



ISSP



Is there a Role for Regional Therapy in Gastric Cancer? (PRO)

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura



 On the Speakers Bureau for Bristol Myers Squibb, Eisai, Lilly, and MSD; Consultant for Amgen, and AstraZeneca.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their products and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Paclitaxel, 5FU, Doxorubicin, Oxaliplatin, and Cisplatin will be discussed.





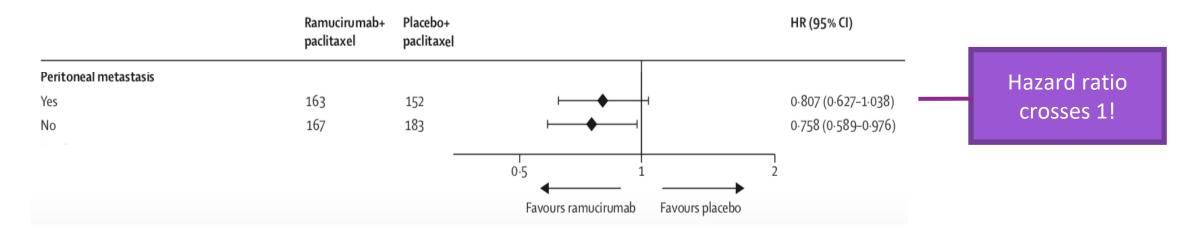
Regional therapies for Gastric Cancer

Peritoneal metastasis is a poor prognostic factor to systemic therapy

Unmet need for GCPM

- Systemic therapies benefit patients with GCPM, but the magnitude of benefit is lower
- Peritoneal metastasis is a poor prognostic factor to systemic therapies in

1L SPIRITS, 2L REGARDS, RAINBOW, 3L TAGS and ATTRACTION-2



RAINBOW - 2L GC

Koizumi W Lancet Oncol 2008, Fuchs CS Lancet 2014, Wilkie H. Lancet Oncol 2014; Shitara K. Lancet Oncol 2018; Kang YK. Lancet 2017

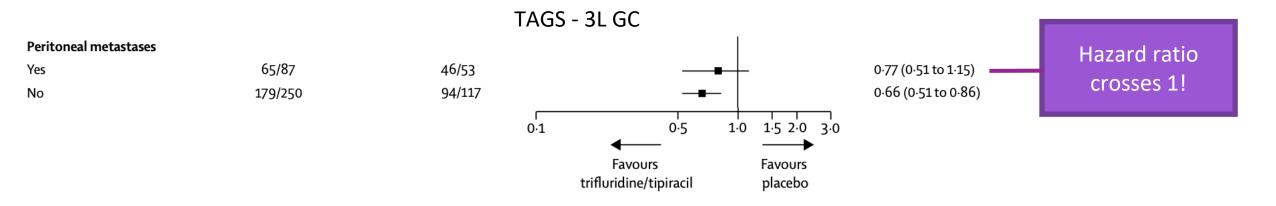


Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

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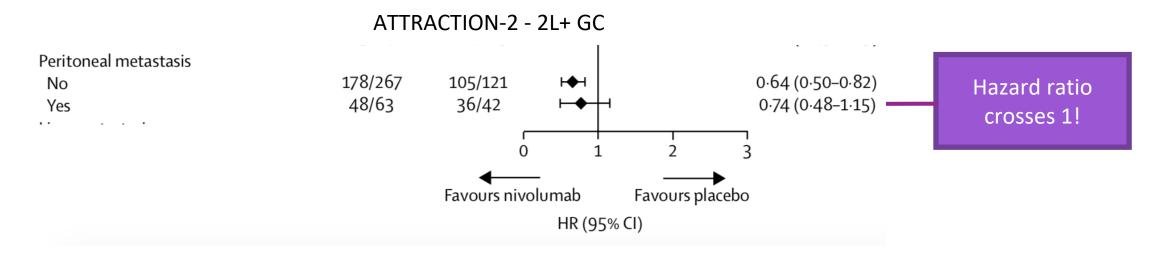
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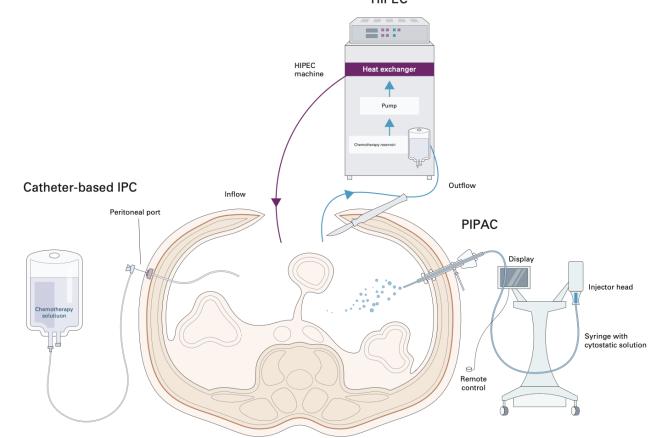






Regional therapies can potentially overcome deficiencies of systemic therapies

Challenges of systemic therapy



HIPEC

- Plasma-peritoneal barrier
- Poor blood supply
- Immune-evasive milieu

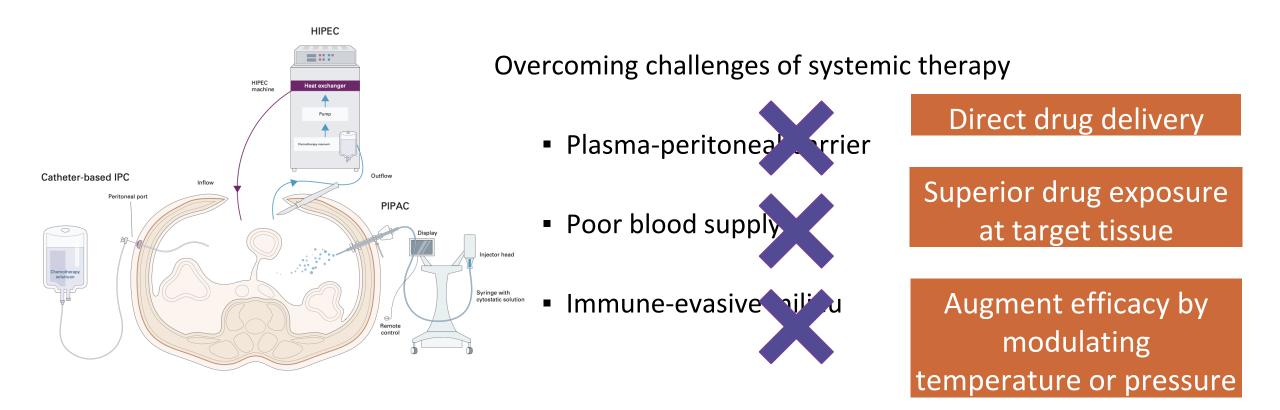
Gwee YX. J Clin Oncol. 2022







Regional therapies for GCPM



Gwee YX. J Clin Oncol. 2022



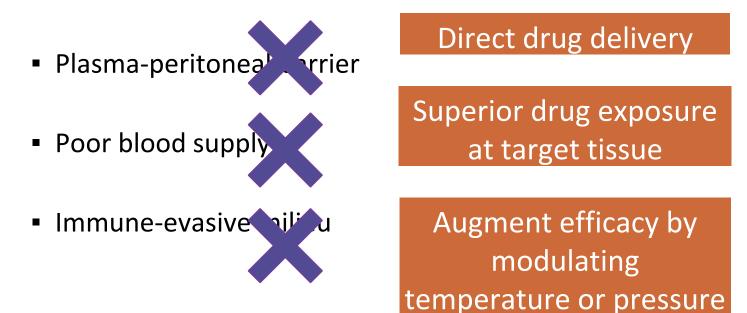


AND PER

Regional therapies for GCPM

Drugs	MW	pAUC/sAUC						
Doxorubicin	380	230						
Melphalan	305	93						
Mitomycin C	334	32.5						
Cisplatin	300	7.8						
Gemcitabine	299	500						
Miroxantron	517	115-255						
Oxaliplatin	387	16						
Etoposide	568	63						
Irrinotecan	677	NA						
Paclitaxel	853	10,000						
Docetaxel	861	552						
5-FU	130	250						
carboplatin	371	10						

Overcoming challenges of systemic therapy

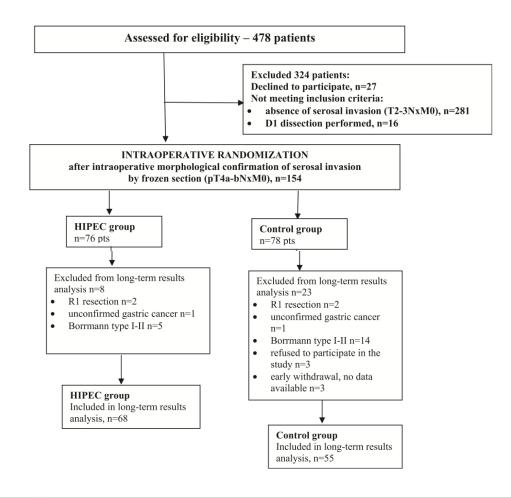


Gwee YX. J Clin Oncol. 2022

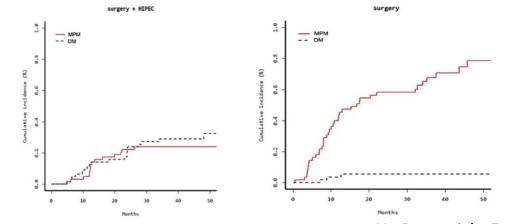


Regional therapies reduce peritoneal relapse in locally advanced GC

Prophylactic HIPEC - Belarus study



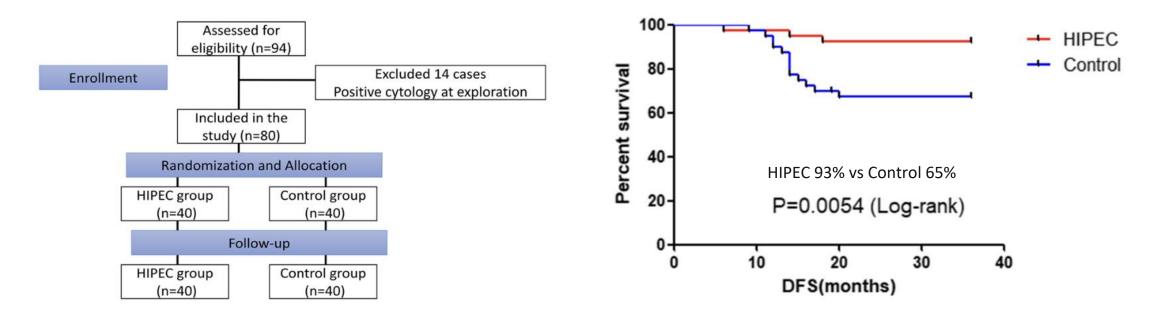
- 3-year PFS survival in T4 GC was higher in the HIPEC group cisplatin 50 mg/m2 + doxorubicin 50 mg/m2 compared with the control group (47% vs 27%, p = 0.0024).
- Fewer peritoneal recurrences.
- No G4/5 toxicities



Yu Reutovich. Eur J Surg Onc. 2019



Prophylactic HIPEC - China study



- 3-year PFS survival T3/4 GC was higher in the HIPEC group cisplatin 50 mg/m2 compared with the control group (93% vs 65%, p = 0.0024). Adjuvant XELOX after surgery.
- Fewer peritoneal recurrences (3% vs 23%, P < 0.05).
- No significant difference in post op morbidity.

Beeharry MK. BMC Cancer 2019



Meta-analysis supports adjuvant HIPEC

Study or Subgroup	Gastrectomy+ Events		Gastrect Events		Weight M.	Risk Ratio H, Random, 95% Cl		Risk Ratio M-H, Random, 95	5% CI																		
RCTs																											
Cui 2014	10	96	16	96	23.5%	0.63 [0.30, 1.31]																					
Fujimura 1994	1	22	10		11.5%	0.08 [0.01, 0.58] -		•																			
Huang 2015	8	21	2	21	16.0%	4.00 (0.96, 16.66]			Gastrectomy		Gastrec			Risk Ratio		Risk F											
Subtotal (95% CI)		139		135		0.66 [0.11, 3.81]		Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, I	Rando	m, 95% Cl										
Total events	19		28					RCTs																			
Heterogeneity: Tau*=	1.91; Chi#= 10.5	4, df = 2	(P = 0.005)	5); I# = 8	1 %			Cui 2014	32	96	49	96	23.2%	0.65 [0.46, 0.92]													
Test for overall effect	Z = 0.47 (P = 0.6	4)	010-002-022-02					Fujimura 1994	7	22	14		12.9%	0.41 [0.21, 0.79]	-	-											
								Huang 2015	12	21	8		12.9%	1.50 [0.78, 2.90]				Gastrector			trectomy			Ratio	Risk Ratio		
NRCTS								Subtotal (95% CI)		139		135	48.9%	0.73 [0.39, 1.36]		◄.	Study or Subgroup	Events	Tota	al Even	its Tot	al Weig	ht M-H, Rand	fom, 95% CI	M-H, Random, S	5% CI	
Fujimoto 1989	2	10	12	22	17.3%	0.37 [0.10, 1.34]		Total events	51		71						RCTs										
Yarema 2014	0	19	9		7.2%	0.05 [0.00, 0.84] +		Heterogeneity: Tau*= I			P = 0.02);	P=749	6				Hamazoe 1994	18	4	42	21 4	10 9.4	% 0.82	[0.52, 1.29]			
Yonemura 1995	14	79	17	81	24.5%	0.84 [0.45, 1.59]		Test for overall effect 2	Z = 0.99 (P = 0)	.32)							Ikeguchi 1995	39	7	78	52 5	96 18.3	% 0.92	[0.69, 1.23]	-		
Subtotal (95% CI)		108		122	49.0%	0.42 [0.12, 1.45]											Kaibara 1989	12	4	42	16 4	10 5.8	% 0.71	[0.39, 1.32]	-+		
Total events	16		38					NRCTS									Yonemura 2001	19			27 4	17 10.5		[0.45, 1.06]			
Heterogeneity: Tau* =	0.71; Chi# = 5.17	, df = 2 (P = 0.08);	P= 619	6			Akiyama 1998	16	29	21		20.0%	0.92 [0.60, 1.41]		-	Subtotal (95% CI)		21	10	22	23 44.0	0.82	[0.67, 1.00]	•		
Test for overall effect	Z = 1.38 (P = 0.1	7)						Koga1988	10	59	26		13.2%	0.51 [0.27, 0.97]		•	Total events	88		1	16						
								Yarema 2014	10	19	15	19		0.67 [0.41, 1.08]		•	Heterogeneity: Tau ² =	0.00; Chi#=	1.49, df = 3	3 (P = 0.	68); IF = (1%					
Total (95% CI)		247		257	100.0%	0.55 [0.23, 1.30]		Yonemura 1995	36	79	48	81	0.0%	0.77 [0.57, 1.04]			Test for overall effect:	Z=1.91 (P=	0.06)								
Total events	35		66					Subtotal (95% CI)	2.0	107	10.07	132	51.1%	0.72 [0.51, 1.01]		•											
Heterogeneity: Tau ^a =	0.69; Chi# = 15.8	i3, df = 5	(P = 0.008	i); I[#] = 6	58%	0.	04	Total events	36		62						NRCTS										
Test for overall effect:						0.	Fa	Heterogeneity: Tau ^a =			P = 0.27);	I" = 249	6				Kang 2013	18				33 15.0		[0.44, 0.87]			
Test for subgroup diff	ferences: Chi# = ().17, df=	1 (P = 0.6)	8), # = (0%			Test for overall effect 2	Z = 1.93 (P = 0)	.05)							Koga1988	14				78 7.3		[0.35, 1.02]			
								Tetal INER CIT		240		267	100.05	0.74 10 23 0.003			Kunisaki 2002	23				79 12.7		[0.79, 1.68]	+		
								Total (95% CI)		246		267	100.0%	0.71 [0.53, 0.96]		•	Yonemura 1995	45				31 21.0		[0.71, 1.19]	1		
		Be	ette	rΊ	Lyr C	15		Total events	87		133		100				Subtotal (95% CI)		21			21 56.0	0.81	[0.60, 1.09]	•		
				• •	-y- C			Heterogeneity: Tau ^a =			(P = 0.06); I*= 52	96		0.01 0.1	_	Total events	98			90						
								Test for overall effect: 2							Favours (experime	ntal	Heterogeneity: Tau ² =			3 (P = 0.	05); 12 = 8	52%					
								Test for subaroup diffe	erences: Chi# =	= 0.00, df =	1 (P = 0.9						Test for overall effect:	Z = 1.39 (P =	0.16)								
												Rc	++c	er 3yr OS	2												
												DC	τις	si byi U.)		Total (95% CI)		42		54	44 100.0	0.82	[0.70, 0.96]	•		
														•			Total events	186			06				w		
																	Heterogeneity: Tau ² =			7 (P = 0.	22); I ² = 2	26%			0.01 0.1	10	100
											-						Test for overall effect:								Favours [experimental] Fav		100
								11 D	CTc	anc	171		RC.	Ts (2520) nation	tc	est for subgroup diff	erences: Chi	r= 0.01, d	if = 1 (P =	= 0.94), l ^a	= 0%	- -				C
								тти		ant		. 1 1	INC.	13 (2326	γραιισπ	13							Ret	ter	5yr OS		С
														•	-		-										

Significant reduction in rates of PM recurrence (risk ratio = 0.63) compared with gastrectomy alone.

Desidero J. Eur J Cancer Cancer 2017



Meta-analysis supports adjuvant HIPEC

Castrectomy Starty of Statprog Cut 2014 Construction Cut 2014 Con	tomy	Risk Ratio MH. Random, 95% Ci	Risk Ratio M-H, Random, 95% Cl
Internal of the state of t	40 9.4% 96 18.3% 40 5.8% 47 10.5% 74 31 35 50 0.05); P =	0.82 [0.52, 1, 29] 0.92 [0.69, 1, 23] 0.71 [0.39, 1, 32] 0.69 [0.45, 1, 06]	
"Our study demonstrates a survival advantage of the use of HIPEC as a prophylactic strategy and suggests that patients whose disease burden is limited to positive cytology and limited nodal involvement may benefit the most from HIPEC "	(22); P = = = 0.94).		The feontroll

Desidero J. Eur J Cancer Cancer 2017





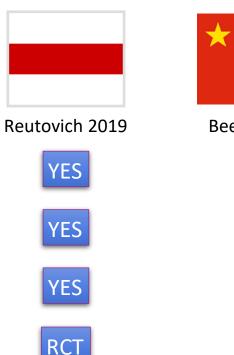
Is there a role for HIPEC in adjuvant setting?

Is adjuvant HIPEC safe?

Does it reduce PM?

Does it improve DFS?

Level of evidence?





Beeharry 2019

YES YES

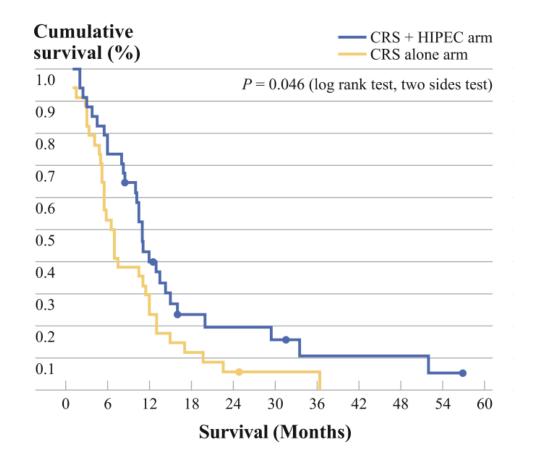






Regional therapies (CRS + HIPEC) reduce peritoneal relapse in GCPM

CRS + HIPEC has superior PFS



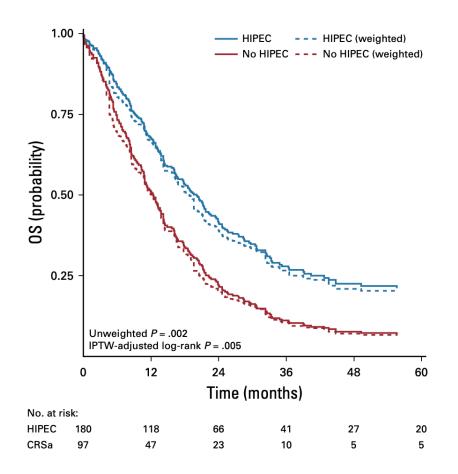
- HIPEC mitomycin C 30 mg and cisplatin 120 mg
- median PCI 15.
- CRS + HIPEC is better than CRS alone 11.0 months vs
 6.5 months (P = 0.046)
- SAE occurred in 4 from CRS group (11.7%) and 5 from CRS + HIPEC group (14.7%) (P = 0.839).

Yang XJ. Ann Surg Oncol. 2011





CYTO-CHIP: Well designed, retrospective large cohort study



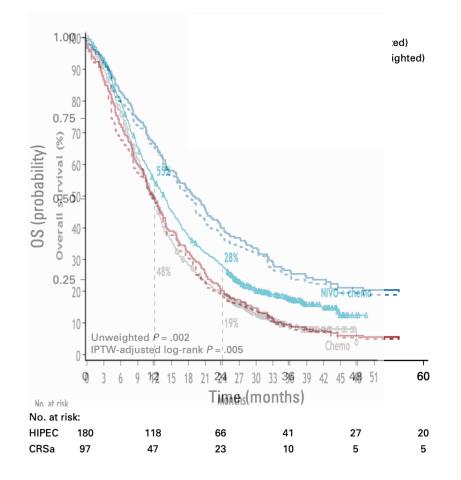
- In low PCI score GC, CRS-HIPEC has superior median OS compared to CRSa groups, 18.8 versus 12.1 months upon IPTW analysis
- 3- and 5-year OS rates were 26.21% and 19.87% versus
 <20% 3- OS in CM-649
- Better outcomes than those previously reported with the gold-standard treatment of systemic chemotherapy
- The major 90-day morbidity rates, surgical complications and post op mortality were similar between CRS-HIPEC and CRSa patients.

Bonnot P-E. J Clin Oncol. 2019





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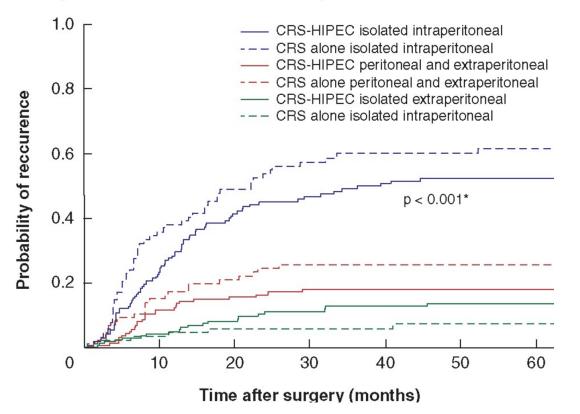
Bonnot P-E. J Clin Oncol. 2019





Pattern of recurrence after HIPEC

b Impact of CRS-HIPEC on recurrence pattern



- HIPEC (*P* < 0.001) were associated with fewer peritoneal recurrences.
- The impact of HIPEC was consistent irrespective of histology, with the benefit of HIPEC being more pronounced in the non-PCC population.

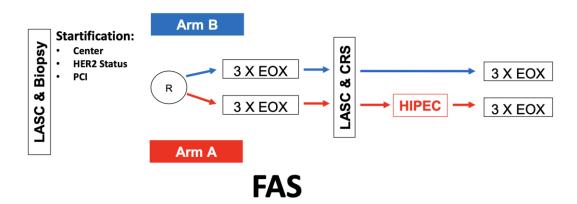
Bonnot P-E. Brit J Surgery. 2021

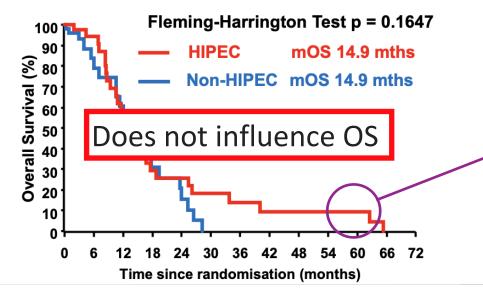






GASTRIPEC I - a missed opportunity





- Early study termination due to low accrual.
- High rate of drop outs 52% due to tumor progression (20%), and non-resectable (23%); only 36 received HIPEC.
- HIPEC with CDDP and MMC for 60 minutes significantly increase PFS (7.1 vs 3.5 months), and distant metastasis free survival (10.2 vs 9.2 months).
- Possible signal of a long term survival seen with HIPEC (similar observation in CYTO-CHIP and Yang study.

Rau B. ESMO 2021; Rau B. ESSO 2021





Is there a role for adjuvant HIPEC in therapeutic setting?

CYTO-CHIP 2019 Yang 2011 YES YES YES NO YES YES nonRCT RCT



Is CRS + HIPEC safe?

Does it reduce PM?

Does it improve OS?

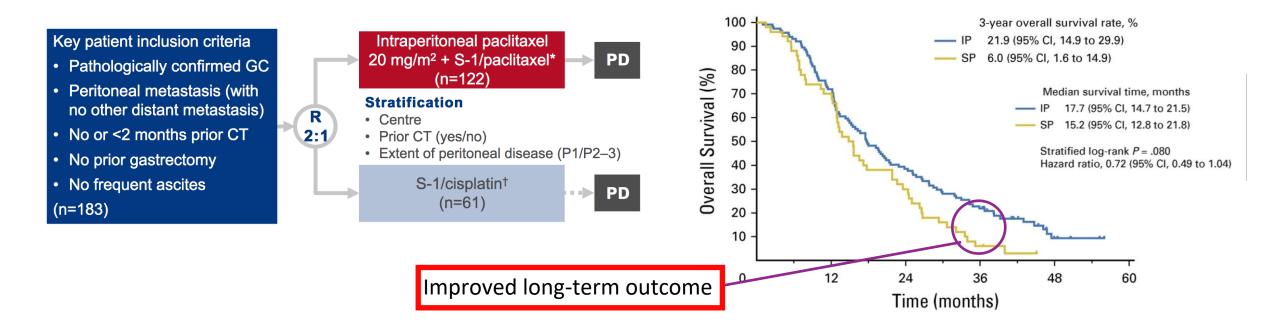
Level of evidence?





Regional therapies alter long-term survival of GCPM

PHOENIX TRIAL - NIPS



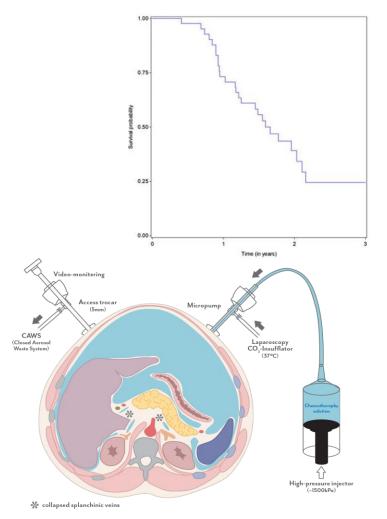
Additional post hoc sensitivity analysis adjusted for baseline ascites using the FAS, overall survival was longer in the IP arm than in the SP arm (adjusted HR, 0.59; 95% CI, 0.39 to 0.87; P = .008).

How would an inactive treatment produce one of the best OS comparable to ATTRACT-4?

Ishigami H. J Clin Oncol 2018



PIPAC



- PIPAC cisplatin and doxorubicin is safe.
- Co-administered with systemic therapy (n=42), with median delay in restarting chemotherapy 14 days, range 4-28 days.
- OS 19.1 months; nearly 50% had 2L chemotherapy.
- Six (14.3%) patients became eligible for CRS and HIPEC with PCI dropped from initial 13 to 3.
- On-going confirmatory PIPAC EstoK 01 study.



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Alyami M. Eur J Surg Oncol 2019

Is there a role for NIPES/PIPAC/HIPEC in palliative setting?

PHOENIX GC 2018 Ishigami 2017* Alyami 2019 YES YES Is safe with systemic therapy? Maybe Maybe Does it improve OS? nonRCT RCT

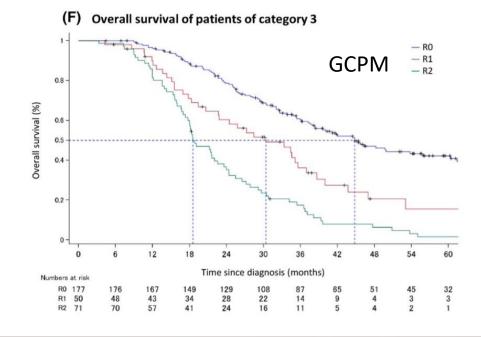
Level of evidence?





Prolonged survival in PM achieving R0 following CRS or conversion surgery

- Promising data from retrospective studies in GCPM with complete resection
 - 5-year OS was 24.8% in CC-0 in CYTO-CHIP study
 - mOS 44.8 mo in GCPM patients with R0 resection in CONVO-GC-1 study







Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura



Altering long-term survival with conversion surgery

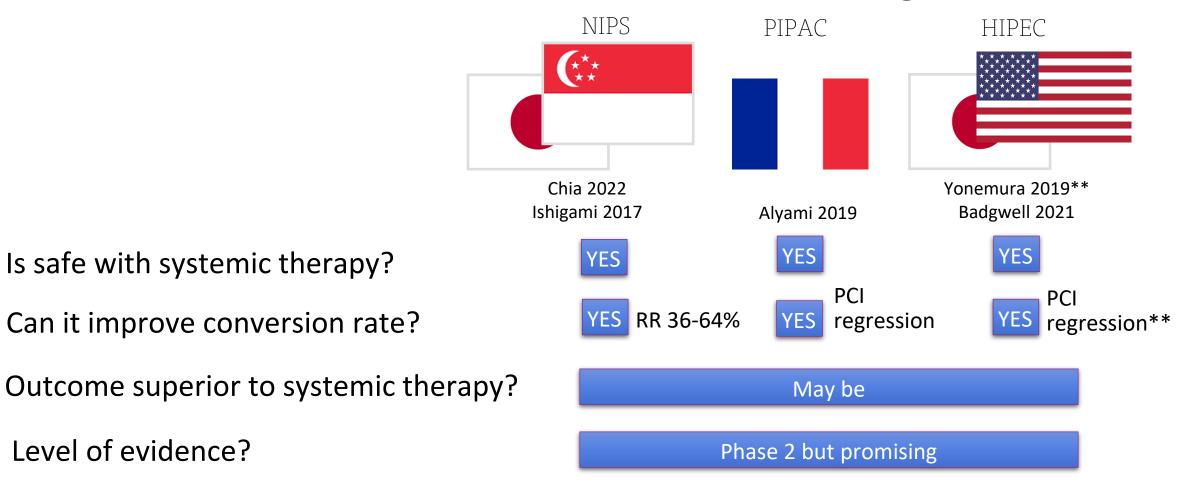
- NIPS conversion rate 36-64%, mOS 24.2-30.5 months.
- PIPAC, lap HIPEC had demonstrated to reduce PCI score even in patients refractory to systemic chemotherapy.
- Surgery aiming at R0 operation after induction chemotherapy + regional therapy is a promising strategy for for GCPM.



2021

Chia D Ann Oncol Surg 2022, Ishigami H J Clin Oncol 2018, Alyami M. Eur J Surg Oncol 2019, Badgwell

NIPES/PIPAC/HIPEC in conversion surgery







International guidelines

NCCN National Comprehensive Cancer Network® NCCN Guidelines Version 2.2022 Gastric Cancer

NCCN Guidelines Index Table of Contents Discussion

PRINCIPLES OF SURGERY

• Hyperthermic intraperitoneal chemotherapy (HIPEC) or laparoscopic HIPEC may be a therapeutic alternative for carefully selected stage IV patients in the setting of ongoing clinical trials and is under further clinical investigation.¹⁶⁻²⁰

Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

Annals of Oncology (2022) Authors: F. Lordick, F. Carneiro, S. Cascinu, T. Fleitas, K. Haustermans, G. Piessen, A. Vogel & E. C. Smyth, on behalf of the ESMO Guidelines Committee

 A lower PCI score has been associated with better prognosis, and patients with limited peritoneal metastases might be appropriate candidates for cytoreductive surgery and hyperthermic intraperitoneal ChT (HIPEC); however, evidence is still limited and risks must be balanced carefully against uncertain benefits.





Thank you!

