Diffusion or perfusion of Innovation: The case for HIPEC in Ovarian Cancer

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(Disclosure: NPS MedicineWise, CRE in Implementation Science in Oncology)

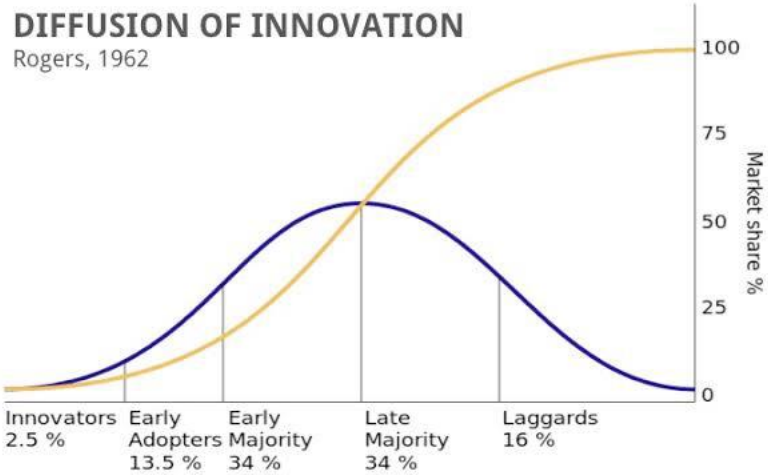
Objectives

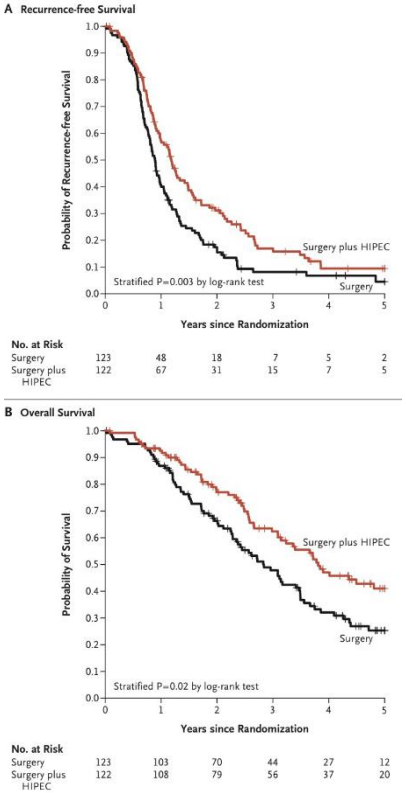
- Discuss the principles of intraperitoneal chemotherapy with a focus on HIPEC, in particular the constructive criticisms of OVHIPEC
- Discuss diffusion of innovation and its' relevance to intraperitoneal chemotherapy
- Consider some barriers to implementation and how to move forward

Diffusion is a slow, passive process

- 1978 - Dedrick Model Proposed
- 1982 – Ozols - Phase I adriamycin IP
- 1994 - Loggie - hyperthermia chemotherapy
- 2000 – PIPAC in pigs
- 2006 - Armstrong Protocol
- 2013/14 – Reymond – PIPAC in humans
- 2015 - NCI 'Announcement' regarding IP chemotherapy
- 2018 – OVHIPEC

- So much for 17 years!





Great result, but…

- We don’t like your experiment:
  - Why intraperitoneal?
  - Why not just give an extra dose of IV chemo?
  - Do you really need the heat

Why Intra-Peritoneal? Dedrick Model

- Intraperitoneal delivery should enable exposure of tumour present in the peritoneal cavity to substantially higher concentrations of cytotoxic drugs compared to systemic delivery. The ideal agents for IP:
  - Known systemic activity against the tumour type
  - Dose or duration (AUC) relationship
  - Not vesicant
  - Slow clearance from peritoneal cavity and rapid systemic clearance
  - Extensive first pass metabolism
  - Does not require hepatic activation to active metabolite

Markman 2007

Drug	Cp/Cs	AUC
Carboplatin		18
Cisplatin	20	12
Cytarabine	664	474
Doxorubicin	474	
5-fluorouracil	298	367
FUDR		1000
Melphalan	93	65
Methotrexate	92	
Mitoxantrone		1400
Paclitaxel	1000	1000

Coccolini, Pharm Res 2017 and Lemoine 2019

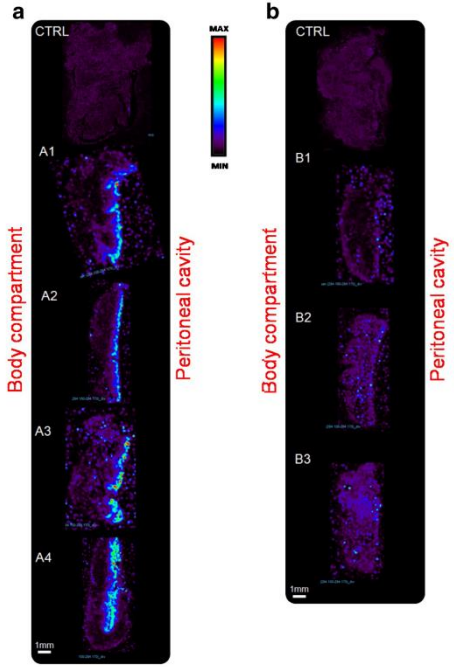


Fig. 2 Penetration of PTX in peritoneal tissue of rabbits assessed by MSI, after perfusions of *nab*-paclitaxel((**a**), $n = 4$) or CRE-paclitaxel ((**b**), $n = 3$). One representative section of three analyzed for each rabbit is shown. Control tissues (CTRL) are from a rabbit perfused with solution without drug.

TABLE 2 Pharmacologic parameters

Characteristics	HIPEC-BSA	HIPEC-CONC	*P* value
Patients (*n*)	15	16	
Total oxaliplatin, mg	853.30 (779.70-903.90)	1150.00 (1150.00–1380.00)	*<0.001*
Volume of perfusate, L	6 (6-8)	5 (5-6)	0.439
Volume of perfusate end of HIPEC, L	5.30 (4.75-6.05)	5.35 (5.08-6.16)	0.606
Pt retained in the body after 30 min, %	36.97 ± 24.27	36.42 ± 10.47	0.940
AUC plasma	86.62 ± 18.58	126.89 ± 35.59	*0.001*
AUC UF	72.93 ± 13.07	106.26 ± 28.78	*0.001*
AUC PF	1702.67 (1467.95-1900.08)	2599.58 (2420.24-2730.13)	*<0.001*
Pharmacologic advantage	17.97 (16.44-29.65)	18.95 (16.39-27.15)	0.599
Pt concentration tumor nodule at the end of HIPEC, ng/mg wet tissue	26.10 (19.00-52.26)	77.60 (27.26-107.36)	*0.047*
Urine output during HIPEC, mL	69.50 (40.13-219.25)	62.00 (33.00-140.00)	0.513
Pt cleared via the urine during HIPEC, %	0.62 (0.05-1.02)	0.30 (0.02-0.53)	0.214

Abbreviations: AUC, area under the curve; BSA, body surface area; CONC, concentration; HIPEC, hyperthermic intraperitoneal perioperative chemotherapy; Pt, platinum; PF, peritoneal fluid; UF, ultrafiltrate.
Data are presented as mean ± SD, median with interquartile range.
The values that are presented in italics are below the threshold of $P < 0.05$ and are considered statistically significant.

And so IP therapy was studied (Tewari, JCO 2015)

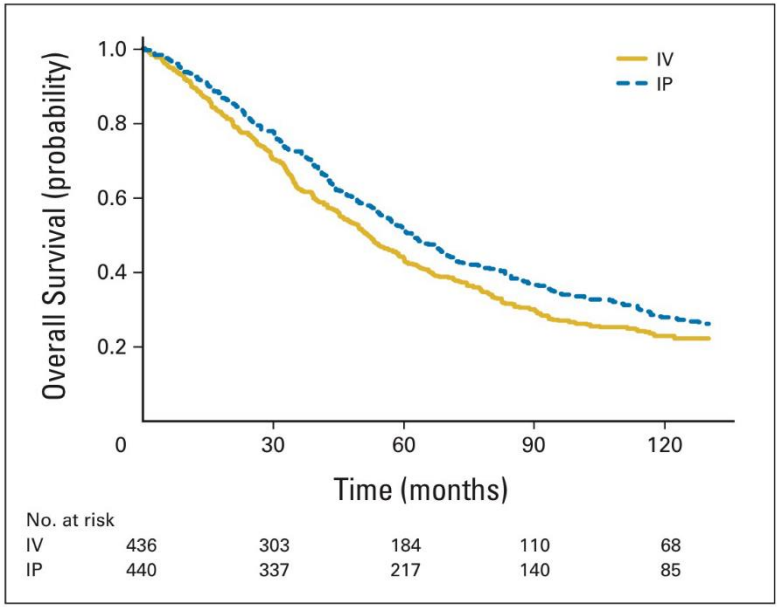


Fig 2. Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy ($P = .04$).

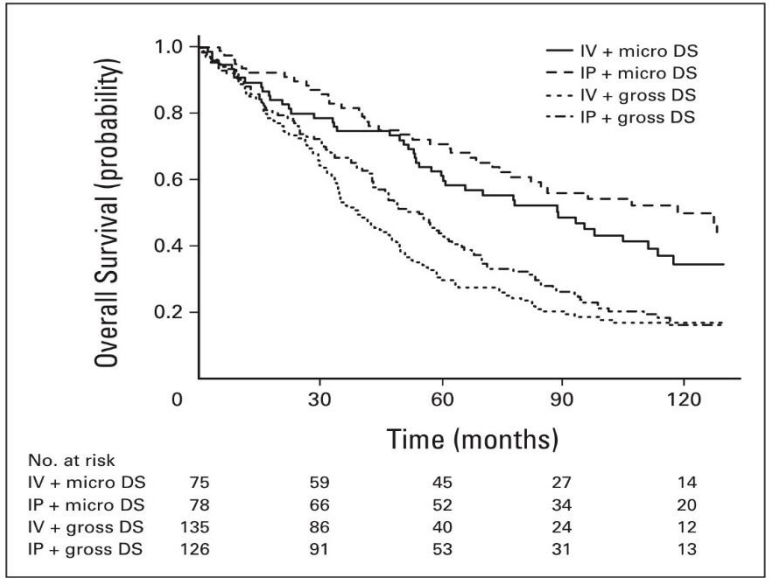


Fig 3. Long-term overall survival of patients treated with intravenous (IV) versus intraperitoneal (IP) chemotherapy based on extent of residual disease (DS; $P < .001$). NOTE. Gross residual defined as ≤ 1 cm; micro residual defined as no visible disease.

But the HIPEC arm got a whole extra cycle of chemotherapy (Hess, Cancer 2010)

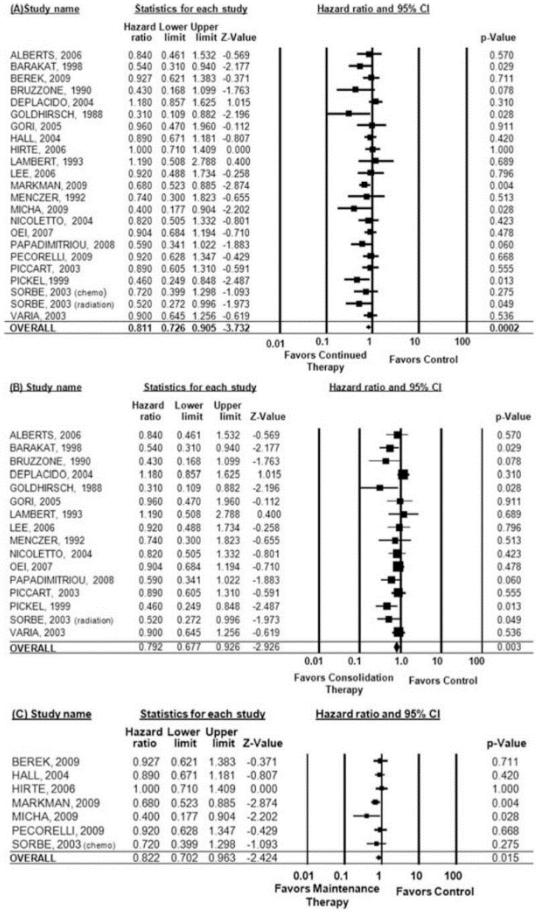


Figure 2.
Pooled progression-free survival is shown for (A) all studies, (B) consolidation therapy studies, and (C) maintenance therapy studies. CI indicates confidence interval.

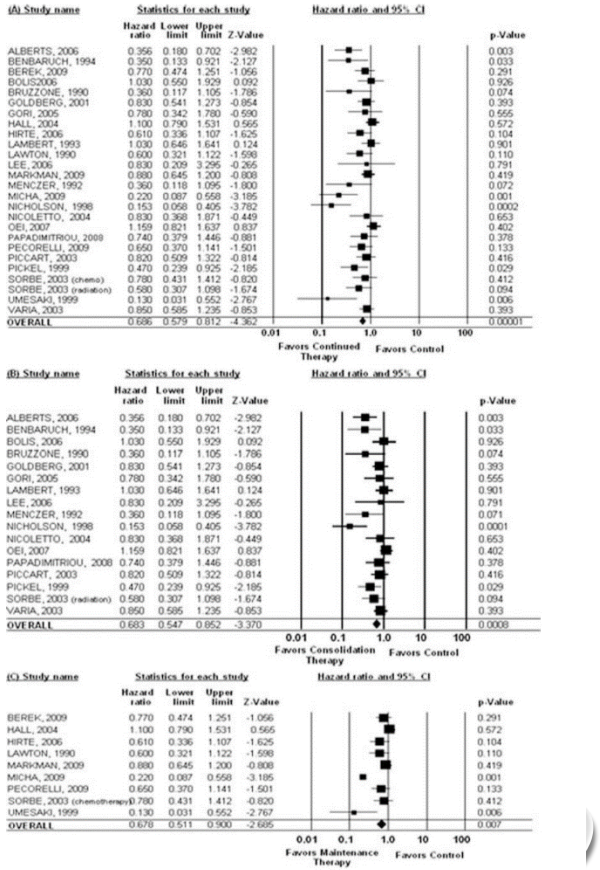
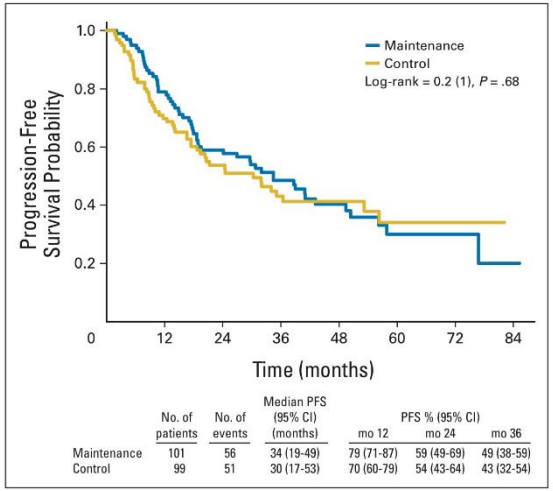


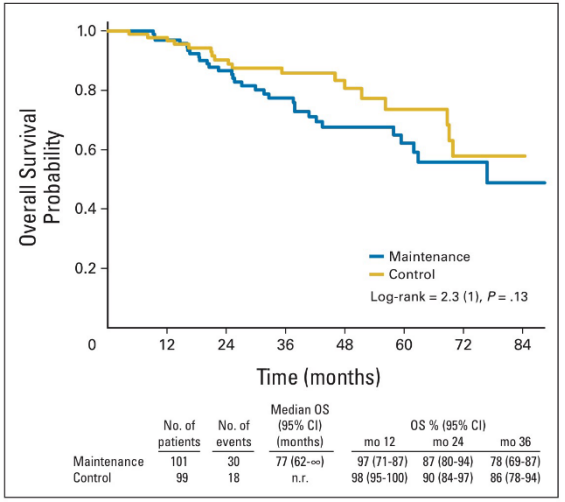
Figure 3.
Pooled overall survival is shown for (A) all studies, (B) consolidation therapy studies, and (C) maintenance therapy studies. CI indicates confidence interval.

Pecorelli, JCO 2009 – extra 6 cycles paclitaxel



	No. of patients	No. of events	Median PFS (95% CI) (months)	PFS % (95% CI) mo 12	mo 24	mo 36
Maintenance	101	56	34 (19-49)	79 (71-87)	59 (49-69)	49 (38-59)
Control	99	51	30 (17-53)	70 (60-79)	54 (43-64)	43 (32-54)

Fig 2. Progression-free survival (PFS) according to intention-to-treat analysis.



	No. of patients	No. of events	Median OS (95% CI) (months)	OS % (95% CI) mo 12	mo 24	mo 36
Maintenance	101	30	77 (62-∞)	97 (71-87)	87 (80-94)	78 (69-87)
Control	99	18	n.r.	98 (95-100)	90 (84-97)	86 (78-94)

Fig 3. Overall survival (OS) according to intention-to-treat analysis.

Gore, JCO 1998, AUC 6 v 12 carboplatin

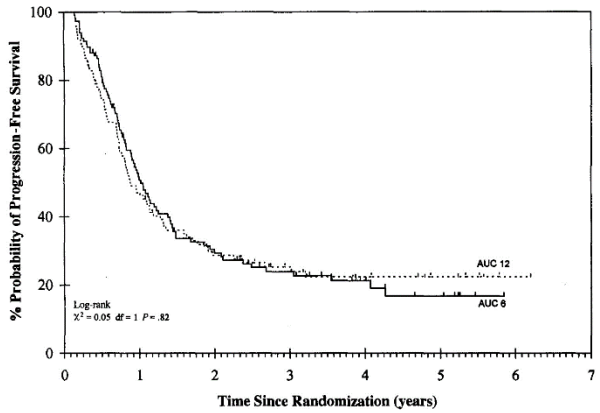


Fig 1. Progression-free survival. Carboplatin AUC 6, n = 117; carboplatin AUC 12, n = 110.

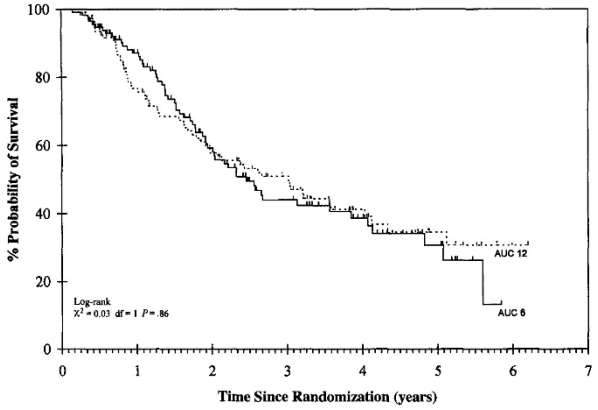


Fig 2. Overall survival. Carboplatin AUC 6, n = 117; carboplatin AUC 12, n = 110.

What about the hyperthermia?Do we need it? Multiple possible effects

- Altered cytoskeleton, protein synthesis and desaturation, RNA/DNA synthesis and gene expression
- Temperature and exposure time relationships in in vitro radiation models
- Tumour micro environment alteration: reduced blood supply aggravating hypoxia and acidosis
- Extravasation of lymphocytes into tumour microenvironment, pro-inflammatory cytokines and T cell activation
- Concomitant dysregulation of heat shock proteins
- Altered pharmacokinetics and thermal enhancement of cytotoxicity e.g. cisplatin (up to 3.9 fold thermal enhancement ratio)

Piche, Ann Surg, 2011

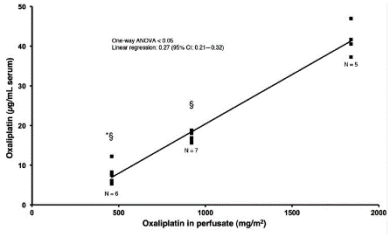


Figure 2. Effect of the dose of oxaliplatin in perfusate on the concentration of oxaliplatin in systemic serum at 40°C. *, Significant difference from 920 mg/m² using post hoc Sheffe test. §, Significant difference from 1840 mg/m² using post hoc Sheffe test.

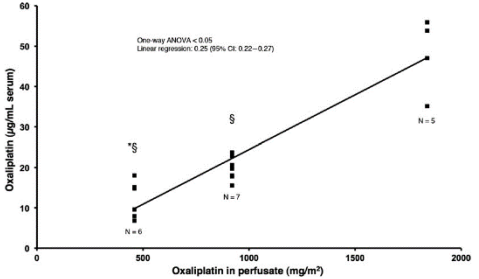


Figure 3. Effect of the dose of oxaliplatin in perfusate on the concentration of oxaliplatin in portal serum at 40°C. *, Significant difference from 920 mg/m² using post hoc Sheffe test. §, Significant difference from 1840 mg/m² using post hoc Sheffe test.

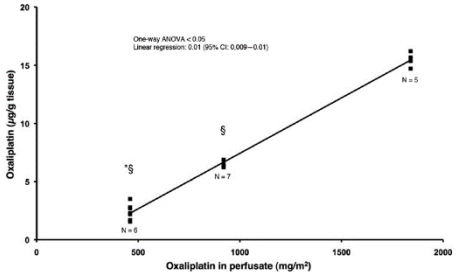


Figure 4. Effect of the dose of oxaliplatin in perfusate on the concentration of oxaliplatin in peritoneal tissue at 40°C. *, Significant difference from 920 mg/m² using post hoc Sheffe test. §, Significant difference from 1840mg/m² using post-hoc Sheffe test.

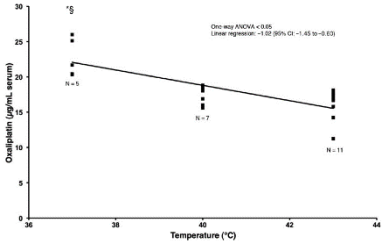


Figure 5. Effect of temperature on the concentration of oxaliplatin in systemic serum. Dose of oxaliplatin in perfusate = 920 mg/m². *, Significant difference from 40°C using post hoc Sheffe test. §, Significant difference from 43°C using post hoc Sheffe test.

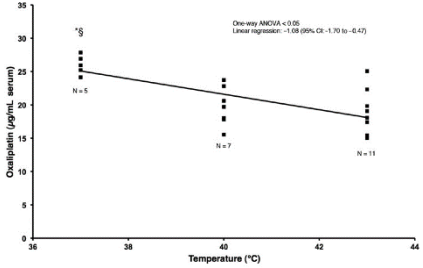


Figure 6. Effect of temperature on the concentration of oxaliplatin in portal serum. Dose of oxaliplatin in perfusate = 920 mg/m². ^, Significant difference from 40°C using post hoc Sheffe test. §, Significant difference from 43°C using post hoc Sheffe test.

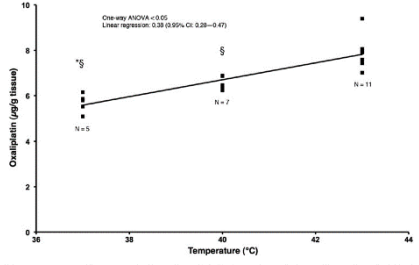


Figure 7. Effect of temperature on the concentration of oxaliplatin in peritoneal tissue. Dose of oxaliplatin in perfusate = 920 mg/m². ^, Significant difference from 40°C using post-hoc Sheffe test. §, Significant difference from 43°C using post hoc Sheffe test.

Klaver, Ann Surg 2011
Klaver, Ann Surg Onc 2012
Graziosi, in Vito 2012
Pelz, BMC Cancer 2006

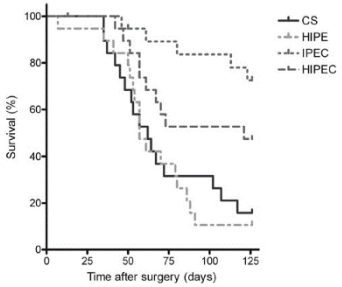


FIGURE 4. Kaplan–Meier survival curves, per group. CS, cytoreductive surgery, HIPE = CS + perfusion with NaCl at 41°C; IPEC = CS + perfusion with mitomycin at 37°C; HIPEC = CS + perfusion with mitomycin at 41°C. CS vs. HIPEC: $P = 0.022$, CS vs. IPEC: $P = 0.002$, hazard ratio 0.36, 95% CI 0.19–0.69, CS vs. HIPE: nonsignificant.

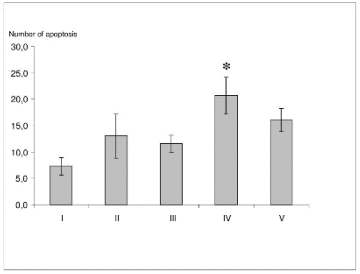


Figure 1
The mean number of apoptotic cells in 5 high-power fields of non-necrotic areas. (group I: control; group II: sham operated animals; group III: hyperthermia alone; group IV: HIPEC; group V: MMC i.p. alone) * p < 0.036 group IV versus group I; (Kruskal-Wallis test)

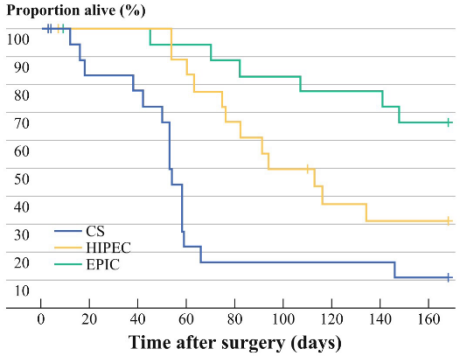


FIG. 4 Kaplan–Meier analysis of overall survival, per group

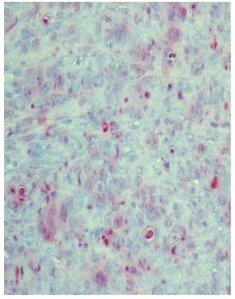


Figure 2
Immunohistochemical staining for group IV (HIPEC): Apoptosis are represented by red clusters. The index represented the number of visible apoptotic cancer cells in five fields.

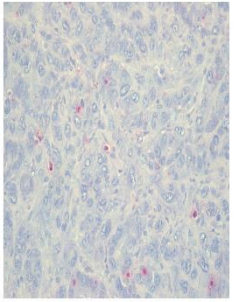


Figure 3
Immunohistochemical staining group I (control): Apoptosis are represented by red clusters. The index represented the number of visible apoptotic cancer cells in five fields

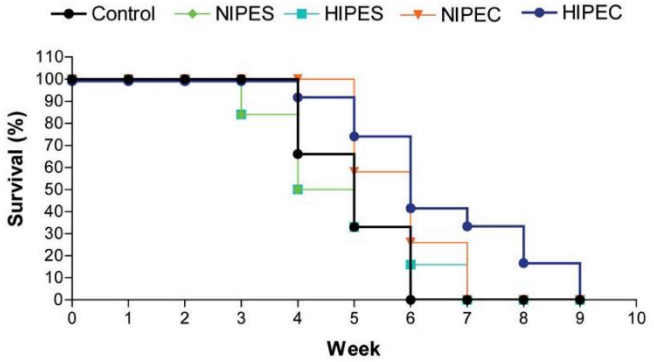


Figure 4. *Effects of HIPEC treatment on survival curve after induction of peritoneal dissemination. After one day from MKN45 cell inoculation, animals were randomized into five groups of 8-10 each and treated by HIPEC, NIPEC, NIPES, HIPES or no treatment, and survival curve was recorded.*

Table I. *Molecular effects of hyperthermic intraperitoneal chemotherapy (HIPEC): downregulated genes. HIPEC treatment one day after MKN45 cell inoculation down-regulated the expression of APC, ITGB3, CXCR4, SYK, VEGFR3/FLT4, COL4A2 and CTBP1 genes ($p < 0.01$ versus the untreated control group). Microarray analysis was performed using 3 peritoneal nodules from different mice for each experimental group.*

Gene	Fold change
Adenomatous polyposis coli (*APC*)	4.76
Beta(3) subunit of the integrin gene (*ITGB3*)	6.57
Chemokine stromal cell-derived factor-1 receptor (*CXCR4*)	8.48
Spleen tyrosine kinase (SYK)	17.35
Vascular endothelial growth factor receptor 3/Fms-related tyrosine kinase 4 (*VEGFR3/FLT4*)	34.7
Collagen, type IV, alpha 2 (*COL4A2*)	581
C-Terminal binding proteins 1 (*CTBP1*)	3524

ANNU SYDN

The take home

- It is not as simple as just giving more chemotherapy
- How you give it counts:
  - IP versus IV (or bidirectional)
  - Concentration / dose
  - Temperature
  - Pressure
  - Carrying solution / formulations /excipients

Let's assume some of the audience are convinced by OVHIPEC – what next?

- The requirements for diffusion of innovation (as adapted by Sanson-Fisher, MJA 2004, from Rogers):
  - Relative advantage "the degree to which the innovation is perceived as being better than the idea it supersedes' – but the (dis)advantage might be from the perspective of the clinician not necessarily just evidence-based medicine
  - Compatability "the degree to which an innovation is perceived as compatible with existing values, past experiences and the needs of potential adopters" – HIPEC might not be compatible with current surgical practice, oncologists beliefs about IP therapy, etc.

Continued

- Complexity “degree to which an innovation is perceived as difficult to understand and use”
- Trialability “degree to which an innovation can be trialled and modified”
- Observability “degree to which the results of the innovation are visible to others” – role models and key opinion leaders (see Keown, Health Affairs, 2014)

EXHIBIT 3

Top Three Cultural Dynamics In Terms Of Prevalence In The Eight Countries In The Global Diffusion Of Healthcare Innovation Study

Cultural dynamic	All countries	Australia	Brazil	England	India	Qatar	South Africa	Spain	US
Harnessing the efforts of patients and the public as coproducers of well-being	2	2	NR	1	3	3	2	2	2
Addressing concerns of health care professionals about outcomes and sustainability	3	3	2	3	NR	NR	3	3	3
Adapting innovations to suit the local context	NR	NR	NR	NR	NR	NR	NR	NR	NR
Identifying and supporting champions who embrace and support change	1	1	1	2	1	2	1	1	1
Creating time and space for learning and new ways of working	NR	NR	NR	NR	2	NR	NR	NR	NR
Delayering old and ineffective ways of working	NR	NR	3	NR	NR	NR	NR	NR	NR
Improving the next journey of system transformation	NR	NR	NR	NR	NR	1	NR	NR	NR

But barriers to diffusion of innovation about: qualitative research (Barnett, BMC Health Services Research 2011)

- Role of evidence
  - Proof of effectiveness
  - A means of diffusion
  - A precondition
- Role of partnerships
  - Especially interorganisational
- Role of people-based resources
  - Consider champions and opinion leaders but also administrators
  - Difficulty getting multiple disciplines to align
- Role of contextual factors
  - Intra-organizational
  - Extra-organizational
    - Economy/politics/ideological

& there are the paradoxes of innovation (Dixon-Woods, BMJ Qual SAF 2011)

- some innovations diffuse rapidly, yet are of unproven value or limited value, or pose risks, while other innovations that could potentially deliver benefits to patients remain slow to achieve uptake
  - E.g. OVHIPEC (+ trial) approach might not lead to uptake of HIPEC in ovarian but PRODIGE7 (- trial) might lead to uptake in colorectal
- participatory, cooperative approaches may be the best way of achieving sustainable, positive innovation, yet relying solely on such approaches may disrupt positive innovation
  - Need to manage conflict within co-operatives!
- improvement clearly depends upon change, but change always generates new challenges
  - We can't keep up with the changes (e.g. add in bevacizumab/PARP to the mix)

What do I see as the Oz-HIPEC Barriers?

- Ownership – med-oncs and gynae-oncs must want to do it
  - Around the world GI surgical oncologists are the advocates for and custodians of HIPEC
  - Medical oncologists are mostly not engaged and they don't see cancer in the peritoneal cavity as different from any other site of metastatic disease
- Gynae-oncs must deal with professional and philosophical challenges
  - Maximal surgical effort to achieve R0/CC0 'optimal' cytoreduction
    - OVHIPEC had the inverse optimal cytoreduction rate to GOG172 and the control arms of EORTC 55971 and Chorus
    - Both the completeness of cytoreduction and the toxicity (toxicity threshold) are in the hands of the surgeon
  - Volume-outcome relationships must be considered – consolidation must occur
    - 54 hospital performed an ovarian cancer operation in NSW in 2016/17 and of these only 14 performed more than 10, only 5 performed more than 30

What do I see as the Oz-HIPEC Barriers?

- General evidence issues related to dissemination of IP therapy / HIPEC
  - One positive, well-designed ovarian trial which doesn't tackle the upfront surgery scenario + regular IP therapy not embraced
  - One negative, poorly-designed colorectal trial (with best ever survival in both arms)
    - No phase II
    - Pre-clinical data all contradicts the oxaliplatin protocol used in PRODIGE7
  - Roles in appendix ca (including PMP) and mesothelioma not likely to be tested (although there is an RCT comparing different drugs in appendix ca.
  - Gastric cancer has positive, poorly designed trial. French study in progress.
- Resource implications
  - Cost-effectiveness needs to be shown
  - Local infrastructure requirements manageable
  - Human resource – the team – is really important as is learning curve of the whole team

But there may be willingness to adopt new ways

TABLE 3. CGOs reporting of surgical procedures performed for advanced EOC, and by whom

	Performed 2017 (n = 47) and 2007 (n = 34)						
	Yourself, n (%)		With Colleague, n (%)		Rarely or Never, n (%)		
Procedure	**2017**	**2007**	**2017**	**2007**	**2017**	**2007**	***P***
Excision of bulky pelvic lymph nodes	45 (96)	33 (97)	2 (4)	1 (3)	0	0	1.0
Small bowel resection	43 (91)	34 (100)	4 (9)	0	0	0	ns
Large bowel resection	38 (81)	30 (88)	9 (19)	4 (12)	0	0	0.54
En bloc resection of uterus/rectosigmoid	31 (66)	27 (79)	14 (30)	6 (18)	2 (4)	1 (3)	0.48
Stripping/resection of diaphragmatic disease	27 (57)	11 (32)	17 (36)	4 (12)	3 (6)	19 (56)	**<0.001**
Splenectomy	23 (49)	14 (41)	21 (45)	15 (44)	3 (6)	5 (15)	0.08
Bulky upper para-aortic lymph nodes	22 (48)	16 (47)	17 (37)	5 (15)	7 (15)	13 (38)	**0.02**
Resection and reimplantation of ureter	11 (23)	18 (53)	30 (64)	11 (32)	6 (13)	5 (15)	**0.01**
Distal pancreatic resection	9 (19)	9 (26)	27 (57)	11 (32)	11 (23)	14 (41)	0.08
Resection of parenchymal liver metastases	4 (9)	1 (3)	26 (55)	12 (35)	16 (34)	21 (62)	**0.02**
Resection of porta hepatis metastases	5 (11)	*	16 (34)	*	26 (55)	*	*

P value performed using Fisher exact test or χ^2 where appropriate.
*Not surveyed in 2007.

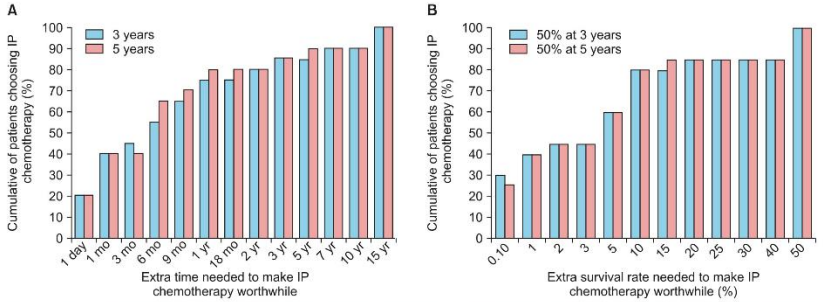
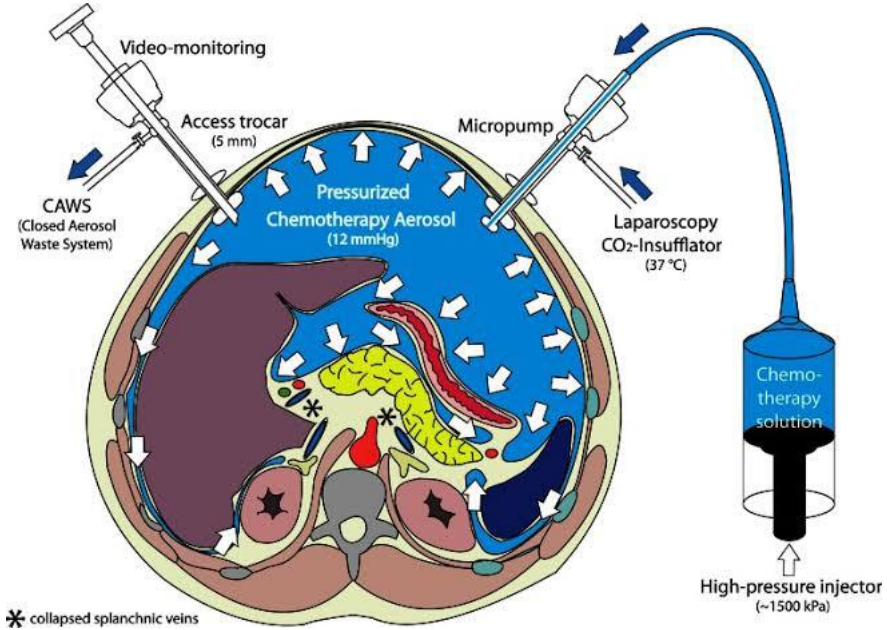


Fig. 2. Cumulative proportions of patients considering whether intraperitoneal (IP) chemotherapy would be worthwhile for various improvements in (A) survival times of 3 and 5 years and (B) survival rates of 50% at 3 years and 5 years (n=20).

Blinman JGO 2013

And new technology is coming!

- PIPAC – pressurised intra-peritoneal aerosol chemotherapy



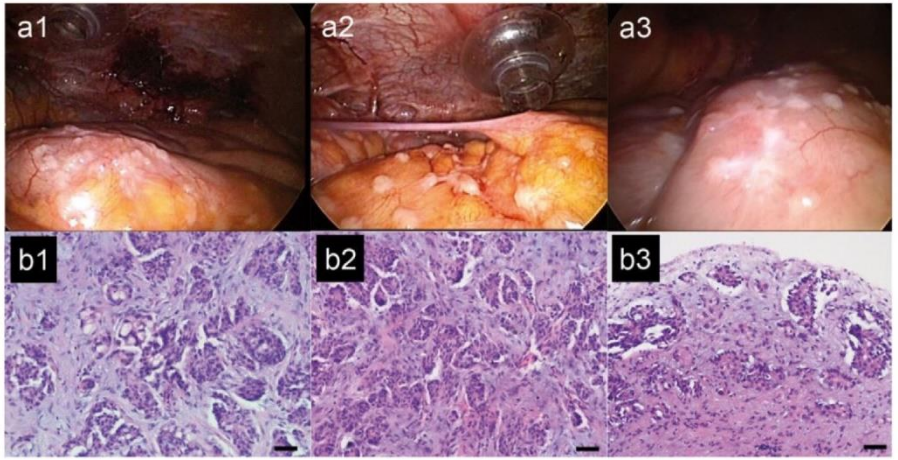


Fig. 2. Intraoperative findings (macroscopy) during laparoscopy before the 1st, 2nd, and 3rd pressurized intraperitoneal aerosol chemotherapy (PIPAC) treatment cycles (panels a1, a2, and a3, respectively). During the course of therapy, sclerosis of peritoneal nodules was observed as well as scarring of the visceral and the parietal peritoneum. Corresponding histological specimens taken during the 1st, 2nd, and 3rd PIPACs demonstrated regressive tumor changes, fibrosis, and acute and chronic inflammation (panels b1, b2, and b3, respectively).

- 53 pts, median 3 cycles prior chemotherapy
- 62% RECIST RR
- 76% Histopathological Response and PCI reduction

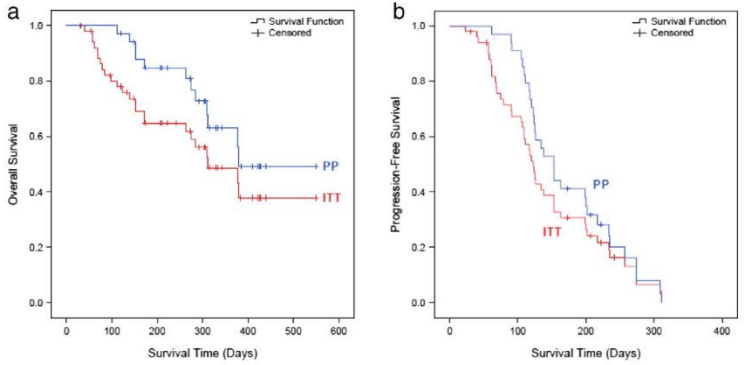


Fig. 3. Overall survival (panel a) and progression-free survival (panel b) of 53 women who had undergone at least one pressurized intraperitoneal aerosol chemotherapy (intention-to-treat population; ITT) and of 34 women who had undergone all three PIPAC cycles (per-protocol population; PP).

Diffusion is not enough – we must perfuse this into our organisations

- Train gynae-oncs and get the med-oncs on board
- Establish new gynaecological cancer surgical centres of excellence with capacity to do HIPEC, in conjunction with GI cancer HIPEC centres, and with minimal caseloads
- Benchmarking
  - Standardized surgical operation reports to establish baseline disease, cytoreduction scores
- Maintain prospective (National) registries
- Conduct/participate in further trials