

Staging of Gastric Cancer

Natalie Coburn, MD, MPH Hepato-biliary and Surgical Oncology Sherif and MaryLou Hanna Chair in Surgical Oncology Research Associate Professor-University of Toronto



when it matter MOST



Disclosures









Disclosures



- Lead, Cancer Care Ontario/Program in Evidence-Based Care Gastric Cancer Guidelines
- Sherif and MaryLou Hanna Chair in Surgical Oncology Research



when it matters MOST National Comprehensive NCCN Cancer

Network[®]

NCCN Guidelines Version 3.2015
 Gastric Cancer

NCCN Guidelines Index Gastric Cancer Table of Contents Discussion



Version 3.2015, 03/23/15 @ National Comprehensive Cancer Network, Inc. 2015, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.



Version 3.2015, 03/23/15 @ National Comprehensive Cancer Network, Inc. 2015, All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®

GAST-2





MOST



• Why?







MOST





- T1N0, <3 cm
 - Consideration of endoscopic removal
- Locally advanced
 - Consideration of downstaging
- M1 disease
 - Consideration of multimodal options



• CT scan Chest, Abdo, Pelvis

- T-stage-72% accuracy
- N-stage-66% accuracy
- M-stage-81% accuracy
 - Review of 40 articles (3758 patients)
 - Seevaratnam et al, 2012



• CT scan Chest, Abdo, Pelvis

- T-stage-72% accuracy
- N-stage-66% accuracy
- M-stage-81% accuracy
 - Review of 40 articles (3758 patients)
 - Seevaratnam et al, 2012
- Ontario data, 2005-08
 - 2414 patients with GC at 116 hospitals
 - NPV for local invasion 87%
 - NPV for nodes 43%
 - NPV for M1 53%
 - Kagedan et al, under review



- CT scan Chest, Abdo, Pelvis
 - T-stage-72% accuracy
 - N-stage-66% accuracy
 - M-stage-81% accuracy
 - Low NPV for M1 disease
- Diagnostic Laparoscopy for T3/T4, N+, Diffuse
 - Changes management up to 43% of cases
 - Leake et al,2012
- EUS, PET, MRI
 - In situations where management will change







Laparoscopy Rates

- Ontario
 - 4.6% of curative resections
 - 52.3% (205 of 392) of the non-therapeutic OR group » Coburn, JSO, 2010
- US
 - 8% of curative resections
 - 19% of the non-therapeutic OR group
 - » Karanicolas, JACS, 2011





Laparoscopy Rates

- Ontario
 - 4.6% of curative resections
 - 52.3% (205 of 392) of the non-therapeutic OR group » Coburn, JSO, 2010
- US
 - 8% of curative resections
 - 19% of the non-therapeutic OR group
 - » Karanicolas, JACS, 2011







Questions?





The Best Chance for Cure

Natalie Coburn, MD, MPH Hepato-biliary and Surgical Oncology Sherif and MaryLou Hanna Chair in Surgical Oncology Research Associate Professor-University of Toronto



when it matters MOST











anyhow





All gastric cancer patients should be discussed at an MCC



All gastric cancer patients should be discussed at an MCC





MOST





Adjuvant Chemo-radiation (MacDonald/0116 Protocol)

- Surgery alone vs.
 Surgery then 5FU + 45Gy
 - "Curative" surgery
 - Very selective trial enrollment
 - 32% needed change in XRT plan
 - <u>30% couldn't complete Rx</u>
 - 1% mortality in C-XRT arm
 - D2 LN dissection was specified in protocol
 - 10% D2
 - 36% D1
 - 54% D0



MacDonald, NEJM, 2001

Neoadjuvant Chemotherapy (MAGIC Protocol)

Surgery Alone (n=250) vs. ECF/Surgery/ECF (n=253)

- •Only 41.6% completed all 6 cycles of chemo
- •Only 50% had post-op chemo

А

•Despite lack of completion of therapy- OS and DFS benefits



Cunningham, NEJM, 2006

Adjuvant Chemotherapy (Japanese Protocol)

Surgery Alone vs. Surgery + chemotherapy •5-FU analog

•May have different responsiveness in Asian populations





ARTIST trial-JCO 2012

- XP vs XP and Rads following D2 gastrectomy
 - -458 patients
 - Excluded Stage Ia and Ib (T2aN0), positive margins, M1 on final path, D1 dissection
 - -75% completed XP
 - 82% completed XP/XRT/XP
- "Negative Trial"



ARTIST trial—Was it "Negative"?





when it matters MOST

ARTIST trial—Was it "Negative"?



Power Calculations

- 448 patients
- 80% power to detect HR 1.450 with 2 sided alpha=0.05
- Final analysis scheduled at 227 events, but performed at 127 events
 - Fewer deaths than expected due to accrual of more patients with stage 1b/2 than expected

when it matters MOST

Sunnybrook

HEALTH SCIENCES CENTRE



ARTIST trial "Negative"?



- 60% of patients were Stage 1b and 2
- Estimated 8 years of follow-up before planned analysis could occur
- ARTIST-2 trial
 - Node positive patients



So, which is the better treatment?

MacDonald



ARTIST



Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

The median duration of survival was 27 months in the surgeryonly group and 36 months in the chemoradiotherapy group. The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 169 of the 281 patients in the chemoradiotherapy group and 197 of the 275 patients in the surgery-only group died during the follow-up period.







Evidence-Based Series #2-14 Version 3.2011

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer

G. Knight, C.C. Earle, R. Cosby, N. Coburn, Y. Youssef, K.Spithoff, R. Malthaner, R.K.S. Wong, and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: April 5, 2011

2011 Guidelines-CCO/PEBC considers them equivalent Underscores the importance of discussing <u>each</u> case at a multidisciplinary tumor board



D1 vs D2?

To be, or not to be, that is the question: Whether 'tis Nobler in the mind to suffer The Slings and Arrows of outrageous Fortune,

Or to take Arms against a Sea of troubles, And by opposing end them...

William Shakespeare



when it matters MOST



D2 LND for curative intent resection D1 for palliative, T1, or comorbidities

Extent of LN dissection

D1 Resection

D2 Resection


MRC RCT: D1 vs D2 Dissection Lancet 1996



Dutch RCT: D1 vs D2 Dissection NEJM 1999







1990's D1 vs D2 trials

Old-school resection

- Protocol included a distal panc and splenectomy
- Most of the complications/deaths came from the distal panc/splenectomy
- Low surgeon volumes of resection in both



1990's D1 vs D2 trials

Old-school resection

- Protocol included a distal panc and splenectomy
- Most of the complications/deaths came from the distal panc/splenectomy
- Low surgeon volumes of resection in both



Copyright @1026 by The Molvav-Hill Companies, Inc. All rights received.



Morbidity and Mortality for D1 and D2 LN dissection, Deguili et al, BJS 2010

- Italian Gastric Study Group
 - 1994, phase II trial to establish safety of D2 dissection, with pancreas-preservation
 - 20.9% morbidity; 3.1% mortality
- Starting June 1998, 267 patients randomized intraoperatively
 - Spleen only removed if tumour was in the left part of the upper stomach
 - Pancreas only removed if direct invasion suspected





MOST



- 20% of registered patients refused trial due to perception that D2 was associated with better survival
- Several surgeons participating in the Phase II trial would not join the RCT (10 of the original 18 surgeons participated)



Morbidity and Mortality for D1 and D2 LN dissection, Degiuli et al, BJS 2010

Table 3 Short-term outcome

	D1 gastrectomy	D2 gastrectomy	P‡	Total	Pş
Non-surgical complications	10 of 133 (7.5)	16 of 134 (11-9)	0.223	26 of 267 (9.7)	
Surgical complications	9 of 133 (6-8)	10 of 134 (7.5)	0.825	19 of 267 (7-1)	
Total morbidity	16* of 133 (12-0)	24† of 133 (17-9)	0.178	40 of 267 (15-0)	
Total gastrectomy	6 of 35 (17)	6 of 31 (19)	0.186	12 of 66 (18)	0.401
Distal gastrectomy	10 of 98 (10)	18 of 103 (17-5)	0.137	28 of 201 (13.9)	
NO	8 of 63 (13)	12 of 57 (21)	0.220	20 of 120 (16-7)	0.563
N+	8 of 68 (12)	12 of 74 (16)	0.446	20 of 142 (14-1)	
< 70 years	10 of 88 (11)	15 of 99 (15)	0.447	25 of 187 (13-4)	0.259
≥70 years	6 of 45 (13)	9 of 35 (26)	0.159	15 of 80 (19)	
In-hospital mortality	4 of 133 (3.0)	3 of 134 (2·2)	0.722¶	7 of 267 (2-6)	
Total gastrectomy	3 of 35 (9)	2 of 31 (6)	1.000¶	5 of 66 (8)	0.011¶
Distal gastrectomy	1 of 98 (1)	1 of 103 (1-0)	1.000¶	2 of 201 (1 0)	
NO	1 of 63 (2)	1 of 57 (2)	1.000¶	2 of 120 (1-7)	0-459¶
N+	3 of 68 (4)	2 of 74 (3)	0.670¶	5 of 142 (3.5)	
< 70 years	2 of 88 (2)	2 of 99 (2)	1.000¶	4 of 187 (2·1)	0-431¶
≥70 years	2 of 45(4)	1 of 35 (3)	1.000¶	3 of 80 (4)	

Values in parentheses are percentages. *Three and †two patients had both surgical and non-surgical complications. $D1 versus D2 (\chi^2 \text{ test except where indicated}); \\ versus other variable in total group (\chi^2 \text{ test except where indicated}); \\ Fisher's exact test.$



Degiuli et al, BJS, 2014

- 267 patients randomized intraoperatively
- Overall survival
 - -66.5 % vs 64.2% (p=0.70)



Degiuli et al, BJS, 2014

- 267 patients randomized intraoperatively
- Overall survival
 - -66.5 % vs 64.2% (p=0.70)

- Is this a 'negative' trial, or simply underpowered?
- Or, have we asked the wrong question?



when it matters MOST

Degiuli et al, BJS, 2014

- 267 patients randomized intraoperatively
- Overall survival

-66.5 % vs 64.2% (p=0.70)

- Disease-specific survivals
 - T1 cancers
 - 98.0% vs 82.9% (p=0.01)
 - T2+ cancers
 - 38.4% vs 59.5% (p=0.055)



Meta-analysis of D1 vs D2 by stage, El-Sedfy et al, ASO 2014



(a)

	D2		D1		Odds Ratio			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M–H, Random, 95% Cl	
Dutch Trial: Bonenkamp'99	65	85	74	98	46.5%	1.05 [0.53, 2.08]	1999		
MRC Trial: Cuschieri'99	27	40	37	48	38.3%	0.62 [0.24, 1.59]	1999		
IGCSG R01: Degiuli'14	32	39	48	49	15.2%	0.10 [0.01, 0.81]	2014		
Total (95% CI)		164		195	100.0%	0.60 [0.23, 1.57]		-	
Total events	124		159						
Heterogeneity: Tau ² = 0.40; Chi ² = 4.77, df = 2 (P = 0.09); l ² = 58%									
Test for overall effect: Z = 1.	.29)					Favours D1 for T1 Favours D2 for T1			

~		
	•	а
•		

	D2	D2 D1		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Events Total Events Total		Weight	M-H, Random, 95% CI	Year	M–H, Random, 95% Cl		
Dutch Trial: Bonenkamp'99	67	152	81	181	51.7%	0.97 [0.63, 1.50]	1999	-	
MRC Trial: Cuschieri'99	22	69	24	63	27.9%	0.76 [0.37, 1.56]	1999		
IGCSG R01: Degiuli'14	42	55	26	42	20.4%	1.99 [0.82, 4.79]	2014	+	
Total (95% CI)		276		286	100.0%	1.05 [0.67, 1.64]			
Total events	131		131						
Heterogeneity: Tau ² = 0.05;	Chi ² = 2.	90, df :	= 2 (P =	0.24); I					
Test for overall effect: Z = 0.	22 (P = 0)	.83)					Favours D1 for T2 Favours D2 for T2		

(a)

(C)										
	D2 D1					Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M–H, Random, 95% Cl		
Dutch Trial: Bonenkamp'99	18	82	15	94	41.0%	1.48 [0.69, 3.17]	1999			
MRC Trial: Cuschieri'99	15	86	9	84	30.1%	1.76 [0.72, 4.28]	1999			
IGCSG R01: Degiuli'14	20	37	16	40	29.0%	1.76 [0.71, 4.36]	2014			
Total (95% CI)		205		218	100.0%	1.64 [1.01, 2.67]		◆		
Total events	53		40							
Heterogeneity: Tau ² = 0.00; Chi ² = 0.12, df = 2 (P = 0.94); l ² = 0%										
Test for overall effect: Z = 2.	00 (P = 0		Favours D1 for T3 Favours D2 for T3							
(d)										

D1 D2

T3

T2

A11

T1



Meta-analysis of D1 vs D2 by stage, EI-Sedfy et al, ASO 2014

	D2	D2 D1				Odds Ratio		Odds Ratio		
Study or Subgroup	Events	nts Total Events Total		Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl			
Dutch Trial: Bonenkamp'99	101	146	121	175	54.7%	1.00 [0.62, 1.61]	1999	+		
MRC Trial: Cuschieri'99	40	78	43	69	35.4%	0.64 [0.33, 1.23]	1999			
IGCSG R01: Degiuli'14	50	57	60	63	9.8%	0.36 [0.09, 1.45]	2014			
Total (95% CI)		281		307	100.0%	0.77 [0.49, 1.22]		•		
Total events	191		224							
Heterogeneity: Tau ² = 0.04; (
Test for overall effect: $Z = 1$.		Favours D1 for N0 Favours D2 for N0								

Node negative

(a)

	D2	2 D1		Odds Ratio			Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl	
Dutch Trial: Bonenkamp'99	56	185	53	205	53.3%	1.24 [0.80, 1.94]	1999	*	
MRC Trial: Cuschieri'99	22	114	20	115	23.3%	1.14 [0.58, 2.22]	1999		
IGCSG R01: Degiuli'14	45	74	30	68	23.4%	1.97 [1.01, 3.84]	2014	-	
Total (95% CI)		373		388	100.0%	1.36 [0.98, 1.87]		•	
Total events	123		103						
Heterogeneity: Tau ² = 0.00;	Chi ² = 1.								
Test for overall effect: $Z = 1$.	.85 (P = 0)	.06)						Favours D1 for N+ Favours D2 for N+	

Node positive



(b)

D1 D2



TME?



when it matters MOST





TME? Total Mesogastric Excision



when it matters MOST

D2 LND for curative intent resection D1 for palliative, T1, or comorbidities



Figure 4: Cumulative risk of death due to gastric cancer and due to other causes in patients treated with curative intent (n=711) D1=standardised limited lymphadenectomy. D2=standardised extended lymphadenectomy.

Deaths due to Gastric Cancer, 15-yr Survival of Dutch Trial, Songun, Lancet Oncology 2010





Fig. 2 Kaplan–Meier eurves of a overall and b disease-specific survival for patients treated by D1 or D2 gastreetomy with curative intent. a Hazard ratio (HR) 1-19, 95 per cent confidence internal 0.82 to 1.72 (JP.0.028 kp.engels term) b HB 1.02.0.66

curative intent. a Hazard ratio (HR) 1-19, 95 per cent confidence interval 0.82 to 1.73 (P = 0.358, log rank test). b HR 1-02, 0.66 to 1.59 (P = 0.916, log rank test)

All Stages



T2-4, N+ only

D2

23

28

5

Italian RCT, Degiuli, BJS 2014











Surgery should aim at achieving an R0 margin



- 2005-08 Ontario
 - 2414 GC cases
 - 1476 operations
 - 904 resections
 - 691 'curative' resections
 - 610 full path data
 - 171 positive margins (28%)
 - Unpublished



when it matters MOST

Surgery should aim at achieving an R0 margin

Caveat

Biology is King, Patient selection is Queen

 Extended resections are unlikely to benefit patients with >5 LN positive





Laparoscopic Gastrectomy

- Meta-analysis of 6 RCT
- 629 patients with EGC
 - Patients with ADVANCED CA were EXCLUDED from these trials
- Less post-operative early morbidity RR=0.61, p=0.01
- Longer OR time
 +86 minutes
- Less blood loss
 -108 cc
- Decreased LN harvest -4.88 LN
- Earlier Oral intake -0.48 day
- Shorter hospital stay -2.03 days
- Similar mortality (p=0.32)





MOST



Another look at the Laparoscopic RCT's...

 Oncologic outcomes have not been determined

			Cancer	Number of	Surgeon	Survival
Author	N=	Stage	Location	Institutions	volume	Measured?
Kitano	14/14	EGC	Distal	1	NR	No
Hayashi	14/14	EGC	Distal	1	NR	No
Lee	24/23	EGC	Distal	1	NR	No
Kim, YW	82/82	EGC	Distal	1	NR	No
Kim, HH	179/163	EGC	Distal	10	NR	No
Huscher	30/29	EGC/AGC	Distal	1	NR	Yes
Lee	24/23	EGC	Distal	1	NR	No





KLASS Trials

- KLASS-1 (Ann Surg 2015)
 - 1416 patients with STAGE I GC
 - Randomized Lap vs Open
 - Fewer complications 13% vs 20% open
 - Mostly related to decrease in wound complications
 - Similar leak and operative mortality
 - 0.6% vs 0.3% (open)





KLASS Trials

- KLASS-2
 - Randomized non-inferiority trial
 - cT2-cT4a
 - NO evidence of LN metastasis
 - Subtotal gastrectomy
 - Enrolment-1050 patients





KLASS Trials

• KLASS-3

- T1N0, T1N1, T2N0
- Upper lesions/Total gastrectomy
- Phase II
- 164 patients enrolled Oct 2012-14







Future ways to improve survival?



Fig. 4 Overall survival in patients with serosa-negative tumors (a) and those with serosa-positive tumors (b) by treatment group

• Bursectomy of Lesser Sac

 Underpowered; Trial closed prematurely due to introduction of S-1 adj chemo

JCOG 1001

- T3/T4 cancers
- 1000 patients
- June 2010-2014



MOST

Fujita, Gastric Cancer, 2012



Slides Courtesy of T Sano

HEALTH SCIENCES CENTRE

when it matters MOST Relapse-free Survival: All 505 cases

Overall Survival Surgical T

T2 (MP/SS) (N=276)

Overall Survival Primary tumor location

"**U**" (N=427)

"M" or "L" (N=78)

Overall Survival: Post-op Complications

Infectious complications (N=71)

Splenectomy (N=254)

Spleen-preservation (N=248)

Recommendations

- All patients should be presented at MCC
- CT Chest, Abdo, Pelvis for staging
- Laparoscopy for more advanced cancers
- D2 LND for >T1N0, curative intent
 D1 for EGCT1, co-morbidity, palliation
- Negative margins
 - Extended resections useful only if <5 LN
- Don't perform splenectomy unless direct invasion

when it matters MOST

Questions?

Management of Stage IV Disease

Natalie Coburn, MD, MPH Hepato-biliary and Surgical Oncology Sherif and MaryLou Hanna Chair in Surgical Oncology Research Associate Professor-University of Toronto

when it matters MOST

In M1 cases, non-surgical management is preferred for patients without symptoms

In M1 cases, non-surgical management is preferred for patients without symptoms

- Systematic Review
- 1939 abstracts
- 59 articles studying outcomes in Stage IV patients
- Only 3 were prospective
- Highly variable definitions
 - "Unresectable" "advanced" "incurable"
 "palliative"
- Up to 45% morbidity and 21% mortality
- Large patient selection bias
In M1 cases, non-surgical management is preferred for patients without symptoms

- MSKCC experience
 - 1993-2002
 - 165 patients M1 + at DL
 - 97 followed at MSKCC
 - Median interval from
 DL to procedure: 4 m
 (range 1-35 m)
 - Median survival from first intervention to death: 3 m (range 1-28m)



Sarela, Ann Surg 2009

In M1 cases, non-surgical management is preferred for patients without symptoms

Click on image to enlarge						
TABLE 1. Procedures on the GEJ or Stomach for Relief of Obstruction or Feeding						
	Primary Tumor Location					
	Total	GEJ	Proximal	Body	Antrum	Whole
No. of patients	97	28	16	17	18	18
No. (%) of patients who had intervention	32 (32)	9 (32)	5 (31)	3 (18)	7 (39)	8 (44)
No. of procedures	53	17	7	6	12	11
Type of procedure						
Self-expanding stent	6	6				-
Endoscopic dilatation/laser	11	5	2	1		3
External beam radiation	1	1		-		-
PEG	21	4	3	3	6	5
PEJ	7	1	1		3	2
Laparotomy-gastrojejunostomy	3		<u></u> -	1	2	1444
Laparotomy-gastric/jejunal tube	4	-	1	1	1	1

Conclusion

 "non-curative resection is unlikely to alter disease progression, and pre-emptive surgical palliation is unnecessary"



when it matters MOST PEBC/CCO: In M1 cases, non-surgical management is preferred for patients without symptoms

- REGATTA TRIAL-ASCO 2015
 - -RCT
 - 330 patients with 'limited' metastatic disease
 - Chemo vs Surgery->chemo
 - S-1+Cisplatin



In M1 cases, non-surgical management is preferred for patients without major symptoms

- REGATTA TRIAL-ASCO 2015
 - -RCT
 - 330 patients with 'limited' metastatic disease
 - Chemo vs Surgery->chemo
 - S-1+Cisplatin
 - Trial stopped by DSMB at first interim analysis



MOST

Overall Survival (interim analysis)



PRESENTED AT

Early postoperative complications

%Grade 2-4	Gastrectomy arm (n=87)*
Infection with normal ANC: wound	5.7%
Obstruction: GI-small bowel	2.3%
Pleural effusion	1.1%
lleus	1.1%
Fever	3.4%
OVERALL	16.1 [*] ^{All operated pts}

Late adverse reactions/morbidities

	Chemo (n=73)	Gastrectomy (n=87)*
Grade 2/3/4	6.8%	16.1%
Grade 3/4	0%	9.2%
Grade 4	0%	0% * All operated pts

PRESENTED A

SLIDES ARE THE PROPERTY OF THE AUTHOR. PERMISSION REQUIRED FOR REUSE.

Subgroup analyses by location of primary tumor



HR for Gastrectomy arm*, **2.23**, 95%CI (1.14-4.37)

HR for Gastrectomy arm*, **0.95**, (0.57-1.59)

HR for Gastrectomy arm*, **0.63** (0.33-1.21)

* unstratified Cox proportional hazard model



Number of Implemented Cycles of Chemotherapy

Tumor Location	Median cycles [IQR] Chemotherapy	Median cycles [IQR] Gastrectomy+Cx
U	6 [4-8] (n=16)	3 [2-5] (n=30)
Μ	6 [4.5-8] (n=49)	5 [3.5-8] (n=30)
L	4 [2-6] (n=21)	6 [3-8] (n=29)
Total	6 [3-8] (n=74)	5 [3-7] (n=76)



Summary

- 1. Gastrectomy failed to improve overall survival in AGC with single incurable factor
- 2. Gastrectomy was safely performed with no mortality but associated with an increase of late AEs and morbidities.
- 3. Gastrectomy was associated with more frequent and severe chemotherapy related AEs, especially for U lesion or total gastrectomy.
- In the subgroup analysis, patients with distal gastric cancer had an OS benefit. A second study only in patients with distal gastric cancer may be considered



Questions?

