morbidity.



# **Prophylactic HIPEC**

In high risk cases: T4 cancers **Krukenburg tumours Perforated tumours Positive peritoneal fluid cytology** Minimal synchronous PC

## GI resections in the Elderly: Perioperative Morbidity



	Total	<65 yrs	≥ 65 yrs	<b>P</b> *	<70 yrs	≥ 70 yrs	P\$
Overall morbidity	22.2% (586/2643)	21.7% (472/2171)	24.2% (114/472)	0.253	21.4% (516/2408)	29.8% (70/235)	0.003
Pancreas	39.8% (237/595)	38.7% (191/494)	45.5% (46/101)	0.198	38.3% (210/548)	57.4% (27/47)	0.010
Liver	23.4% (37/158)	23.1% (30/130)	25% (7/28)	0.827	22.3% (33/148)	40% (4/10)	0.245 #
Gall Bladder & Biliary Tract	12.1% (33/273)	11.5% (28/243)	16.7% (5/30)	0.381#	12.3% (32/261)	8.3% (1/12)	1.000 #
Stomach	19.7% (100/507)	18.5% (76/410)	24.7% (24/97)	0.167	18.4% (84/456)	31.4% (16/51)	0.027
Colorectal	16.1% (179/1110)	16.1% (144/894)	16.2% (35/216)	0.972	15.6% (155/995)	20.9% (24/115)	0.144

Batra S et al. Dig Surg 2016

## GI resections in the Elderly: Perioperative Morbidity



**Original Paper** 



Dig Surg 2016;33:146–156 DOI: 10.1159/000443217 Received: July 21, 2015 Accepted: December 7, 2015 Published online: January 29, 2016

### Major Gastrointestinal Cancer Resections in the Elderly in India: Poised for Future Challenges

Swati Batra<sup>a</sup> Kunal Suradkar<sup>a</sup> Sanjay Talole<sup>b</sup> Ashwin Desouza<sup>a</sup> Mahesh Goel<sup>a</sup> Shailesh Vinayak Shrikhande<sup>a</sup>

<sup>a</sup>Department of GI and HPB Surgical Oncology and <sup>b</sup>Department of Biostatistics and Epidemiology, Tata Memorial Hospital, Dr. Ernest Borges Road, Parel, Mumbai, India



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Dig Surg 2016;33:146-56



# Summary

- **Amongst top 10 Indian Cancers**
- Vast majority are locally advanced
- Perioperative chemotherapy and D2 gastrectomy is the standard
- **Proximal gastrectomy is an option in selected tumors**
- Selective use of Laparoscopic subtotal gastrectomy
- No role for adjuvant chemoradiation except in R1 resections







Talent wins matches; Teams win championships



# AND A REPORT OF THE PARTY OF TH

## Prophylactic HIPEC in gastric cancer

Ref.	Type of study	Inclusion criteria	Treatment arms (No. of Patients)	Drugs used for IPC	Curative surgery	Complications	Post-op mortality	Survival	Peritoneal recurrence
Koga <i>et al</i> <sup>[65]</sup> , 1988	RCT	Serosa+	Surgery + HIPEC (26) vs surgery alone (21)	MMC	100% <i>vs</i> 100%	Leak 3.1% <i>vs</i> 7.1%	NA	30 mo 83% <i>vs</i> 67%	NA
Hamazoe <i>et al<sup>[67]</sup>,</i> 1994	RCT	Serosa+	Surgery + HIPEC (42) <i>vs</i> surgery alone (40)	MMC	95% <i>vs</i> 88%	Leak 4.8% vs 7.5%	0% <i>vs</i> 0%	5-yr 64% <i>vs</i> 52% Median survival 77 mo <i>vs</i> 66 mo	39% <i>vs</i> 59% (death due to PC)
Fujimura <i>et al</i> <sup>[72]</sup> , 1994	RCT	Serosa+	Surgery + HIPEC (22) vs surgery + CNPP (18) vs surgery alone (18 controls)	MMC CDDP	NA	30% vs 0% (perfusion vs surgery 40 pts vs 18)	NA	3-yr 68% vs 51% vs 23% (P < 0.01)	9% vs 22% vs 22% (death due to PC)
Ikeguchi <i>et al<sup>[73]</sup>,</i> 1995	RCT	Serosa+	Surgery + HIPEC (78) <i>vs</i> surgery alone (96)	MMC	100% <i>vs</i> 100%	1.2% <i>vs</i> 2.08%	NA	5-yr 51% vs 46% 5-yr 66% vs 44% (in 1-9 LN +)	35% vs 40% (death due to PC)
Fujimoto <i>et al</i> <sup>[74]</sup> , 1999	RCT	Serosa+	Surgery + HIPEC (71) <i>vs</i> surgery alone (70)	ММС	94.3% <i>vs</i> 92.8%	2.8% <i>vs</i> 2.8%	0% <i>vs</i> 0%	2-yr 88% vs 77% 4-yr 76% vs 58% 8-yr 62% vs 49% (P = 0.03)	1.4% vs 23% (P = 0.00008)
Hirose <i>et al</i> <sup>[75]</sup> , 1999	Prospective case control	Serosa+	Surgery + HIPEC (15) <i>vs</i> surgery alone (40)	MMC CDDP Etoposide	NA	60% vs 42.5%	0% vs 12.5%	3-yr 49% vs 29% 5-yr 39% vs 17% Median survival 33 mo vs 22 mo (P = 0.01)	26% vs 45%
Yonemura <i>et</i> al <sup>[76]</sup> , 2001	RCT	Serosa+	Surgery + HIPEC (48) vs Surgery + CNPP (44) vs Surgery alone (47)	MMC CDDP	100% vs 100% vs 100%	19% vs 14% vs 19%	4% vs 0% vs 4%	5-yr 61% vs 43% vs 42%	13% vs 15% (HIPEC vs surgery)
Kim <i>et al</i> <sup>[77]</sup> , 2001	Prospective controlled study	Serosa+	Surgery + HIPEC (52) <i>vs</i> surgery alone (51)	MMC	NA	36.5% <i>vs</i> 33.3%	NA	5-yr 33% vs 27% 5-yr 42% vs 25% (in stage ⅢB)	7.6% <i>vs</i> 25% (isolated PC)



## **Case Selection**

- Benefits of the combined treatment should be considered with its associated morbidity and mortality.
- Patient selection
  - Performance status
  - Peritoneal carcinomatosis index (PCI)



## What we follow at TMH

- PCI < 10 for GC & Performance status
- (Near) complete cytoreduction feasible
- Cytology positive disease (on staging laparoscopy)
- Not progressive under systemic chemotherapy
- Long interval with primary surgery





- Ideal cytotoxic agent;
- Ideal temperature, duration, method
- Multimodal therapy: role of (neo)adjuvant therapy
- Real advantage of HIPEC over CRS alone?? (Prodige 7 French RCT)