



THIRD ANNUAL
ISSPP
Congress 2022

*International Society
for the Study of Pleura
and Peritoneum*



FINAL GREAT DEBATE

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

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**National University
Cancer Institute
Singapore**

Disclosures

- 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



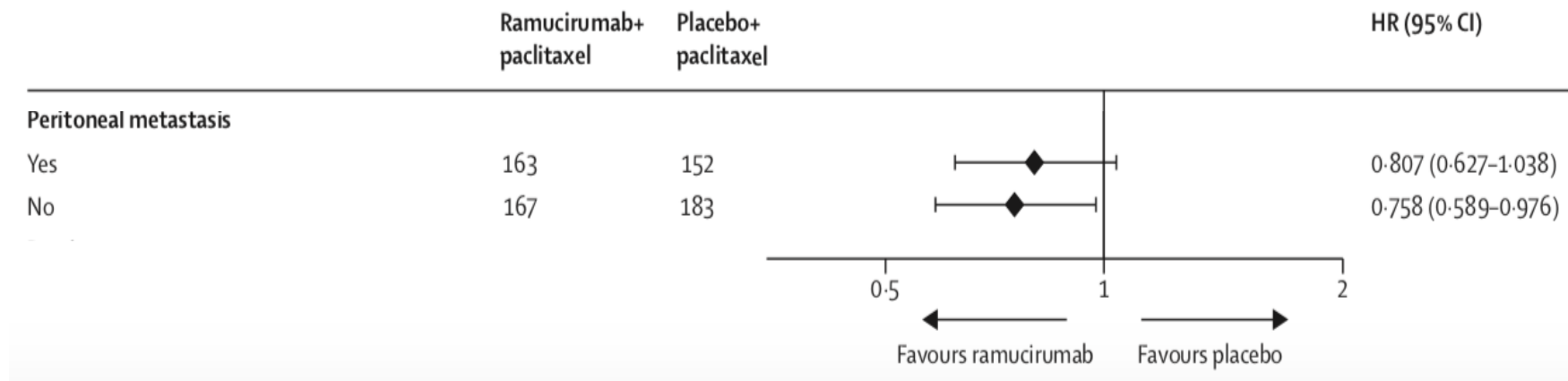
1

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

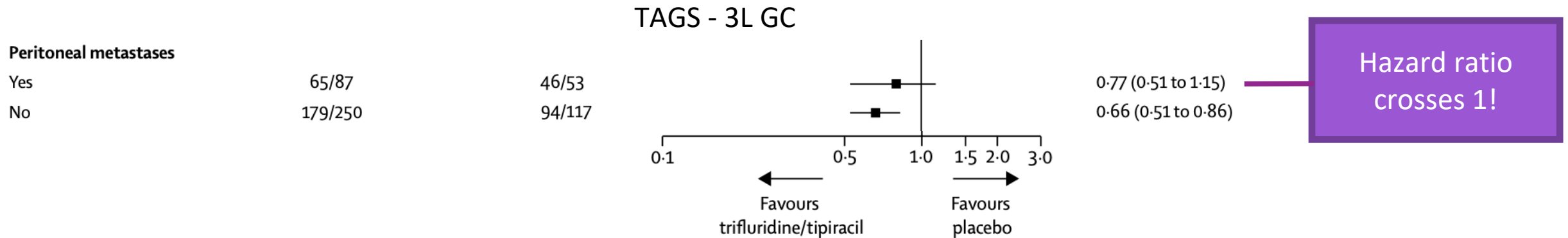


Hazard ratio
crosses 1!

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

Unmet need for GCPM

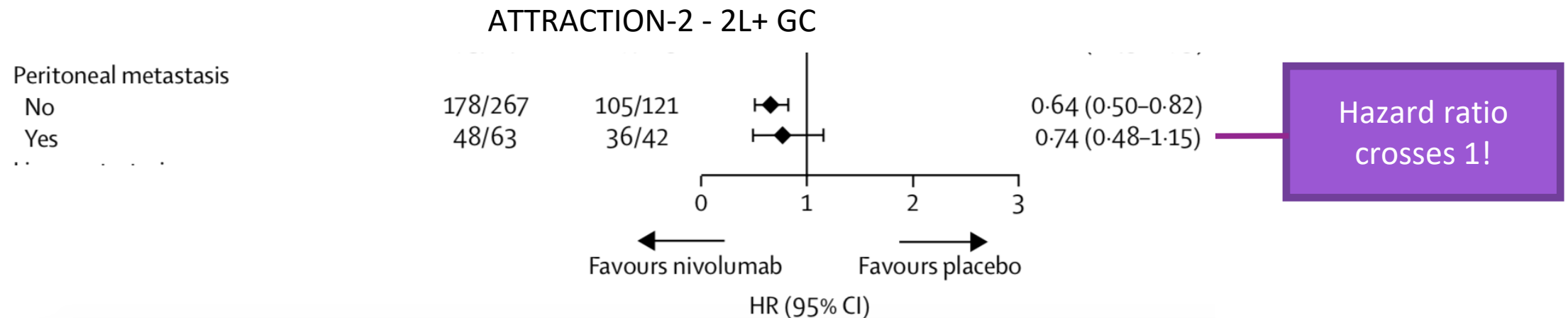
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Unmet need for GCPM

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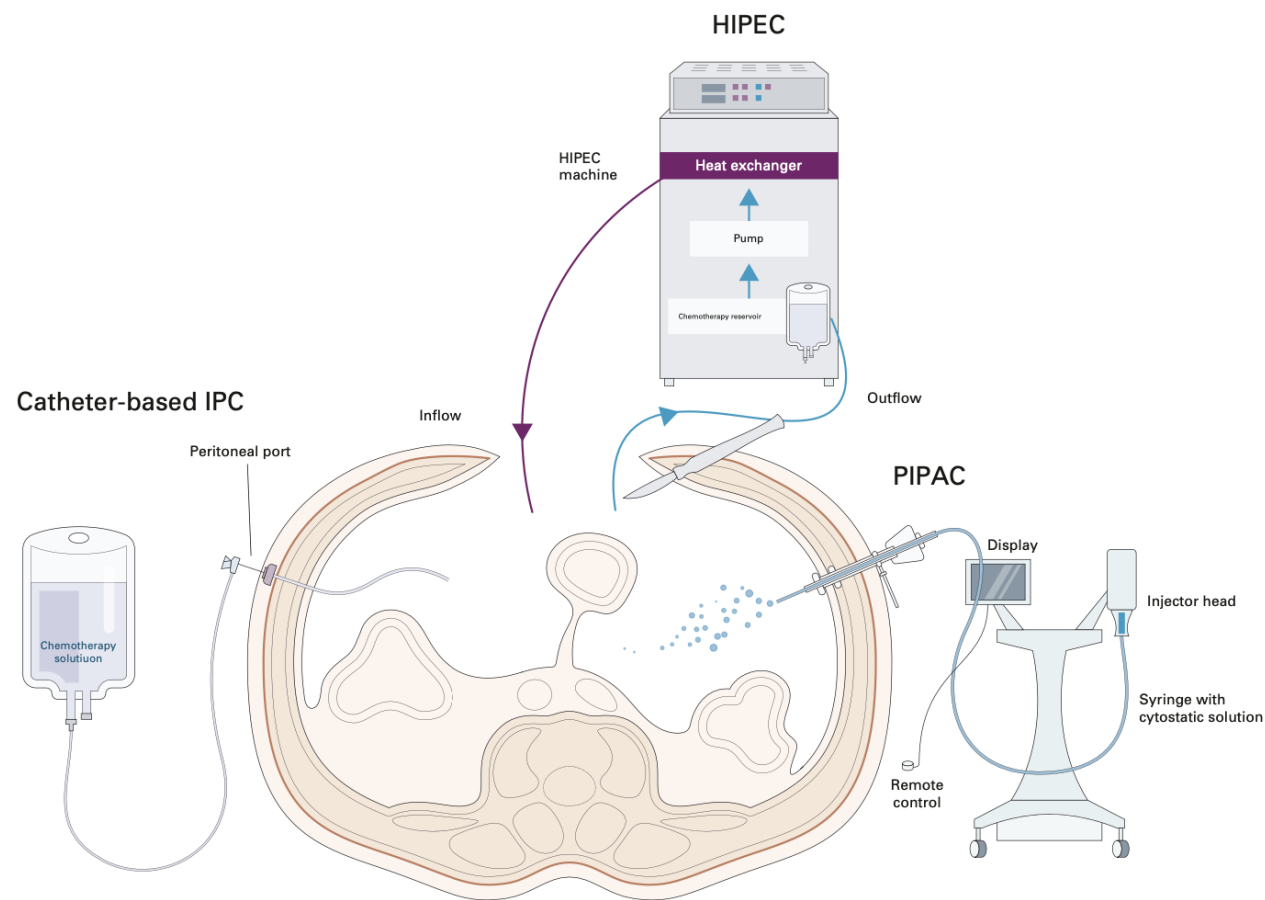


Koizumi W Lancet Oncol 2008, Fuchs CS Lancet 2014, Wilkie H. Lancet Oncol 2014; Shitara K. Lancet Oncol 2018; Kang YK. Lancet 2017

2

Regional therapies can potentially overcome deficiencies of systemic therapies

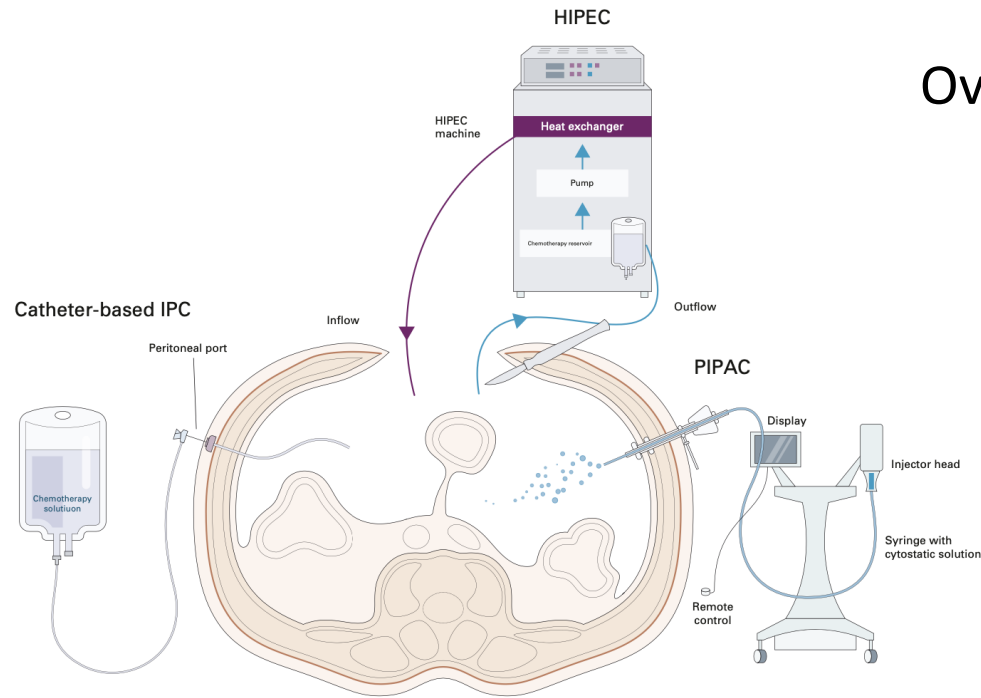
Challenges of systemic therapy



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

Gwee YX. J Clin Oncol. 2022

Regional therapies for GCPM



Overcoming challenges of systemic therapy

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

Direct drug delivery

Superior drug exposure
at target tissue

Augment efficacy by
modulating
temperature or pressure

Gwee YX. J Clin Oncol. 2022

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
Irinotecan	677	NA
Paclitaxel	853	10,000
Docetaxel	861	552
5-FU	130	250
carboplatin	371	10

Overcoming challenges of systemic therapy

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

Direct drug delivery

Superior drug exposure
at target tissue

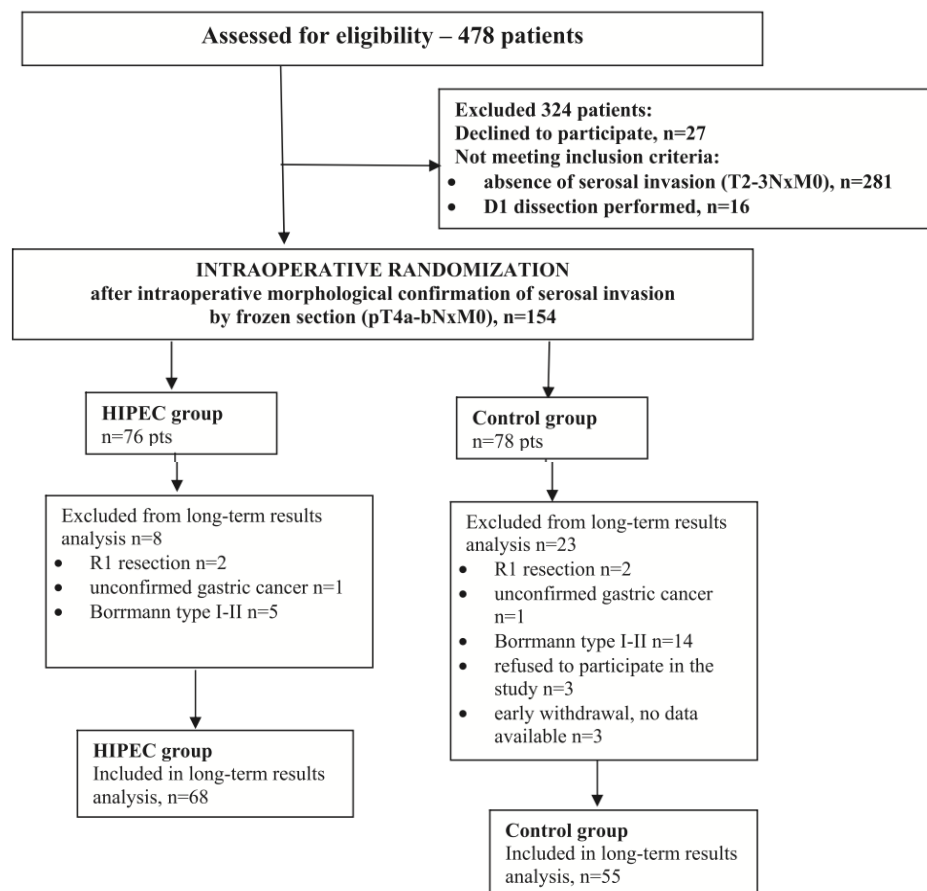
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Gwee YX. J Clin Oncol. 2022

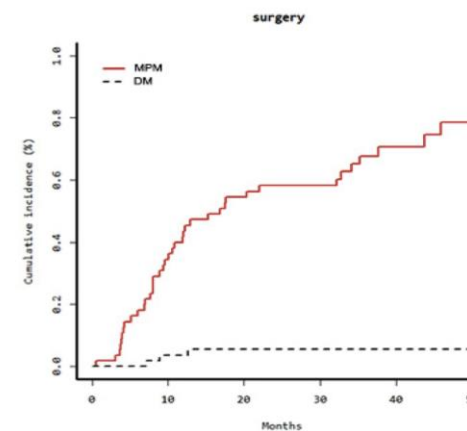
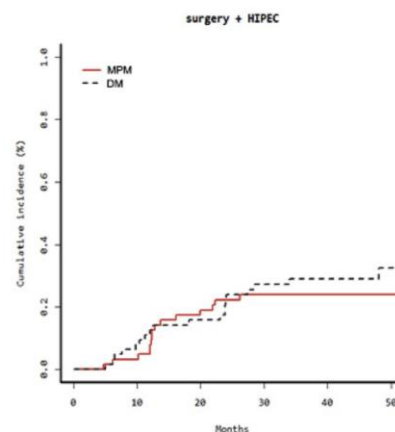
3

Regional therapies
reduce peritoneal
relapse in locally
advanced GC

Prophylactic HIPEC - Belarus study

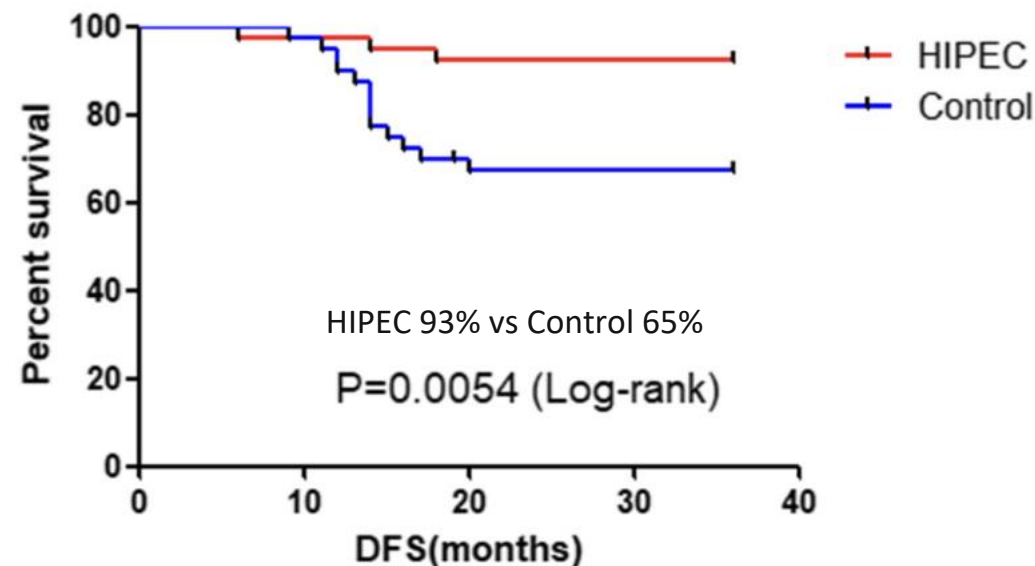
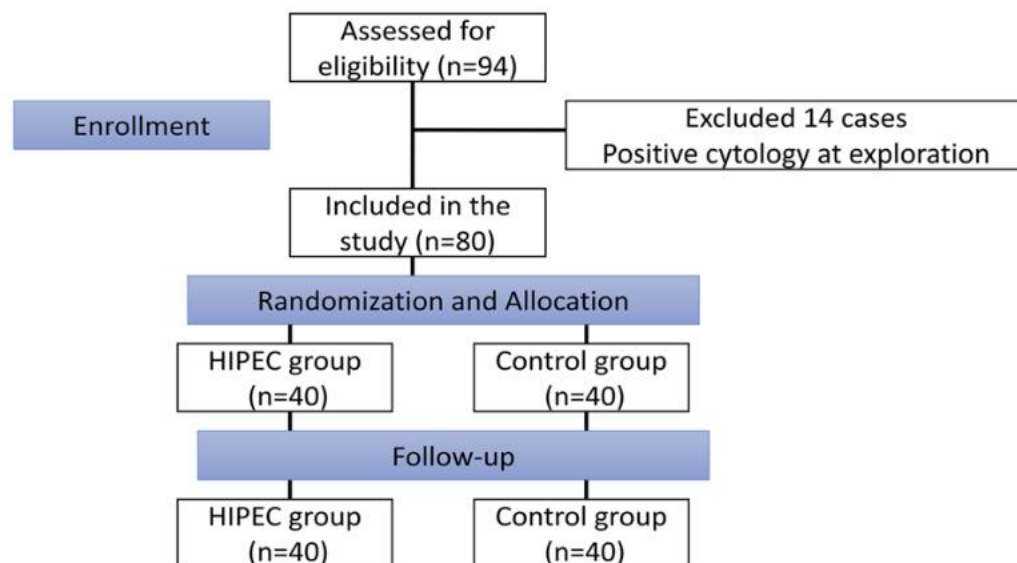


- 3-year PFS survival in T4 GC was higher in the HIPEC group cisplatin 50 mg/m² + doxorubicin 50 mg/m² compared with the control group (47% vs 27%, p = 0.0024).
- Fewer peritoneal recurrences.
- No G4/5 toxicities



Yu Reutovich. Eur J Surg Onc. 2019

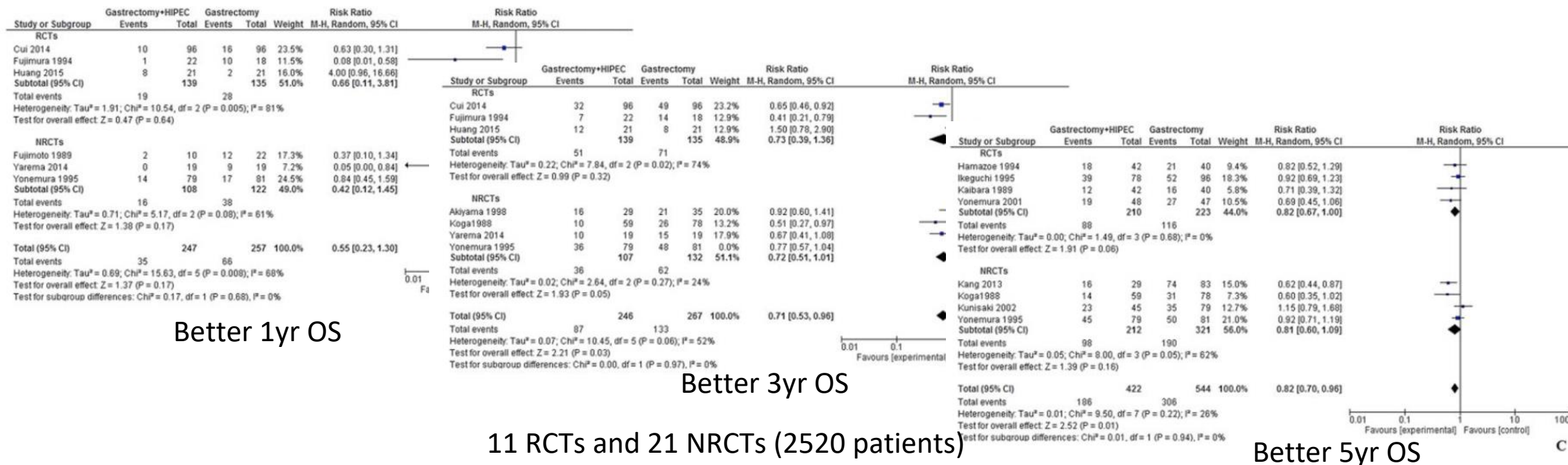
Prophylactic HIPEC - China study



- 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



- 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

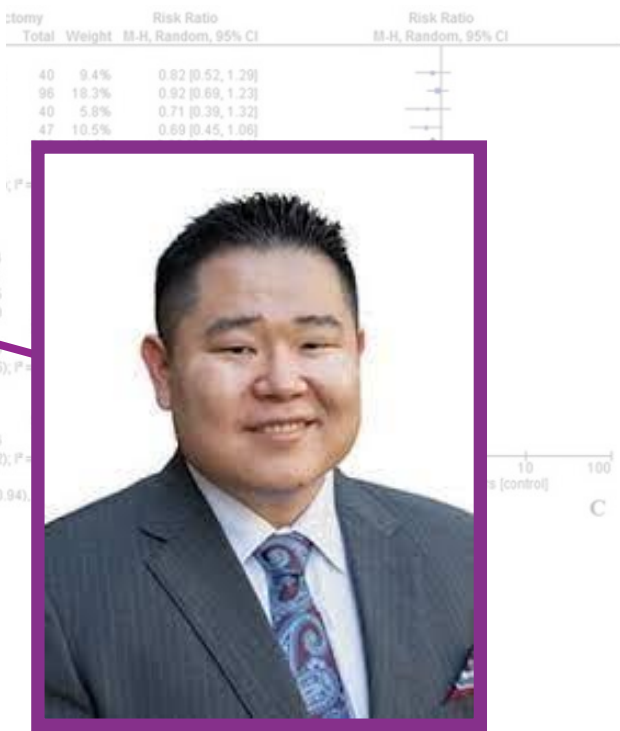
The Thirty-Year Experience - A Meta-analysis of Randomized and High Quality Non-Randomized Studies of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Gastric Cancer

Jacopo Desiderio, MD^{1,2}, **Joseph Chao, MD³**, Laleh Melstrom, MD¹, Susanne Warner, MD¹, Federico Tozzi, MD¹, Yuman Fong, MD¹, Amilcare Parisi, MD², and Yanghee Woo, MD¹

Better 1yr OS

Better 3yr OS

“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 “



Desiderio J. Eur J Cancer Cancer 2017

Is there a role for HIPEC in adjuvant setting?



Reutovich 2019

YES

YES

YES

RCT



Beeharry 2019

YES

YES

YES

RCT

Is adjuvant HIPEC safe?

Does it reduce PM?

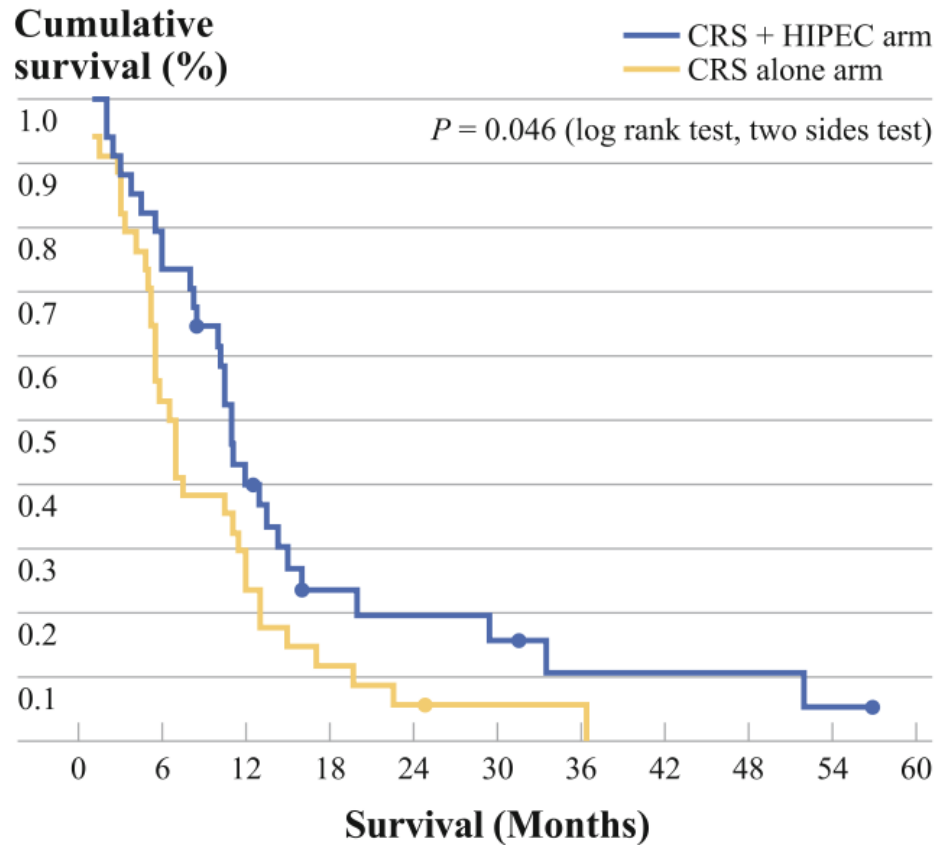
Does it improve DFS?

Level of evidence?

4

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

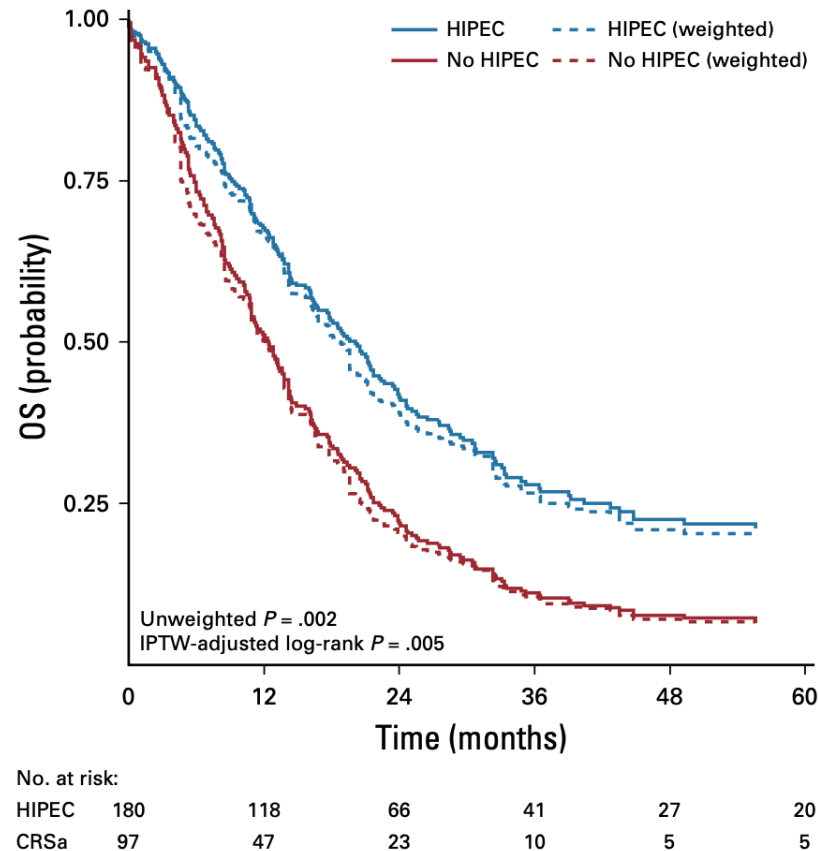
CRS + HIPEC has superior PFS



- 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

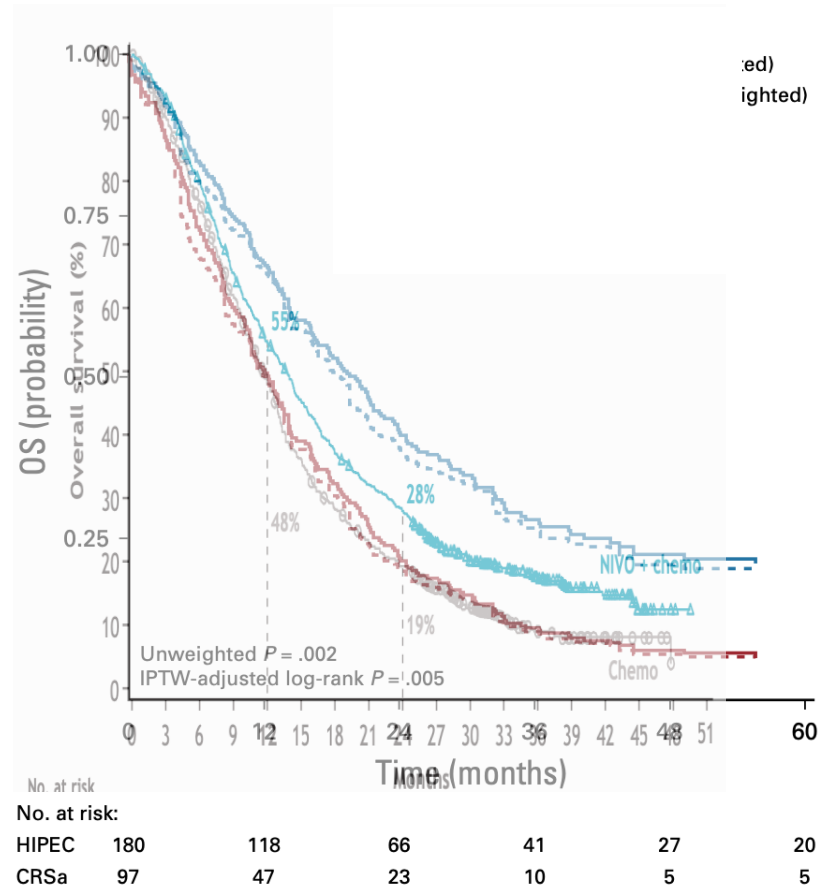
CYTO-CHIP: Well designed, retrospective large cohort study



- 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

CYTO-CHIP: Well designed, retrospective large cohort study

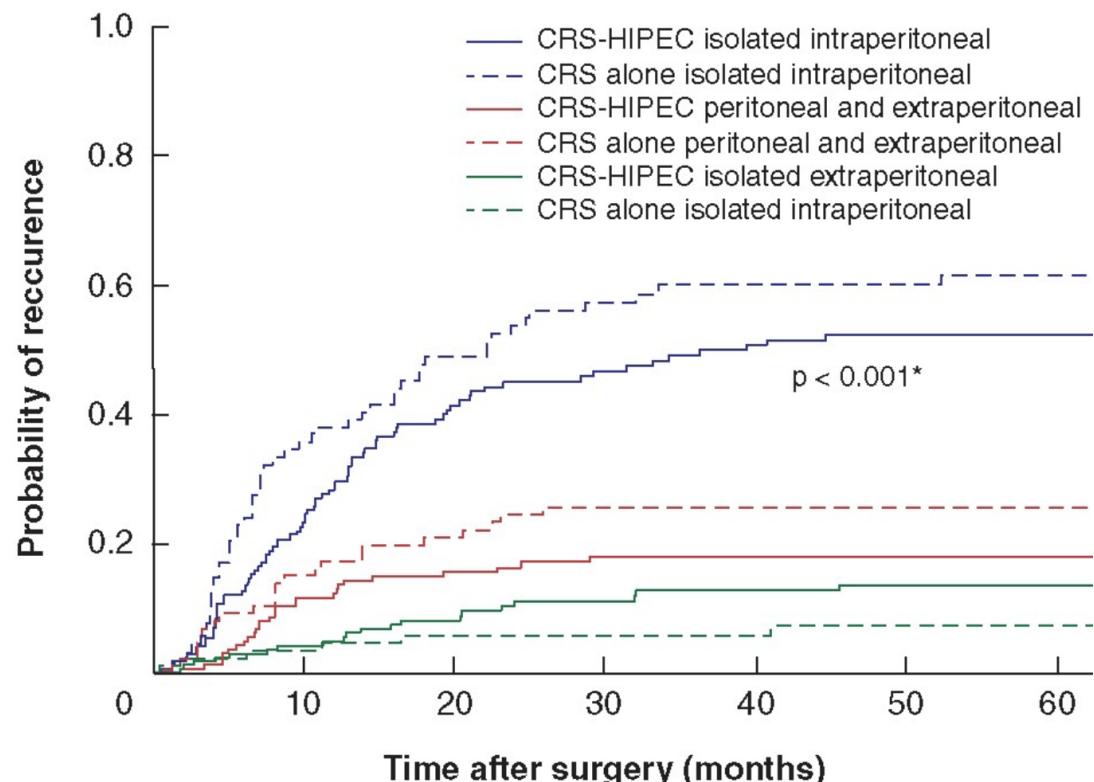


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Bonnot P-E. J Clin Oncol. 2019

Pattern of recurrence after HIPEC

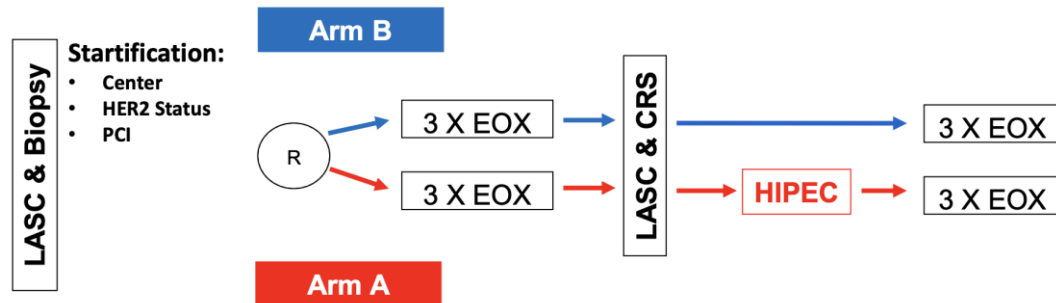
b Impact of CRS-HIPEC on recurrence pattern



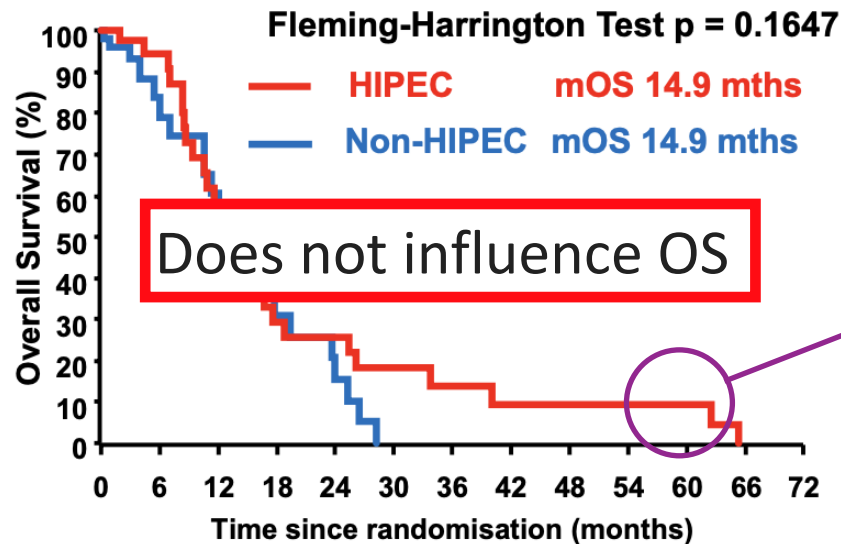
- HIPEC ($P < 0.001$) were associated with fewer peritoneal recurrences.
- The impact of HIPEC was consistent irrespective of histology, with the benefit of HIPEC being more pronounced in the non-PCC population.

Bonnot P-E. Brit J Surgery. 2021

GASTRIPEC I - a missed opportunity



FAS

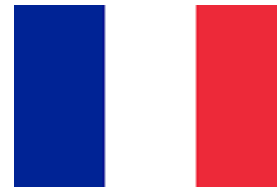


- Early study termination due to low accrual.
- High rate of drop outs 52% due to tumor progression (20%), and non-resectable (23%); only 36 received HIPEC.
- HIPEC with CDDP and MMC for 60 minutes significantly increase PFS (7.1 vs 3.5 months), and distant metastasis free survival (10.2 vs 9.2 months).
- 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?

Is CRS + HIPEC safe?
Does it reduce PM?
Does it improve OS?
Level of evidence?



CYTO-CHIP 2019

YES

YES

YES

nonRCT



Yang 2011

YES

NO

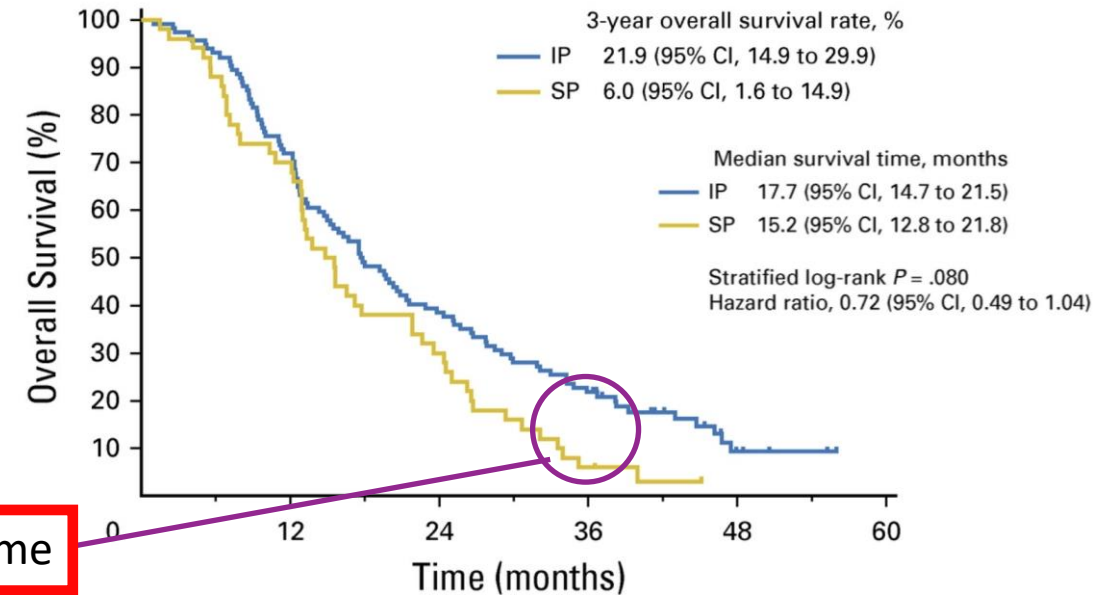
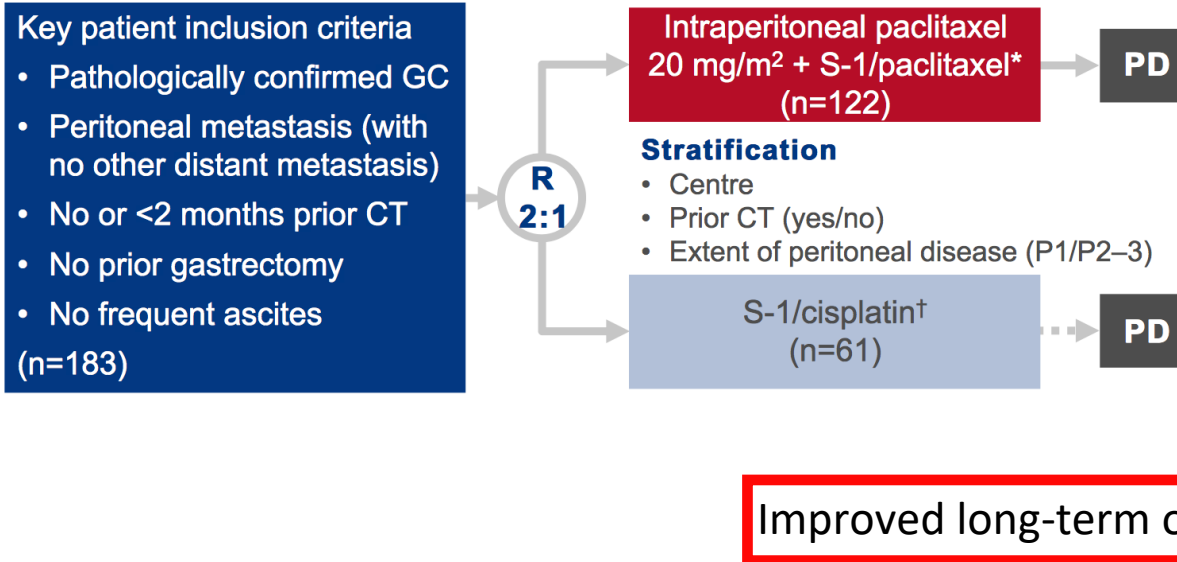
YES

RCT

5

Regional therapies
alter long-term survival
of GCPM

PHOENIX TRIAL - NIPS

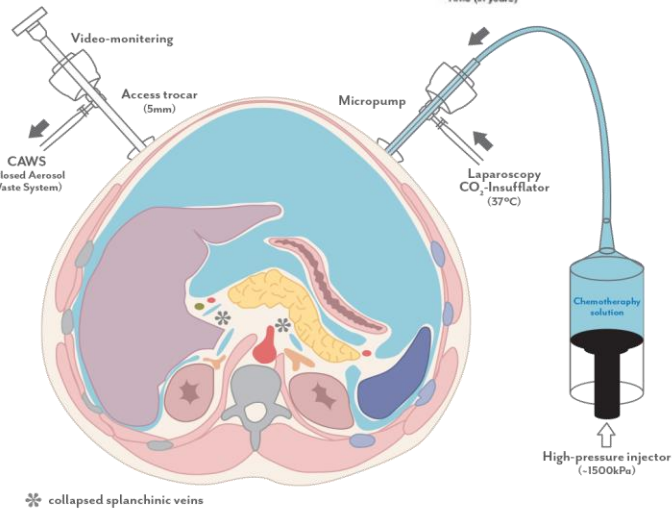
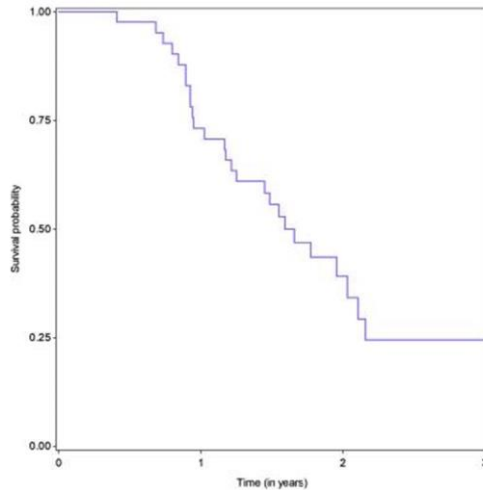


Additional post hoc sensitivity analysis adjusted for baseline ascites using the FAS, overall survival was longer in the IP arm than in the SP arm (adjusted HR, 0.59; 95% CI, 0.39 to 0.87; $P = .008$).

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

Ishigami H. J Clin Oncol 2018

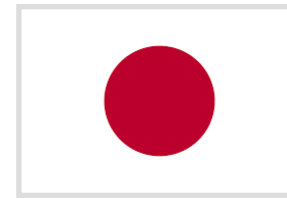
PIPAC



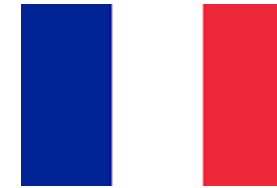
- PIPAC cisplatin and doxorubicin is safe.
- Co-administered with systemic therapy (n=42), with median delay in restarting chemotherapy 14 days, range 4-28 days.
- OS 19.1 months; nearly 50% had 2L chemotherapy.
- Six (14.3%) patients became eligible for CRS and HIPEC with PCI dropped from initial 13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

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

Is safe with systemic therapy?

YES

YES

Does it improve OS?

Maybe

Maybe

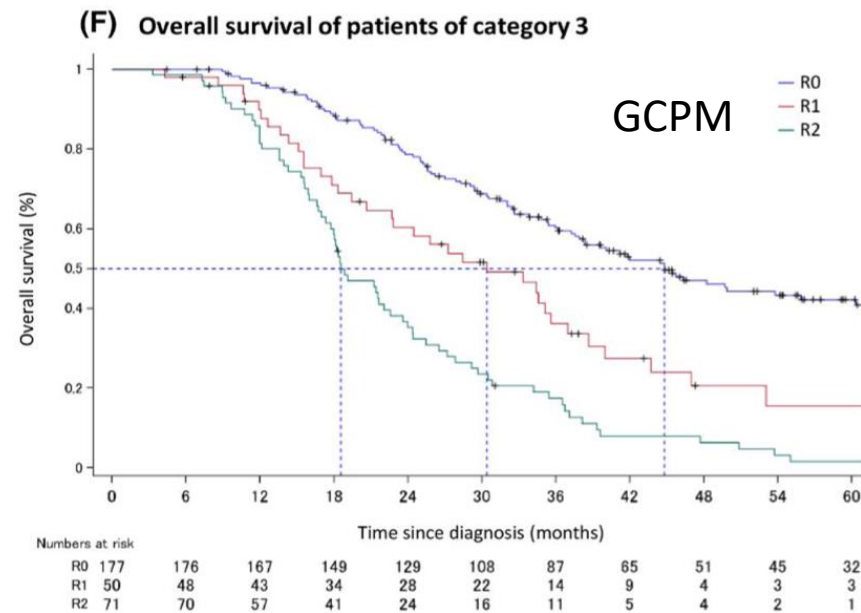
Level of evidence?

RCT

nonRCT

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

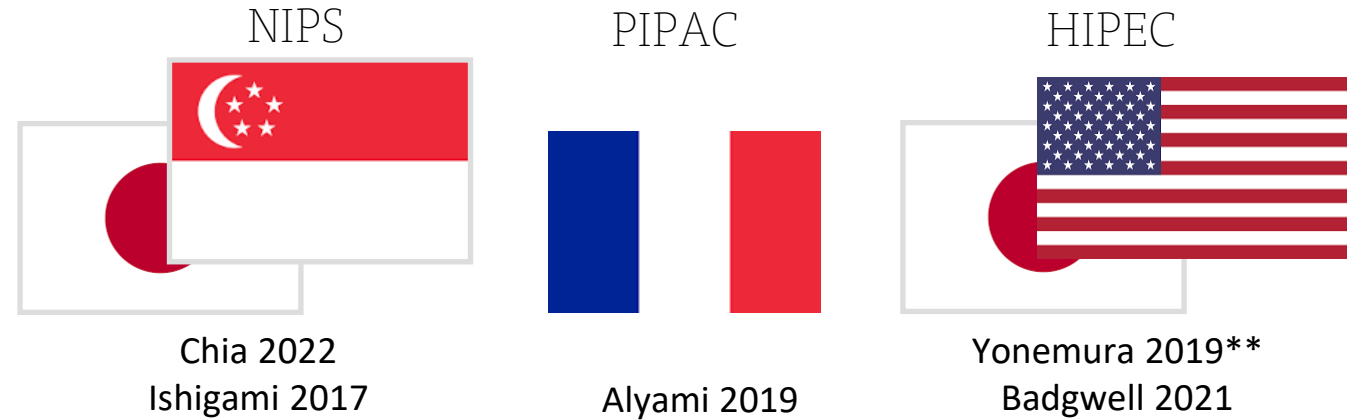


Altering long-term survival with conversion surgery

- 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.

Chia D Ann Oncol Surg 2022, Ishigami H J Clin Oncol 2018, Alyami M. Eur J Surg Oncol 2019, Badgwell 2021

NIPES/PIPAC/HIPEC in conversion surgery



Is safe with systemic therapy?

YES

YES

YES

Can it improve conversion rate?

YES

RR 36-64%

YES

PCI regression

YES

PCI regression**

Outcome superior to systemic therapy?

May be

Level of evidence?

Phase 2 but promising

International guidelines



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 2.2022 Gastric Cancer

[NCCN Guidelines Index](#)
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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.¹⁸⁻²⁰

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!

