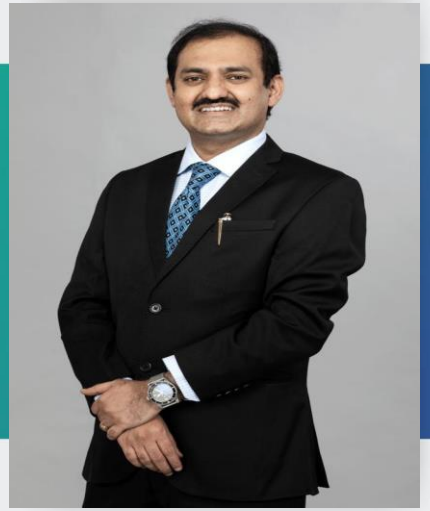
PIPAC In Ovarian Cancer



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DISCLOSURE

- NIL
- Conflict Of Interest NIL

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

BACKGROUND

- Peritoneal Metastasis (PM) is a common occurrence in gynaecological and gastrointestinal cancers and is associated with poor survival.
- The treatment remains a particular challenge
- The traditional palliative treatment options include systemic chemotherapy or palliative surgery
- The efficacy of systemic chemotherapy is poor due to low penetration and relative resistance of peritoneal nodules but with high potential for side effects and complications.
- Combining several agents has increased efficacy but is also associated with considerable risk for side effects with negative impact on Quality of life

** Sugarbaker PH. Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. Cancer Treat Res. 1996;82:79–100. doi: 10.1007/978-1-4613-1247-5_6*

** A. I. Minchinton and I. F. Tannock, "Drug penetration in solid tumours," Nature Reviews Cancer, vol. 6, no. 8, pp. 583–592, 2006.*

BACKGROUND

- Hyperthermic Intraperitoneal Chemotherapy (HIPEC) overcomes some of the pharmacokinetic limitations and improves survival in selected patients

- But at the price of high morbidity and impact on QoL for several months after the procedure

* W. P.Ceelen, L. P˚ahlman, and H.Mahteme, “Pharmacodynamicaspects of intraperitoneal cytotoxic therapy,” Cancer Treatment and Research, vol. 134, pp. 195–214, 2007.
* R. L. DedrickandM. F. Flessner, “Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure,” Journal of the National Cancer Institute, vol. 89, no. 7, pp. 480–487, 1997.
* H. G. Prigerson, Y. Bao, M. A. Shah et al., “Chemotherapy use, performance status, and quality of life at the end of life,” JAMA Oncology, vol. 1, no. 6, pp. 778–784, 2015.

Quality of Life

- PM patients typically present with ascites, abdominal pain, malnutrition, nausea, emesis, and bowel obstruction which significantly compromises the quality of life.

- Quality of Life (QoL) plays an important role in patients with peritoneal metastasis and is constantly deteriorating until death.

- There is an obvious medical need for better therapeutic options in peritoneal metastasis for prolonging survival and preserving QoL by reducing both disease-related symptoms and therapy side-effects

PIPAC

- Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel technique delivering normothermic chemotherapy in the abdominal cavity in the form of aerosol under pressure which has a documented increased absorption by counterbalancing the elevated tumoral interstitial fluid pressure and enhancing drug depth penetration into the peritoneal cavity with minimal systemic absorption ($1/10^{th}$ of systemic dose).

- This concept seems to enhance the effectiveness of intra peritoneal chemotherapy by taking advantage of the physical properties of gas and pressure by generating an artificial pressure gradient and enhancing tissue uptake and distributing drugs homogeneously within the closed and expanded peritoneal cavity

- Preliminary experiences reported in literature has documented the positive outcome of higher local bioavailability Feasibility, safety and tolerance have been described in several studies already and preliminary data on oncological efficacy are encouraging

- PIPAC is currently used in palliative setting in selected patients with trials ongoing.

* Jacquet P, Stuart OA, Chang D, Sugarbaker PH. Effects of intra-abdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. Anticancer Drugs. 1996;7:596–603. doi: 10.1097/00001813-199607000-00016.
* Grass F, Vuagniaux A, Teixeira-Farinha H, Lehmann K, Demartines N, Hubner M. Systematic review of pressurized intraperitoneal aerosol chemotherapy for the treatment of advanced peritoneal carcinomatosis. Br J Surg 2017;104(6):669-78

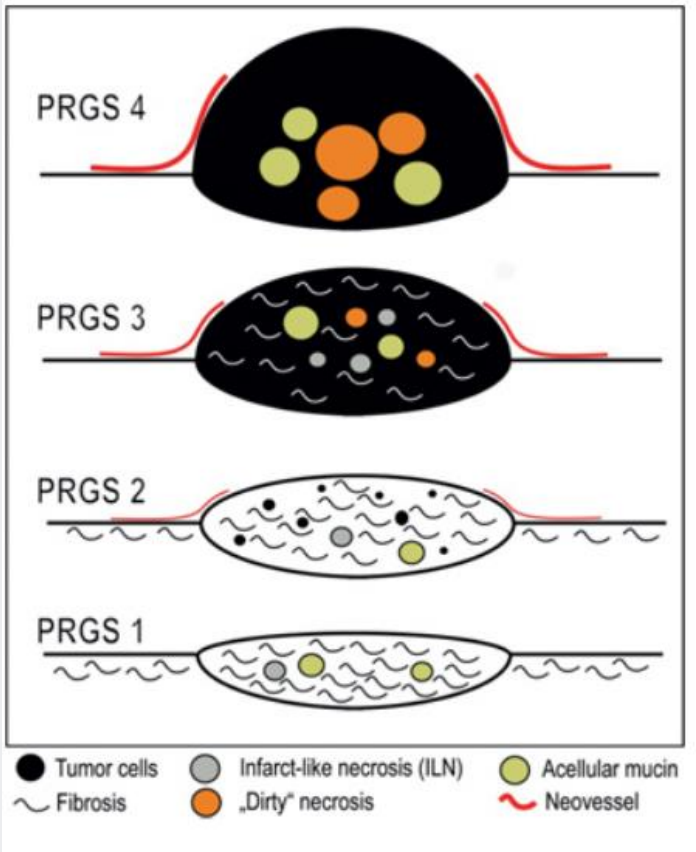
Aims and Objectives

The Aim of the study was to report

- The technical aspects of PIPAC
- The response rates
- Its impact on survival
- Its impact on quality of life

Definition of the peritoneal regression grading score (PRGS).

Grade	Peritoneal regression grading score (PRGS)	
	Tumor cells	**Regression features**
PRGS 1–complete response	No tumor cells	Abundant fibrosis and/or acellular mucin pools and/or infarct-like necrosis
PRGS 2–major response	Regressive changes predominant over tumor cells	Fibrosis and/or acellular mucin pools and/or infarct-like necrosis predominant over tumor cells
PRGS 3–minor response	Predominance of tumor cells	Tumor cells predominant over fibrosis and/or acellular mucin pools and/or infarct-like necrosis
PRGS 4–no response	Solid growth of tumor cells (visible at lowest magnification)	No regressive changes



Wiebke Solass, Christine Sempoux, Sönke Detlefsen, Norman J. Carr, and Frédéric Bibeau, Peritoneal sampling and histological assessment of therapeutic response in peritoneal metastasis: proposal of the Peritoneal Regression Grading Score (PRGS), Pleura Peritoneum. 2016 Jun 1; 1(2): 99–107.

- **This is a interim analysis of a registered trial with registration number REF/2018/08/021223 Registered on Clinical Trials Registry – India (CTRI); www.ctri.nic.in.**

Primary Outcome: Objective Response rate(Recist Criteria 1.1)

Secondary Outcomes : Quality Of life (OLQ C-30) ; Morbidity

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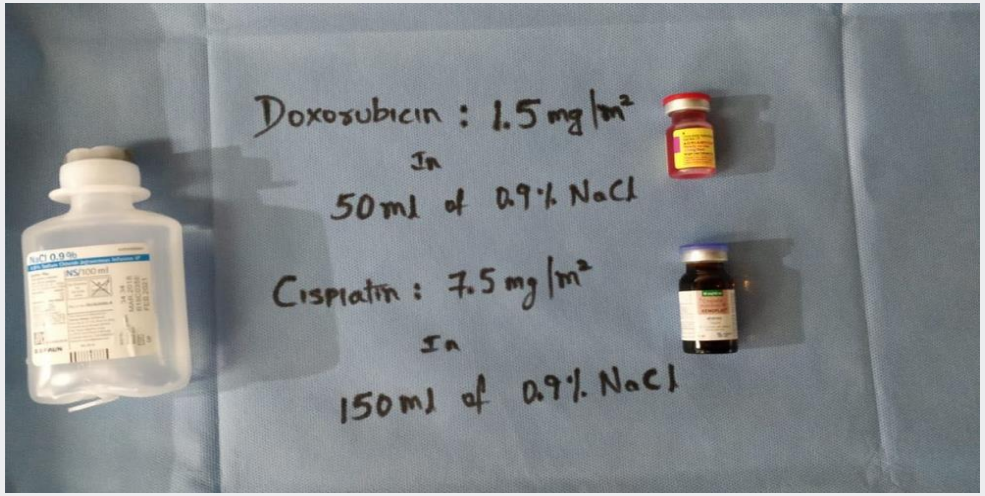
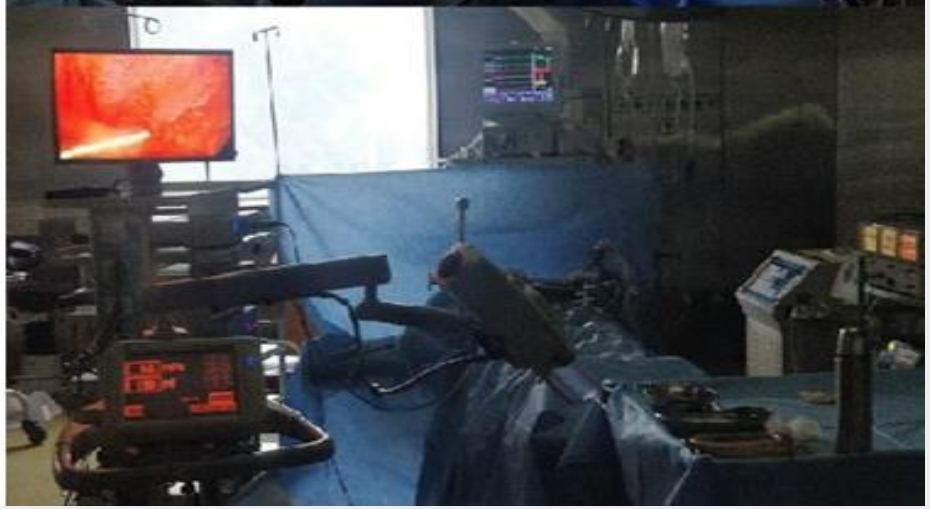
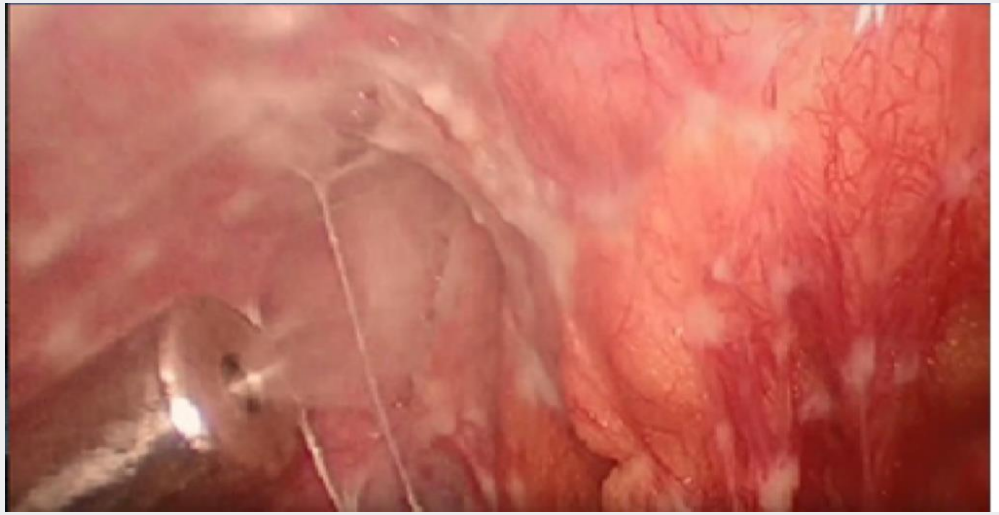


Present Dose

Cisplatin 10.5mg/m2

Doxorubicin 2.1mg/m2





OT setup during PIPAC procedure. All the OT personnel must be out during the procedure. The chemotherapy drug is sprayed intraperitoneally by the Capnopen which is connected to the high-pressure injector

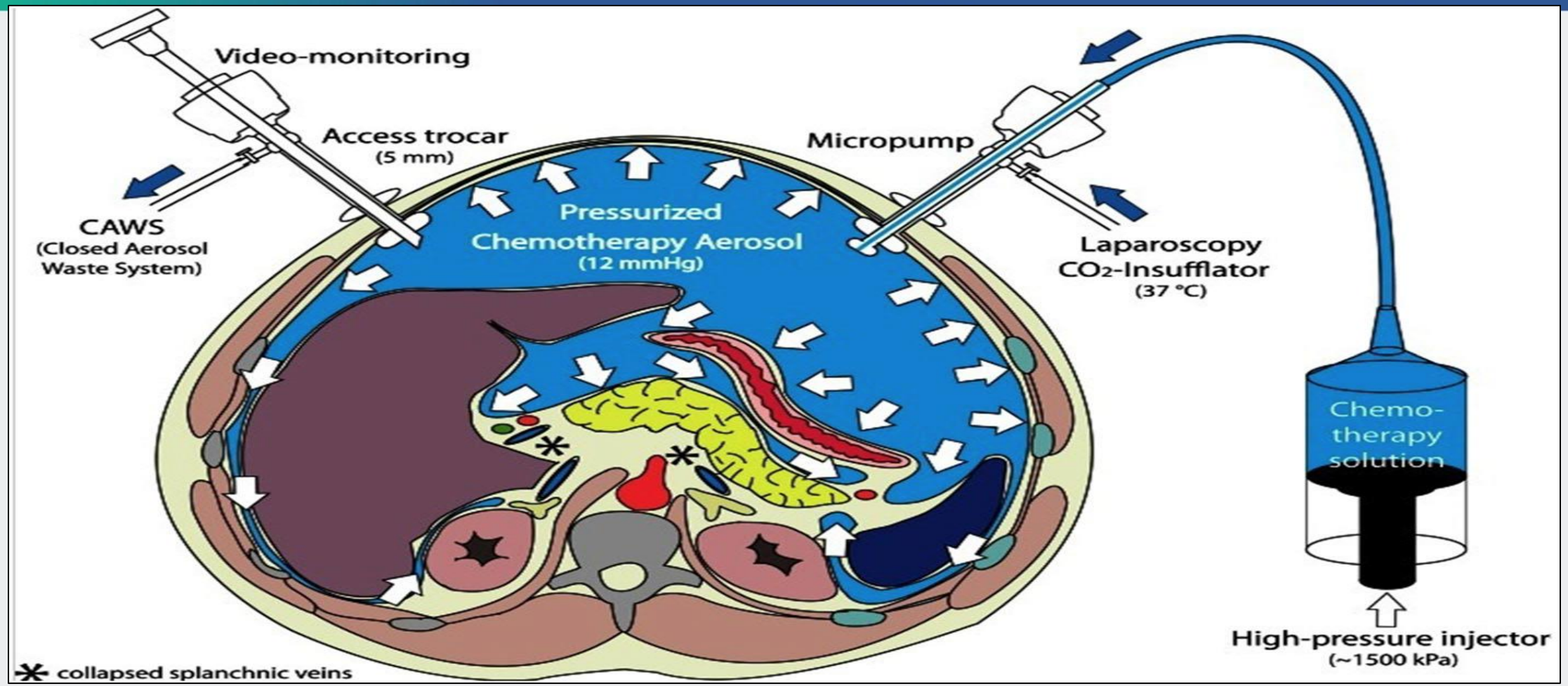
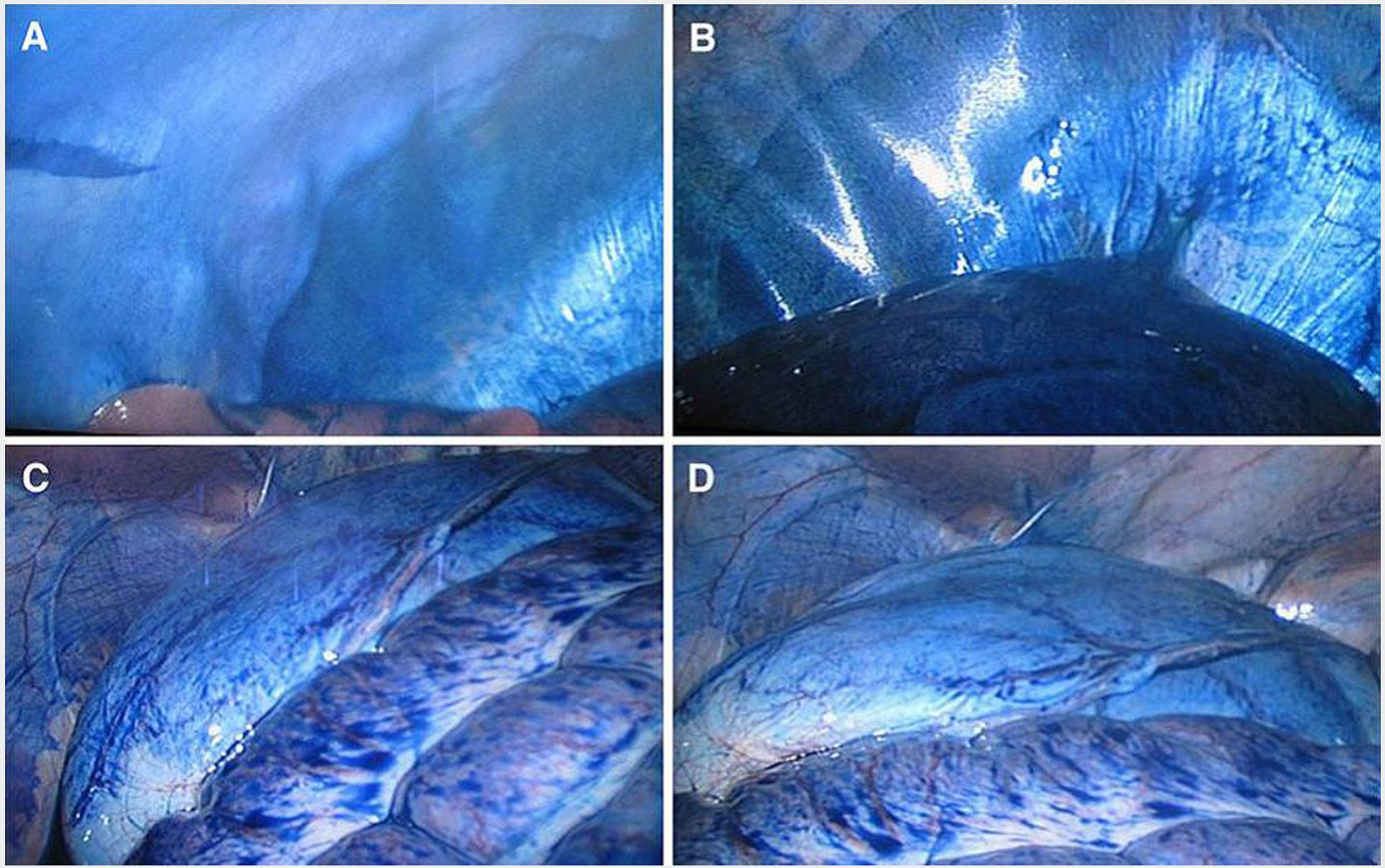


Fig. 2 Diagrammatic representation of pressurized intraperitoneal aerosol chemotherapy. (Reproduced from Ref. 15after permission Prof Marc Reymond)

Distribution of methylene blue by PIPAC



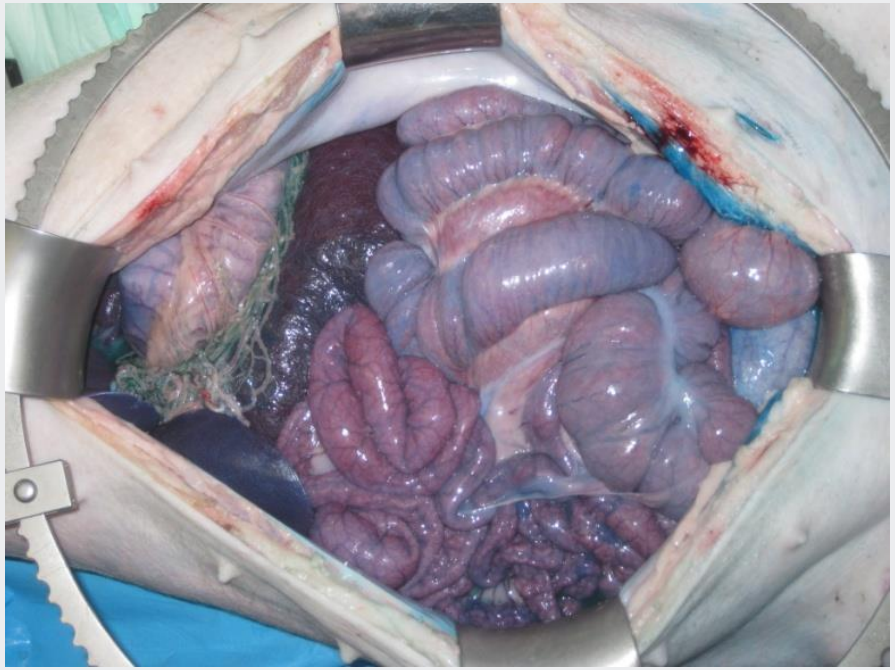
swine model

Methylene blue

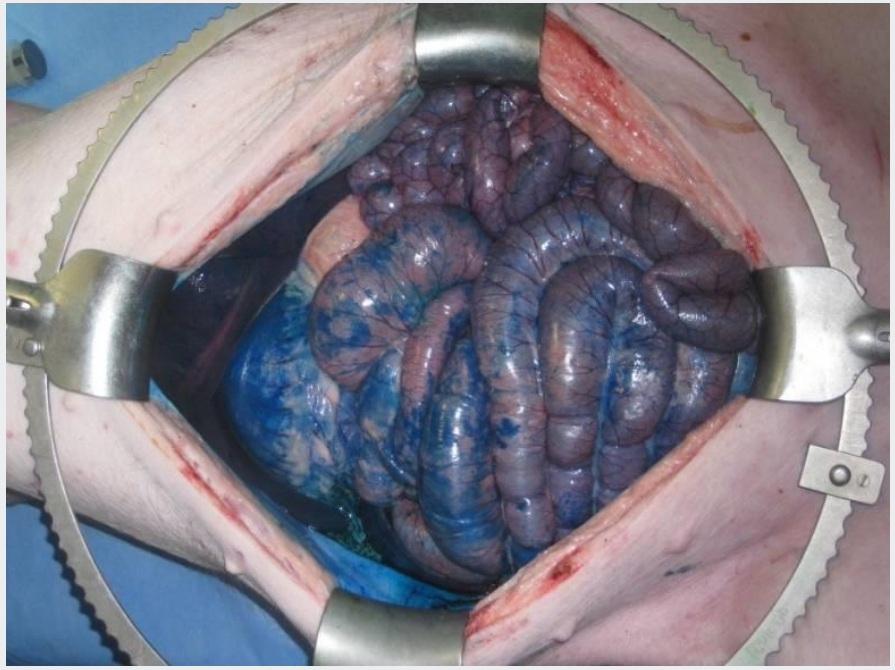
Solass et al Surg Endosc 2013

Distribution: aerosol better than liquid

“HIPEC”



“PIPAC”



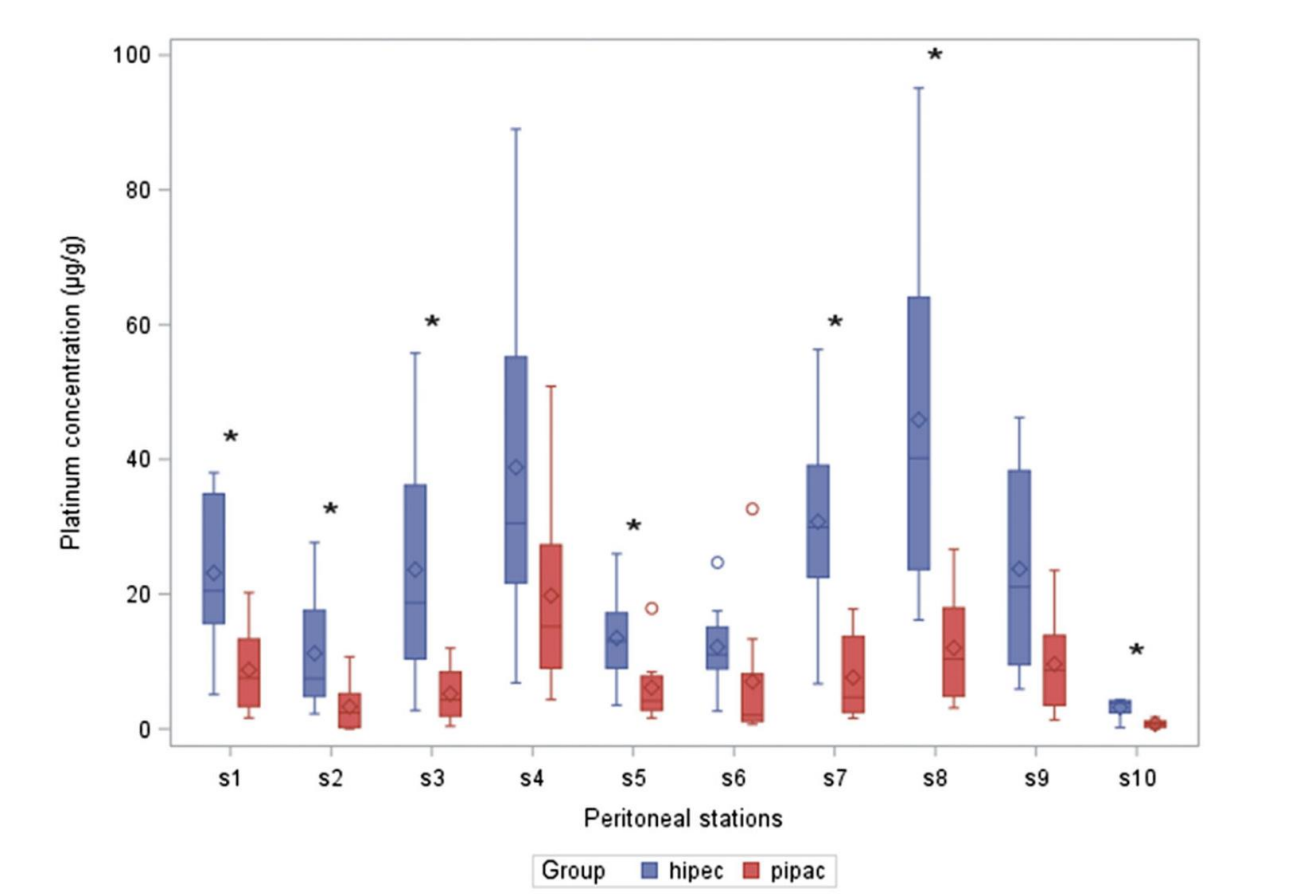
swine model

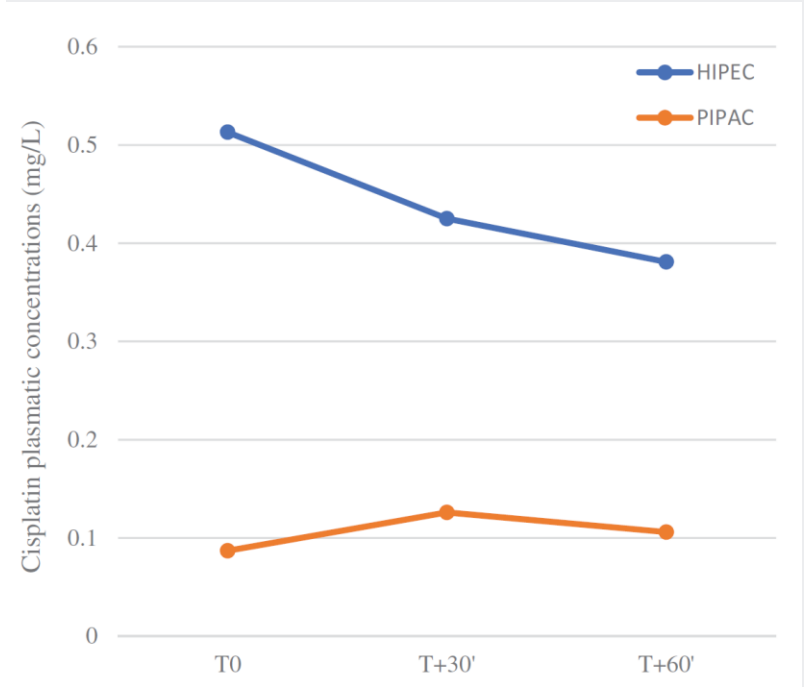
Methylene blue

Solass W et al. Surg Endosc 2013

Pig study: HIPEC versus PIPAC using cisplatin

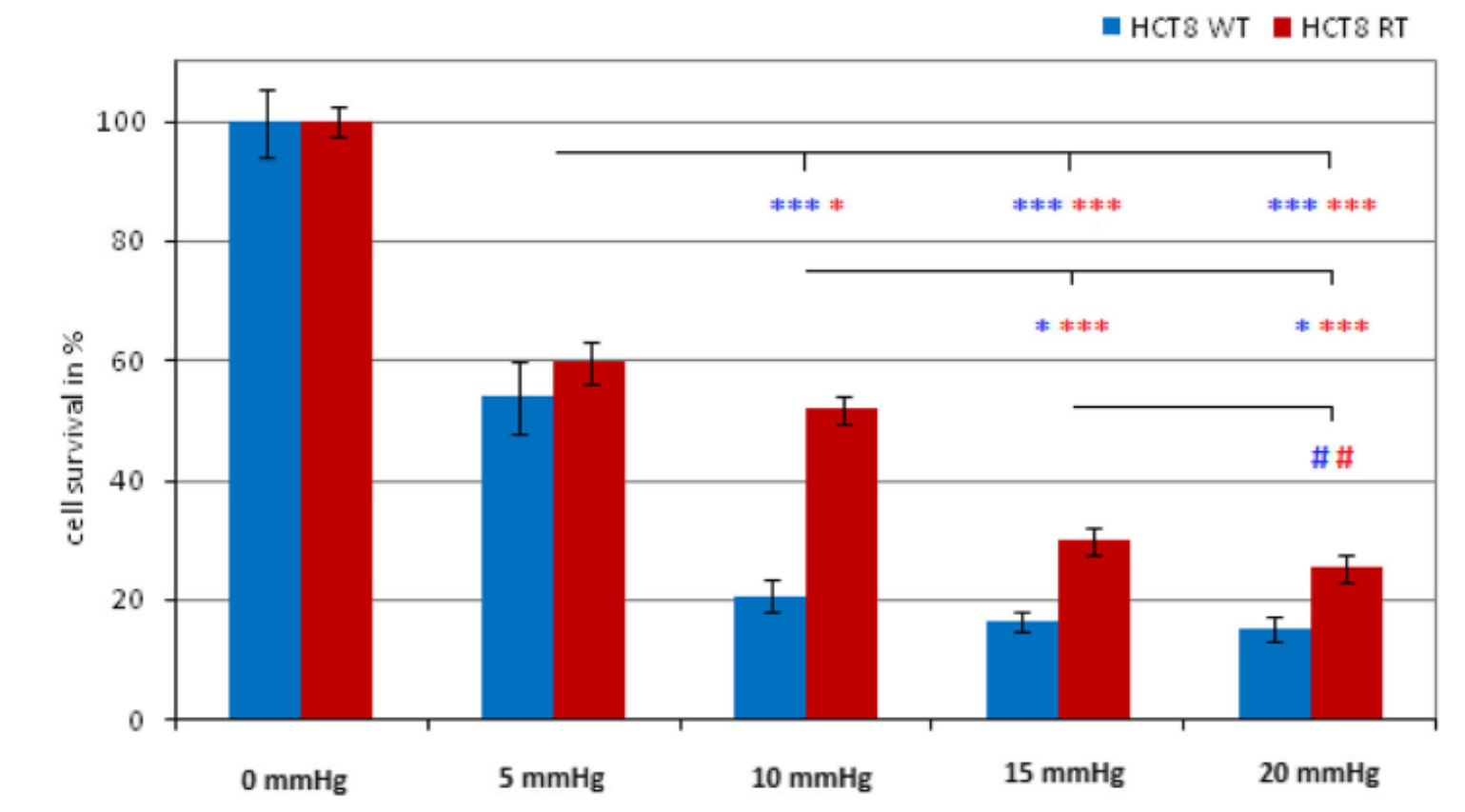
HIPEC: 70 mg/m^2@ 43°C, 60 min
PIPAC: 7.5 mg/m^2,30 min





Davigo Int J Hyperthermia 2020

Higher IP pressure increases cytotoxic effect



In vitro

2 cell lines

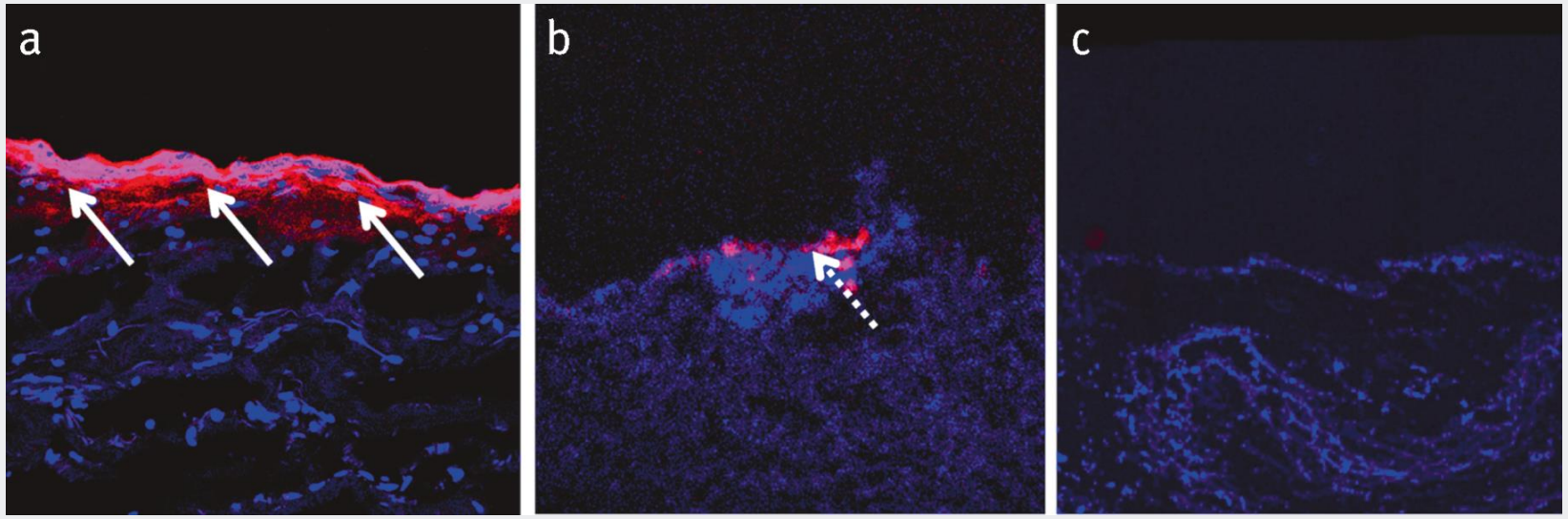
Drug: oxaliplatin

Maximal effect up to 10 mmHg, upwards only marginal effect

Khosrawipour et al, WJSO 2017

Depth of drug penetration

PIPAC | Lavage | Control



Tissue fluorescence down to 1 mm depth

Minimal superficial tissue fluorescence

No tissue fluorescence

Ex vivo: human

Operation specimens

Drug: Cy5-labeled siDNA

Solass W et al. Surg Endoscopy 2012

PIPAC C/D: Phase-I dose escalation study

Methods

ICH-GCP trial (EudraCT 2015-001034-28)
3 steps dose-escalation (3 x 20% = 60%)
Monitor pre-defined CTCAE ¾
CTCAE 4.0; SUSARs, DSMB

Results

MTD was not reached
No SAE CTCAE 3/4/5, no SUSAR
No new safety signals; no systemic tox

Evidence-based dose:
DOX 2.1 mg/m², CIS 10.5 mg/m²
body surface

→ Basis for pivotal phase-III trial (Fixed drug combination in rPROC)

Tempfer CB et al, Gynec Oncol 2018

WORKING DRAFT: therapy of isolated PM of ovarian origin

Legend
HLE high level of evidence
Randomized trial planned

Upfront sitution	Systemic chemotherapy HLE	Always
	Cytoreductive surgery HIPEC (off-label) HLE	Resectable disease Good patient fitness
	PIPAC C/D (off-label) Neoadjuvant Setting[1] Combined IVand PIPAC Therapy[2]	Unresectable disease, under study conditions
Recurrence situation	Systemic chemotherapy HLE	Always (2nd line)
	PIPAC C/D (off-label)	Platin-resistant disease ≥ 3rd line situation Progress under chemotherapy Chemotherapy intolerance Therapy-refractory ascites Pleural effusion: combine PITAC
	Cytoreductive surgery HIPEC (off-label)	Limited disease DESKTOP II criteria

Legend
HLE high level of evidence
Randomized trial ongoing

PIPAC: Indications:

- PIPAC is a promising palliative therapy in isolated PM when no evidence-based treatment is available.
- Possible indications:
  - PIPAC with cisplatin/ doxorubicin (PIPAC C/D):
    - ≥ 3rd line situation in ovarian cancer
    - ≥ 2nd line situation in gastric cancer
    - ≥ 2nd line situation in HBP cancer
    - recurrence situation in malignant peritoneal mesothelioma
    - intolerance/ side-effects of systemic chemotherapy
    - Deterioration of QOL on chemotherapy
    - ascites control in the platin-resistant situation
  - PIPAC with oxaliplatin (PIPAC OX):
    - salvage situation in colorectal cancer & other Peritoneal surface malignancy
- First randomized trials evaluating the effect of PIPAC C/D in isolated PM have been initiated.

1.Alyami M et al., EJSO 2019
2.Ploug et al. BMC Cancer (2020.
3.Girshally et al. WJSO (2016)
4.Alyami , Hubner et al Lancet oncol 2019

PIPAC: General contraindications

- Absolute contraindications:
  - Short life expectancy <3 months[4]
  - Bowel obstruction, total parenteral nutrition (TPN), gastric drainage
  - Decompensated ascites

Relative contraindications:

- Extraperitoneal metastasis (Exception of Isolated Malignant Pleural Effusion)
- ECOG > 2
- Simultaneous intestinal anastomosis and PIPAC
- Portal vein thrombosis
- (Previous CRS and HIPEC) [1]
- (Previous anaphylatic reaction to the drug used) [2]
- Severe Renal and Hepatic Impairment
- Myelosuppression
- Severe Myocardial Insufficiency, MI and Arryhthmias

[1] good access chance in the absence of peritonectomy; [2] if possible change the substance

PIPAC: evidence available

	Registry	Phase 1	Phase 2	Randomized trial
Ovarian cancer	NCT03210298	NCT02475772	NCT02475772	PIPAC-OV3 (1)
			NCT02735928	**REF/2018/08/021223***
			NCT03304210	**REF/2018/08/021225#**

1. Bakrin N et al, Pleura Peritoneum 2018; 2. Eveno C et al, Pleura Peritoneum 2018; 3. Götze et al, Pleura Peritoneum 2018;
4. Rau B et al, under review; 5. Dumont F et al, under review; 6. Sgarbura O et al, approved 2019.

* REF/2018/08/021225 - S.P. Somashekhar, K.R. Ashwin, Amit Rauthan, Kumar C. Rohit., Pleura and Peritoneum 2018; 20180110

REF/2018/08/021223- S. P. Somashekhar, K. R. Ashwin,, Pleura and Peritoneum 2019; 20180111

PIPAC: promises kept?

- ✓ Improved **distribution** within the peritoneal cavity
- ✓ Improved **penetration** of drugs into tumor / normal tissue
- ✓ Reduced **escape** into systemic circulation
- ✓ Preserved **biological activity** at reduced dose (10%)

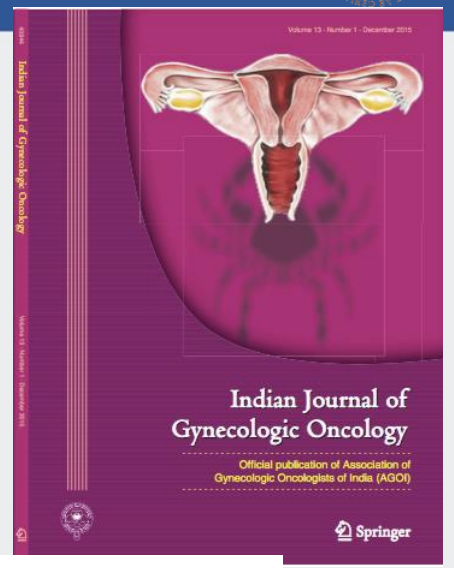
BACKGROUND

Springer

the language of science

DOI 10.1007/s12262-013-1003-4

ORIGINAL ARTICLE



Indian Journal of Gynecologic Oncology (2018)16:25
https://doi.org/10.1007/s40944-018-0193-x

ORIGINAL ARTICLE

CrossMark

First Indian Study on Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) Procedure for Advanced Peritoneal Carcinomatosis Secondary to Epithelial Ovarian Cancer

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Received: 25 March 2018 / Accepted: 27 March 2018

BACKGROUND

After insufflation of a 12 mmHg pneumoperitoneum (with open access or Veress needle), two 5-mm trocars were inserted into the abdominal wall. Ascites was aspirated and sent for cytology testing. Extent of peritoneal carcinomatosis was determined based on PCI score. A centimetric local peritonectomy was performed for peritoneal biopsies in all cases to improve accuracy of anatomopathology. The generation of aerosol requires a disposable 9-mm microinjector (Capnopen®, Capnomed, Villingendorf, Germany) which was connected to an intravenous high-pressure injector (Angiomat®Illumena Injector®, LiebelFlarsheim, USA) and inserted into the abdomen through a 12-mm access port.

Safety measures were taken to prevent any exposure of drugs to the operating team [17]. The procedure was performed in an operating room equipped with laminar air flow. Tightness of the abdomen was documented via a zero flow of CO_2 to prevent OT contamination. The chemotherapy injection was remote-controlled, and nobody remained in the operating room during the application. The laparoscopic and anaesthesia monitors are oriented towards the OT door window to facilitate monitoring by the doctors from outside (Fig. 1).

The patients were treated with pressurized aerosol of cisplatin 7.5 mg/m^2 in 150 ml NaCl 0.9% solution followed by doxorubicin 1.5 mg/m^2 in 50 ml NaCl 0.9% solution [8]. Aerosol flow rate was 30 ml/min, and maximal upstream pressure was 200 psi as per recommendation. The therapeutic capnoperitoneum was then maintained for 30 min. Then, the chemotherapy aerosol was released safely via a closed aerosol waste system into the air waste systems of the hospital or by a Buffalo Filter. Trocars were retracted, and laparoscopy was ended. No drainage of the abdomen was placed. Patients were discharged the following day if there were no adverse effects [17] (Fig. 2).

Data of all patients who underwent PIPAC procedure were included in a prospectively maintained database. Safety, tolerability, and postoperative complications were assessed by physical examination results and laboratory assessments, and adverse events were recorded according to CTCAE criteria.

The four-tier Peritoneal Regression Grading Score (PRGS) was used for assessment of histological response. It allows to maximize staging accuracy in treatment after PIPAC and facilitates comparison by using an uniform terminology and staging system [8]. The proposed scale ranges from 1 (complete response) to 4 (no response) and is based on typical histological features of regression including fibrotic changes, necrosis, and presence of acellular mucin deposits [18].

Results

A total of 9 successful PIPAC procedures were carried out in 3 patients with PC secondary to epithelial ovarian cancer. Two patients had ECOG performance of 2, and the last had performance status of 1. All three patients were symptomatic with abdominal pain and/or sub-acute

Fig. 1 OT setup during PIPAC procedure. All the OT personnel must be out during the procedure. The chemotherapy drug is sprayed intraperitoneally by the Capnopen which is connected to the high-pressure injector

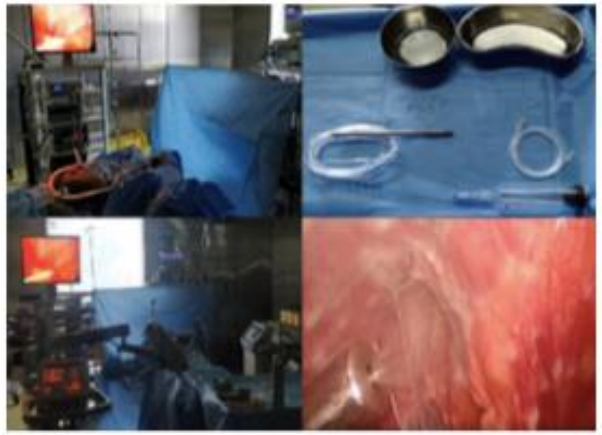

Table 2 Operative findings and perioperative outcomes

Patient	Previous chemotherapy	PCI before PIPAC	Ascites	PIPAC procedures	Chemotherapy used	Operative time (min)	Hospital stay (days)	Adverse effects (CTCAE 1–4)	Peritoneal Regression Grading Score [18]
1	2 lines	17	Absent	3	Cisplatin + Doxorubicin	100	1	Nil	3
2	1 line	23	Present	3	Cisplatin + Doxorubicin	120	1	Nil	2
3	2 lines	19	Present	3	Cisplatin + Doxorubicin	110	3	Pain (2)	2

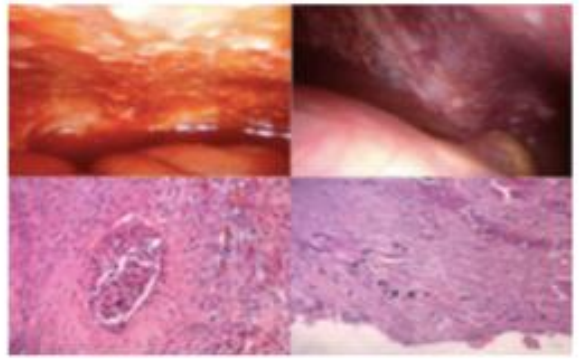

Fig. 2 Intraoperative laparoscopy findings before procedure (diagnostic laparoscopy) and during pressurized intraperitoneal aerosol chemotherapy (PIPAC) (left upper panel) and post-PIPAC changes (right upper panel) confirming major response after 3 settings. Before PIPAC, histology showed peritoneal infiltrativity a poorly differentiated ovarian adenocarcinoma (left lower panel). Follow-up biopsies showed sustained regressive tumour changes, fibrosis, and acute and chronic inflammation (right lower panel)

PIPAC induced high response rates with minimal adverse events and demonstrated its ability to induce the regression of chemoresistant peritoneal metastases [9]. The pharmacological superiority of this drug delivery system over systemic delivery and conventional intraperitoneal chemotherapy for treating peritoneal metastasis is already clear [13–15], inducing high response rates with low adverse events [8, 19]. Owing to the limited penetration of chemotherapy into tumour nodules, intraperitoneal chemotherapy may be best suited for small volume disease [20].

In our series local toxicity of PIPAC was acceptable even with repeated delivery. No patient developed bowel perforation, and no severe gastrointestinal symptoms were registered. These results are in accordance with those reported in similar studies [16]. In accordance with previous observations [8, 16, 19], no significant renal toxicity was documented, probably due to 90% dose reduction as compared to systemic chemotherapy. In patients presenting with worsening quality of life because of peritoneal disease diffusion, the combination of the two treatments enables rapid symptom palliation with PIPAC. In our patients, symptomatic relief and ascites resolution were seen in all the patients. Response was very encouraging with two patients having partial response and one with stable disease.

The safety guidelines have been well established, and following this set of protocol ensures that PIPAC is safe and easily reproducible. Selection is important as patients with multiple abdominal surgeries, intestinal obstruction and poor performance status are unlikely to tolerate or derive any benefit.

PIPAC may not only be considered a palliative treatment, but in combination with systemic chemotherapy, with appropriate drug doses, it could possibly become part of the standard therapeutic course of peritoneal carcinomatosis.

Conclusion

Patients with advanced peritoneal carcinomatosis who are not candidates for curative resection have option of palliative systemic chemotherapy.

Original Article

Pressurized intraperitoneal aerosol chemotherapy procedure for nonresectable peritoneal carcinomatosis: First Indian study

S. P. Somashekhar, K. R. Ashwin, C. Rohit Kumar, Amit Rauthan[1], Sushmita H. Rakshit[2]

Abstract

Background: Peritoneal carcinomatosis (PC) is a common evolution of abdominal cancers and is associated with poor prognosis. A few selected patients have option of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy but majority who are not eligible for curative approach can undergo pressurized intraperitoneal aerosol chemotherapy (PIPAC). It is an emerging field of research with major therapeutic potential. It is a safe and innovative approach, which enhances the effect of chemotherapy without major toxicity. **Methods:** Between June 2017 and December 2017, 21 PIPAC applications in seven patients with standard chemotherapy regimen every 6 weeks at 37°C and 12 mmHg for 30 min was performed. The patients' demographics, perioperative findings, adverse events, and outcomes were prospectively recorded. **Results:** Twenty-one PIPAC administrations were performed in 7 patients with PC from various pathologies. The median hospital stay was 1 day. All the patients had symptomatic relief with complete resolution of ascites. There was no major perioperative complications. CTCAE Grades 1 and 2 were observed in three patients, for abdominal pain and nausea. Renal and hepatic functions were not impaired. Of the seven patients, one patient had complete histological remission, three patients had partial response, one had stable disease and one patient had no response with clinical progression. **Conclusion:** Our results show the feasibility and safety of PIPAC in Indian patients. The procedure has low morbidity with no mortality with the short learning curve. It can be easily adapted for Indian patients with diffuse PC as a palliative option apart from systemic chemotherapy.

Key words: Chemotherapy, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, Indian patients, intraperitoneal, peritoneal carcinomatosis, pressurized intraperitoneal aerosol chemotherapy

Introduction

Peritoneal carcinomatosis (PC) was regarded as a terminal disease with traditional palliative treatment options of systemic chemotherapy or palliative surgery having a poor outcome.[1-3]

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel technique delivering normothermic chemotherapy into the abdominal cavity as an aerosol under pressure which has a documented positive outcome by counterbalancing the elevated tumoral interstitial fluid pressure[4,5] and enhancing drug depth penetration with superior distribution. PIPAC is currently used for palliative setting in selected patients with trials ongoing.

Methods

PIPAC program for patients diagnosed with advanced PC was introduced at Manipal Comprehensive Cancer Center from June 2017. Training was provided to educate the healthcare providers about the technical and safety aspects of the procedure. All patients with histologically verified peritoneal metastasis secondary to mesothelioma, gastric/colorectal/ovarian cancer were presented in the interdisciplinary tumor board, and the indication for therapy was decided on a case-by-case basis. PIPAC was offered where option of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy was not possible because of poor general condition (Eastern Cooperative Oncology Group [ECOG] >2), advanced peripheral component interconnect (PCI), and/or unresectability because of diffuse small bowel involvement. Patients were eligible if they had blood and electrolyte counts, liver, renal, and cardiopulmonary function parameters within 10% of the normal range. All patients were counseled and their informed consent obtained. The Institutional review board and Ethics Committee approval was obtained. We report the technical aspects, our observations, and outcomes with PIPAC procedure in Indian patients.

Technique of pressurized intraperitoneal aerosol chemotherapy

All operations were performed under general anesthesia; a standard operating protocol was followed with emphasis on handling and exposure to chemotherapy. A antibiotic prophylaxis with a single dose of cefuroxime 1.5 g intravenous (IV) was administered 30 min before surgery. After insufflation of a 12 mmHg pneumoperitoneum (with open access or Veres needle), two 5 mm trocars were inserted into the abdominal wall. Ascites was aspirated and sent for cytology testing. Extent of PC was determined based on PCI score. A centimetric local peritonectomy was performed for peritoneal biopsies in all cases to improve accuracy of anatomopathology. The intraperitoneal chemotherapy was given as per standard doses.[6-8] The generation of aerosol requires a disposable 9-mm microinjector (Capnopen®, Capnomed, Villingendorf, Germany) which was connected to an IV high-pressure injector (Angiomat Illumena Injector®, Liebel Flarsheim, USA) and inserted into the abdomen through a 12 mm access port. Safety measures were taken to prevent any exposure of drugs to the operating team. The procedure was performed in an operating room equipped with laminar airflow. Tightness of the abdomen was documented through a zero flow of CO_2 to prevent operation theater (OT) contamination. The chemotherapy injection was remote-controlled and nobody remained in the operating room during the application. The laparoscopic and anesthesia monitors are oriented toward the OT door window to facilitate monitoring by the doctors from outside [Figure 1].

Aerosol flow rate was 30 ml/min, and maximal upstream pressure was 200 psi as per recommendation. The therapeutic

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Correspondence to: Dr. S.P. Somashekhar,
E-mail: [illegible]

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effects [Figure 2].

Results

A total of 21 successful PIPAC procedures were carried out in seven patients with PC. The primary tumor site was one colorectal cancer (14.2%), two epithelial ovarian cancer (28.7%), two mesotheliomas (28.7%), one primary peritoneal cancer (PPC) (14.2%) and one gastric cancer (14.2%); There were 5 males and three females. Two patients had ECOG performance of 2, and the rest had performance status of 0–1. Three patients were symptomatic with abdominal pain and/or subacute obstruction. All patients were pretreated with mean number of 1.3 lines per patient (range 1–3).

Patient's characteristics and preoperative details are summarized in Table 1. In two patients, entry to the abdominal cavity was difficulty due to adhesions and had to undergo minimal adhesiolysis for port access. Mean operating time was 98.6 min (80–120). No intraoperative complications or allergic reactions were noted. The mean hospital stay was 1.85 (range 1–3), and median stay was 1 day. Mean PCI was 17.1 (range 11–23). PIPAC was well tolerated with acute and cumulative local toxicities of PIPAC under control and no severe side effects observed. Adverse events were noted and graded as per CTCAE. Abdominal pain CTCAE ≤2 was noted in 3/7 patients (28.7%). None of the patients needed reoperation. There was no postoperative mortality. The operative findings and perioperative outcomes are described in Table 2.

All the patients completed three cycles of PIPAC and histological response assessment was performed by an oncopathologist by the Peritoneal Regression Grading Score (PRGS). The four-tier PRGS is defined as Grade 1:

Table 1: Patients' characteristics and preoperative details

Variable	Value
Number of patients	7
Sex (male/female)	4:3
Age, years (median)	43
Symptomatic: Asymptomatic	3:4
Primary	
Ovary	2
PPPC	1
Mesothelioma	2
Colorectal	1
Gastric	1
PCI (mean)	17.4
ECOG (median)	1
Previous surgery (%)	3 (42.8)
Previous systemic chemotherapy	
≥2 lines	2
1 line	5

PCI=Peripheral component interconnect, ECOG=Eastern Cooperative Oncology Group, PPPC=Primary papillary peritoneal cancer

is more pronounced after second PIPAC [Chart 1]. In one patient of mesothelioma, there was complete histological remission; three patients had partial response, one had stable disease, and one patient had no response with clinical progression [Figure 3].

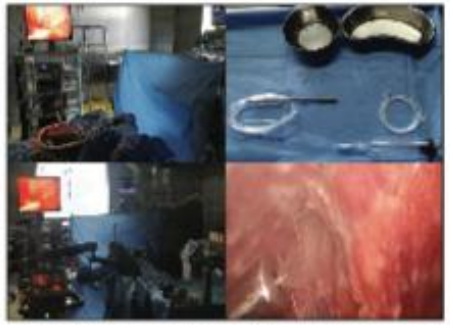


Figure 1: Operation theater setup during pressurized intraperitoneal aerosol chemotherapy procedure. All the operation theater personnel must be out during the procedure. The chemotherapy drug is sprayed intraperitoneally by the Capnopen which is connected to the high-pressure injector

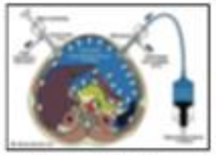


Figure 2: Diagrammatic representation of pressurized intraperitoneal aerosol chemotherapy (reproduced from reference 15 after permission Prof Marc Reymond)

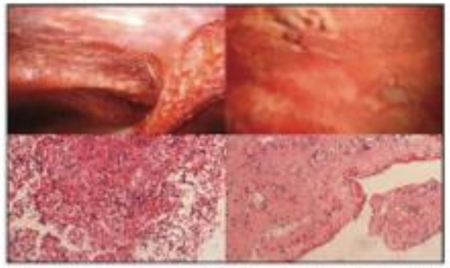


Figure 3: Macroscopic and histological response after pressurized intraperitoneal aerosol chemotherapy. A Fifty-two-year-old male patient with diffuse carcinomatosis from mesothelioma on laparoscopy and microscopy showed papillary fronds of mesothelial proliferation. After 3rd pressurized intraperitoneal aerosol chemotherapy, there was disappearance of peritoneal nodules, and microscopy confirmed complete regression with the pathological complete response

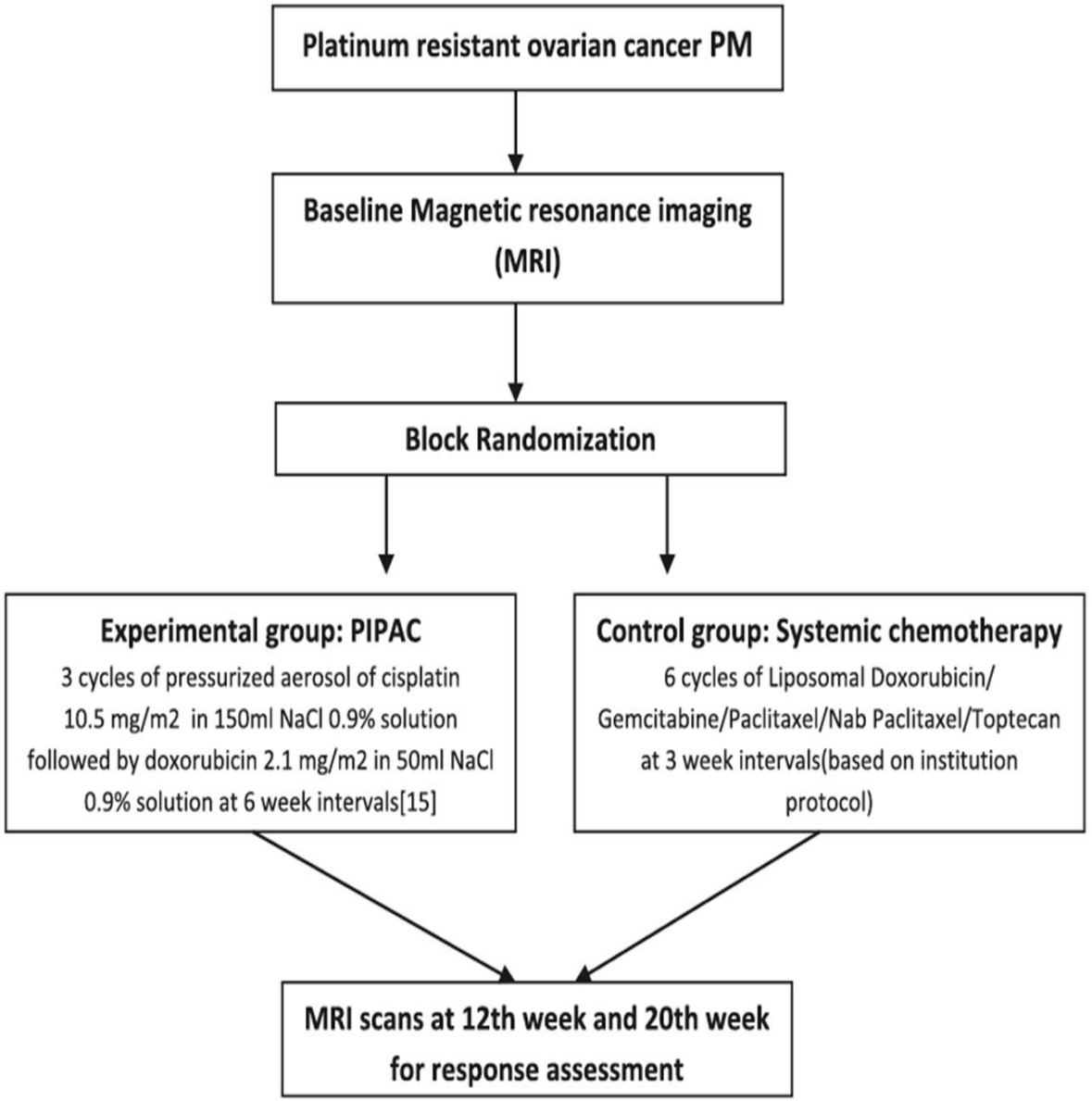
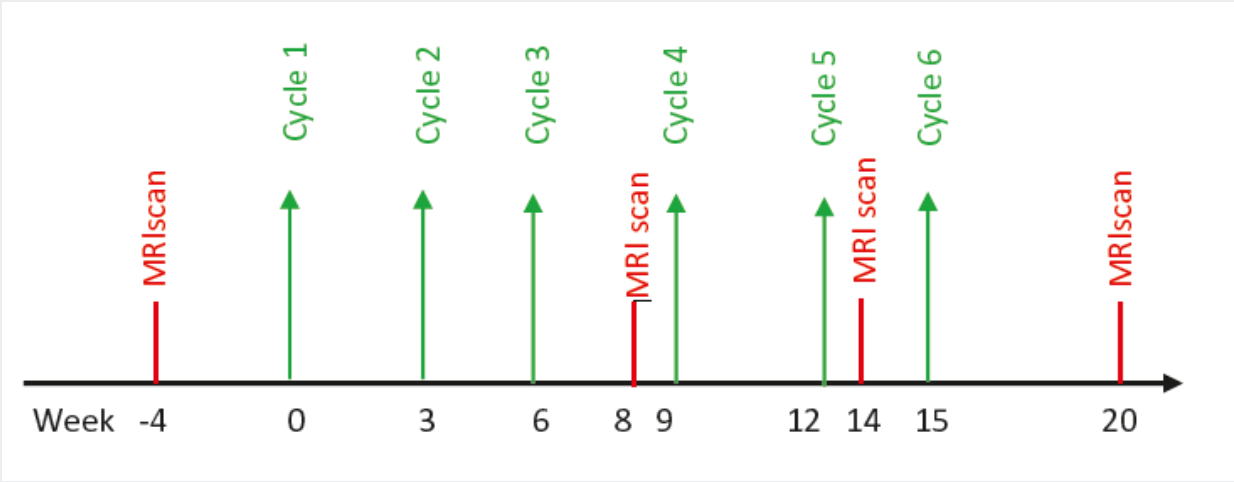
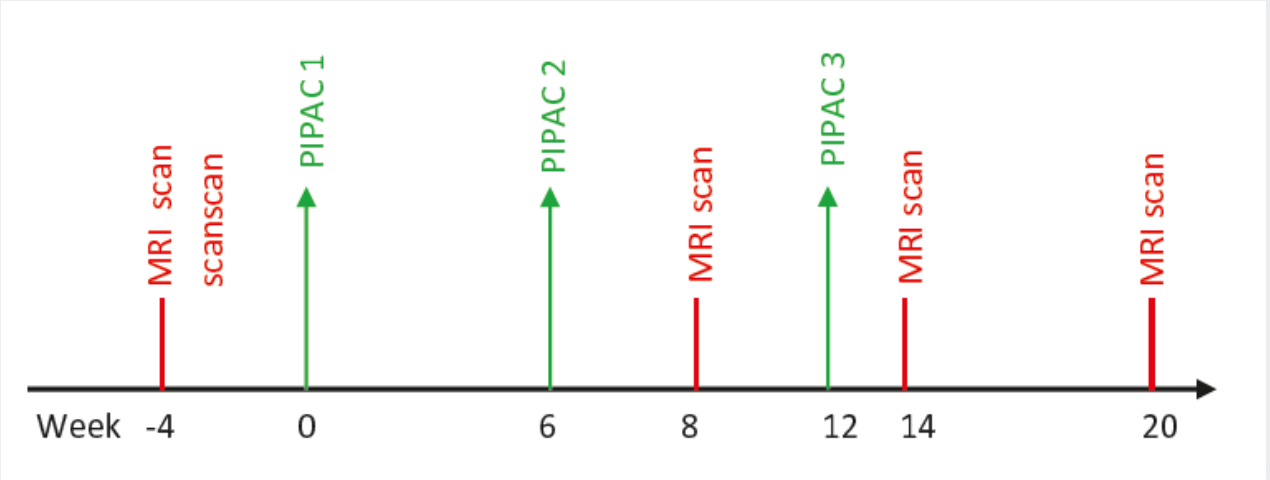


Figure 1: Experimental and control group including time point and technique of randomization.

ALGORITH FOR IV CHEMOTHERAPHY



ALGORITH FOR PIPAC

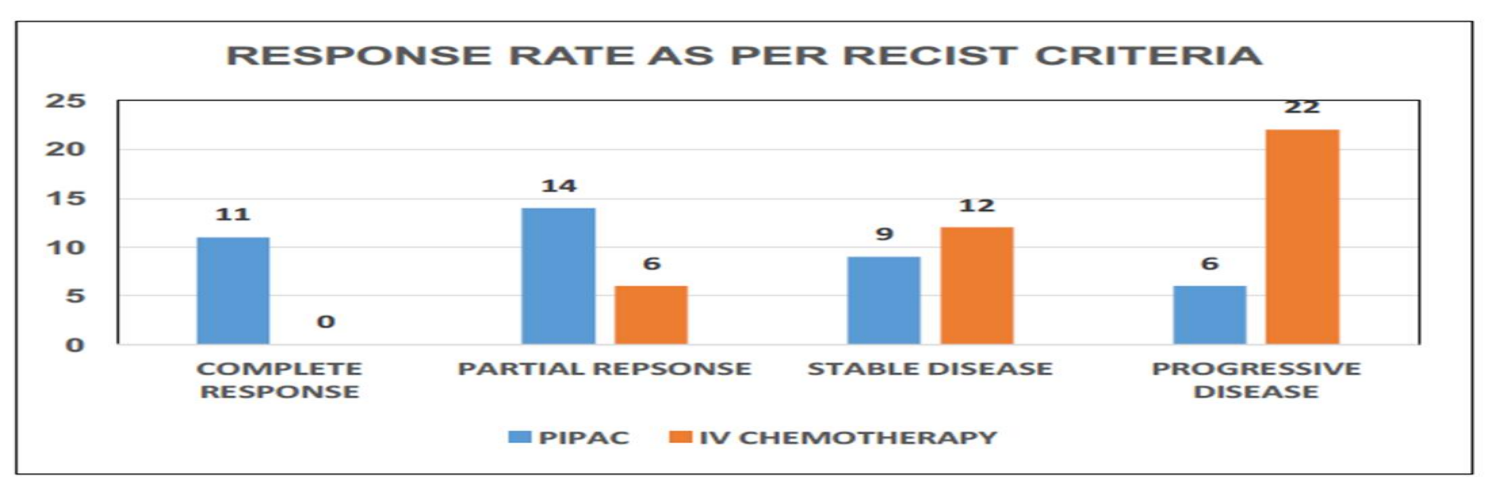


RESULTS

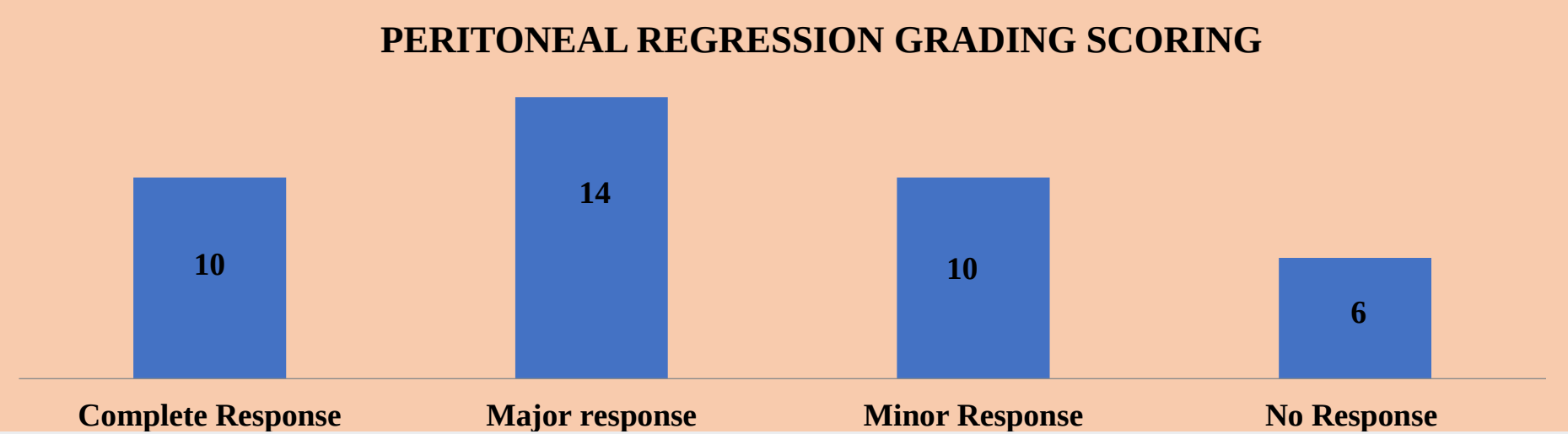
	PIPAC N=40	IV Chemo (N=40)	P – Value
Age (years)	55.5 ± 9.4	54.3± 6.7	0.128
ECOG 0 1 2	 08 20 12	 08 24 08	 0.423
Previous Surgery 1 2	 21 19	 22 18	 0.231
Systemic Chemotherapy 2nd line >2nd line	 24 16	 21 19	 0.746
Serum CA 125 IU/ml	220± 15.4	235± 12.7	0.230
PCI	23.5± 8.7	18.4± 7.5	0.460
No of cycles	3 PIPAC - 30 2 PIPAC - 05 1 PIPAC - 05	6 CYCLES - 25 4 CYCLES - 10 3 CYCLES - 05	___

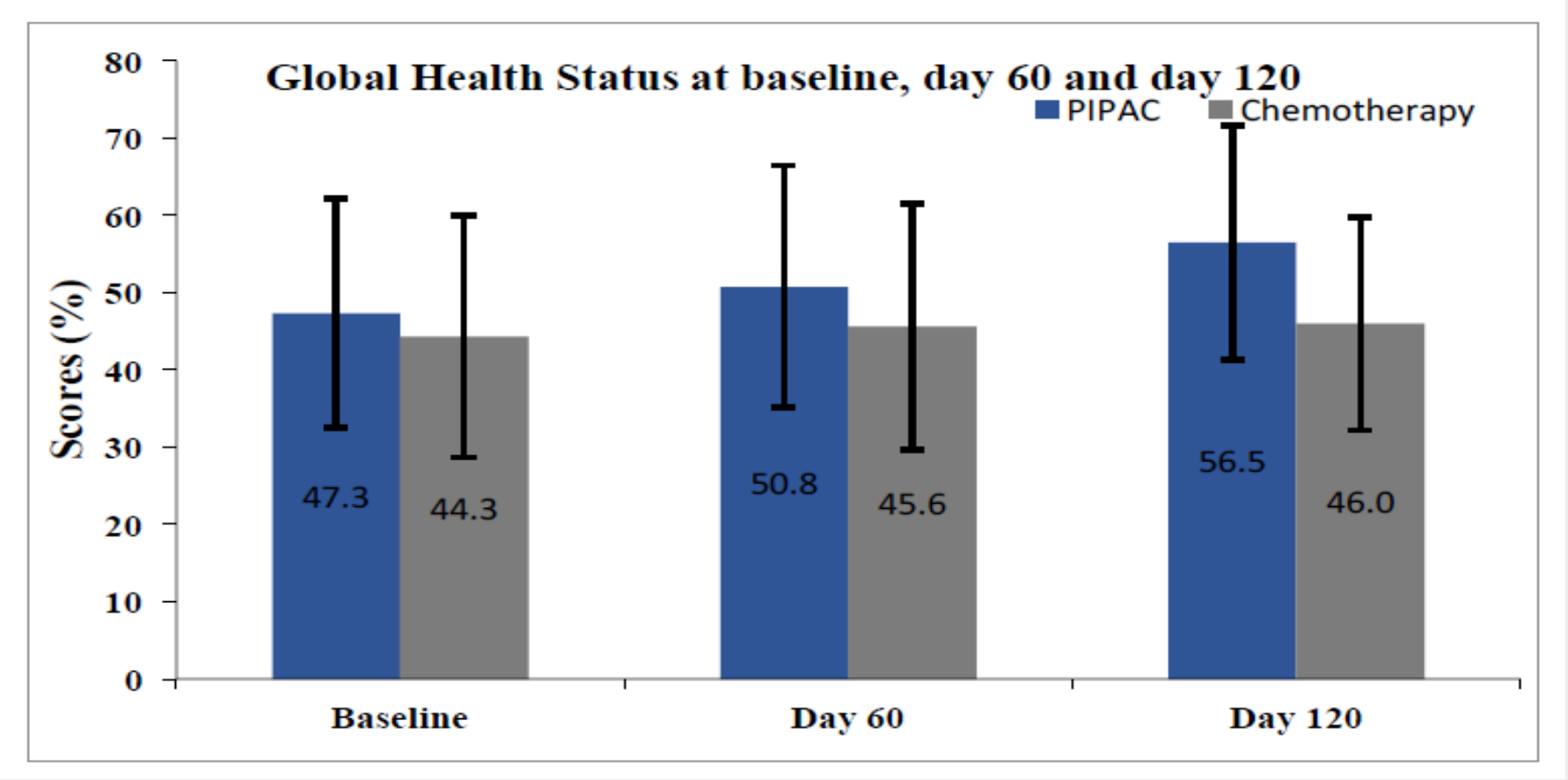
RESULTS

Complications	(G1- G2)		(G3)	
	PIPAC	IV	PIPAC	IV
Nausea/Vomiting	9	9	0	3
Pain	9	13	0	2
SSI	3	0	0	0
Cytopenia	7	6	1(G3)	5
Mucositis	0	12	0	5
Neuropathy	0	9	0	2
Intra-operative Bleeding	0	0	1 (G3)	0
Bowel Perforation	0	0	2(G3)	0
Port Site Metastasis	0	0	1(G3)	0


RESPONSE RATE AS PER RECIST CRITERIA
25
20
15
10
5
0
11
0
14
6
9
12
6
22
COMPLETE RESPONSE
PARTIAL REPSONSE
STABLE DISEASE
PROGRESSIVE DISEASE
PIPAC
IV CHEMOTHERAPY

(P <0.05)


PERITONEAL REGRESSION GRADING SCORING
10
14
10
6
Complete Response
Major response
Minor Response
No Response


Global Health Status at baseline, day 60 and day 120
PIPAC
Chemotherapy
Scores (%)
80
70
60
50
40
30
20
10
0
47.3
44.3
50.8
45.6
56.5
46.0
Baseline
Day 60
Day 120

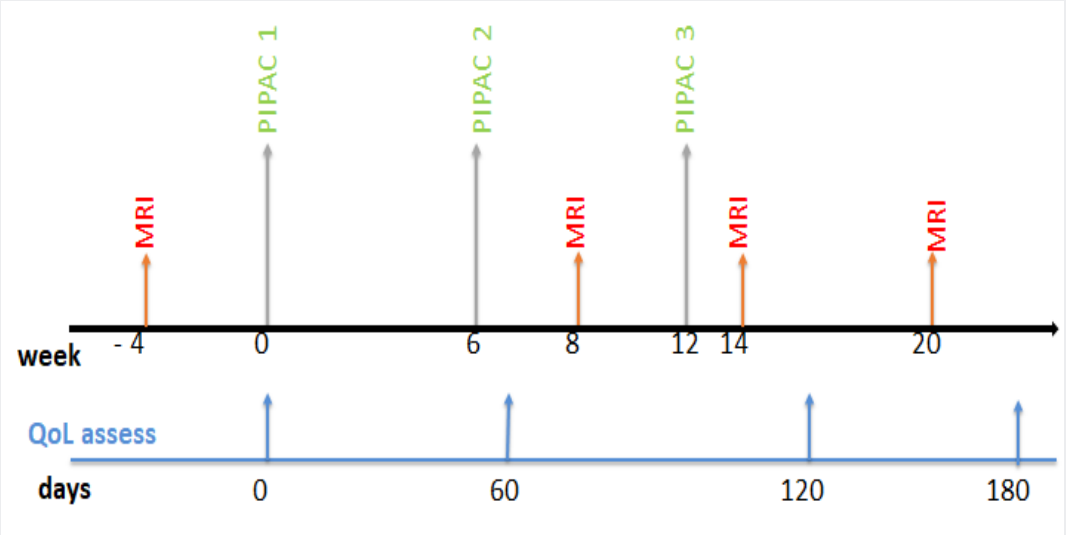
(P <0.05)

COMPARED TO IV CHEMOTHERAPHY PIPAC HAS BETTER RESPONSE RATE AND IMPROVES QUALITY OF LIFE WITH MINIMAL MORBIDITY

First Report Of Clinical Outcomes With Escalated Doses Of Cisplatin And Doxorubicin In PIPAC For Peritoneal Carcinomatosis Of Epithelial Ovarian Cancer

Introduction :

- PIPAC in inoperable recurrent ovarian cancer is safe, feasible and has shown good oncological outcomes.
- However the maximum dose of drug that can be used and its clinical outcomes is not defined yet.



Materials & Methods:

- PIPAC was done at dose of **cisplatin 15mg/m2 and doxorubicin 3mg/m2 for all inoperable advanced ovarian cancer patients eligible as per institutional criteria**
- The patient demographics, perioperative findings, adverse events, and outcomes were prospectively recorded.
- Response rate was graded as Peritoneal Regression Grading Score (PRGS)

RESULTS

	N=6
Age (years)	55.56 ± 9.46
ECOG 0 1 2	 1 3 2
Previous Surgery 1 ≥2	 2 4
Systemic Chemotherapy 1st line 2nd line >2nd line	 1 3 2

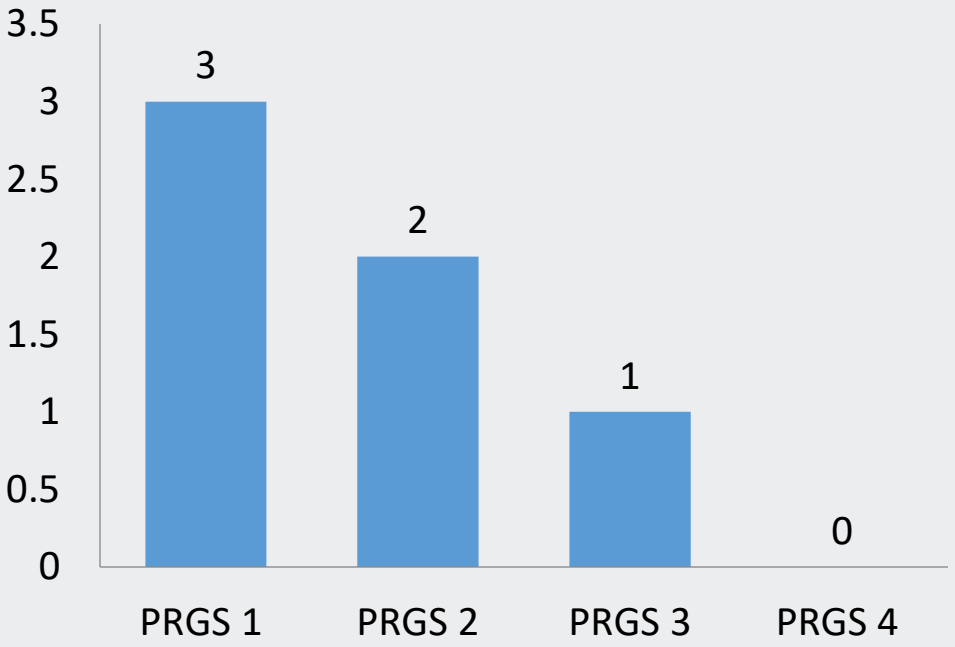
Peri-Operative Finding	N=6
PCI	23.4 ± 8.75
Duration Of Surgery	80minutes± 15.4
Blood loss Mean	10ml± 10.2
Hospital Stay Median (Range)	1.3 (1-5 days)

Complications	Clavien-Dindo (GRADE I-V)
Nausea/Vomiting	3 (II)
Ascites leak	2(1)
Increased AST/ALT	3(II)
Pain	3(III)

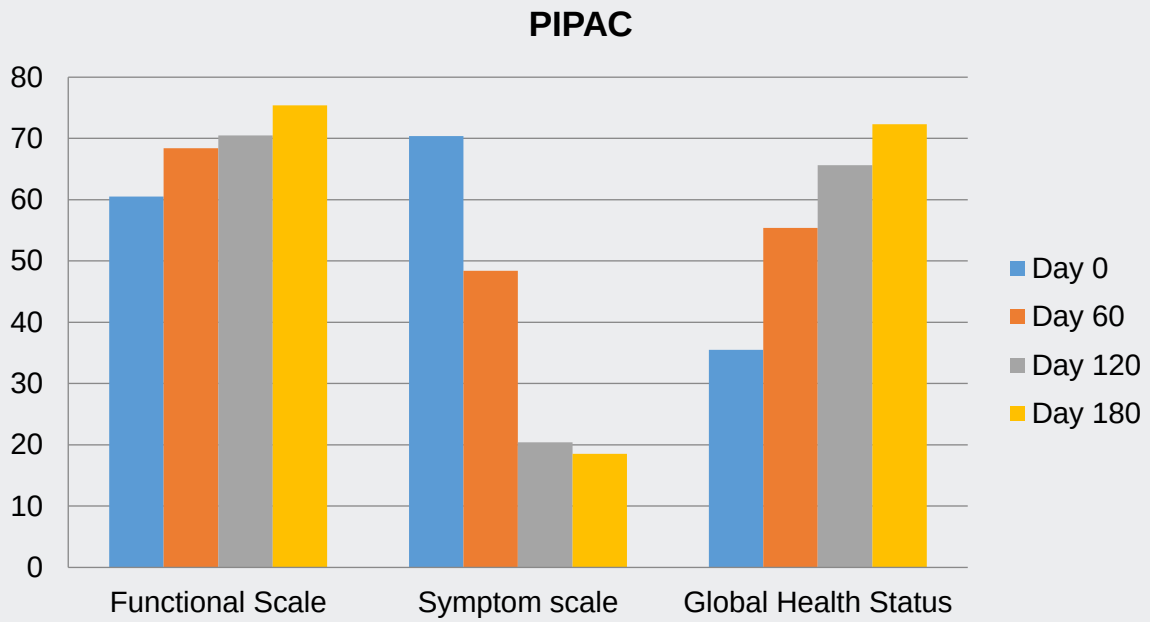
- All patients completed 3 PIPAC
- No Intra-operative Complications
- Transient elevation of CRP in 3 patients
- None of the patients had any renal complications

RESULTS

PRGS Score



QOL Score Overall



CONCLUSION:

- **PIPAC can be performed safely at doses of cisplatin 15mg/m2 and doxorubicin 3mg/m2.**
- **There is better objective & pathological response with this dose with no major complications or side effects to the patients.**
- **There is also improvement in quality of life.**
- **This dose should be new standard of care for FUTURE STUDIES UTILL HIGHER DOSE SCHEDULES STUDIES ARE DONE.**

DISCUSSION

- PIPAC is well tolerated by most patients and has shown promising response in women with end stage PM.
- Good tolerance profile and QoL in PIPAC treatment can allow assessing bidirectional regimens combining systemic and intraperitoneal PIPAC treatment.
- Future prospective studies should present histological regression score results in comparison with QoL.
- Furthermore, PIPAC procedure and treatment algorithms need to be standardized for various pathologies.

CONCLUSIONS

- PIPAC is a **feasible ,effective** and easily reproducible with no postoperative major toxicity, with **good tolerance** .
- Low morbidity and maintains the QoL in patients with advanced peritoneal carcinomatosis.
- Further Prospective studies are needed
- PIPAC can be considered as an effective option in palliative setting in patients with advanced recurrent Ovarian cancers who are not candidates for curative resection .

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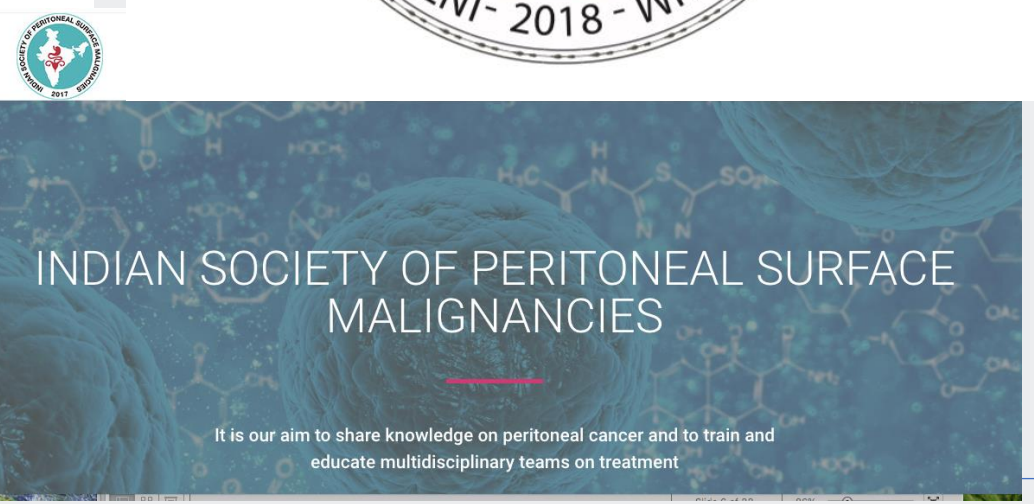
PIPAC RCT'S In Progress



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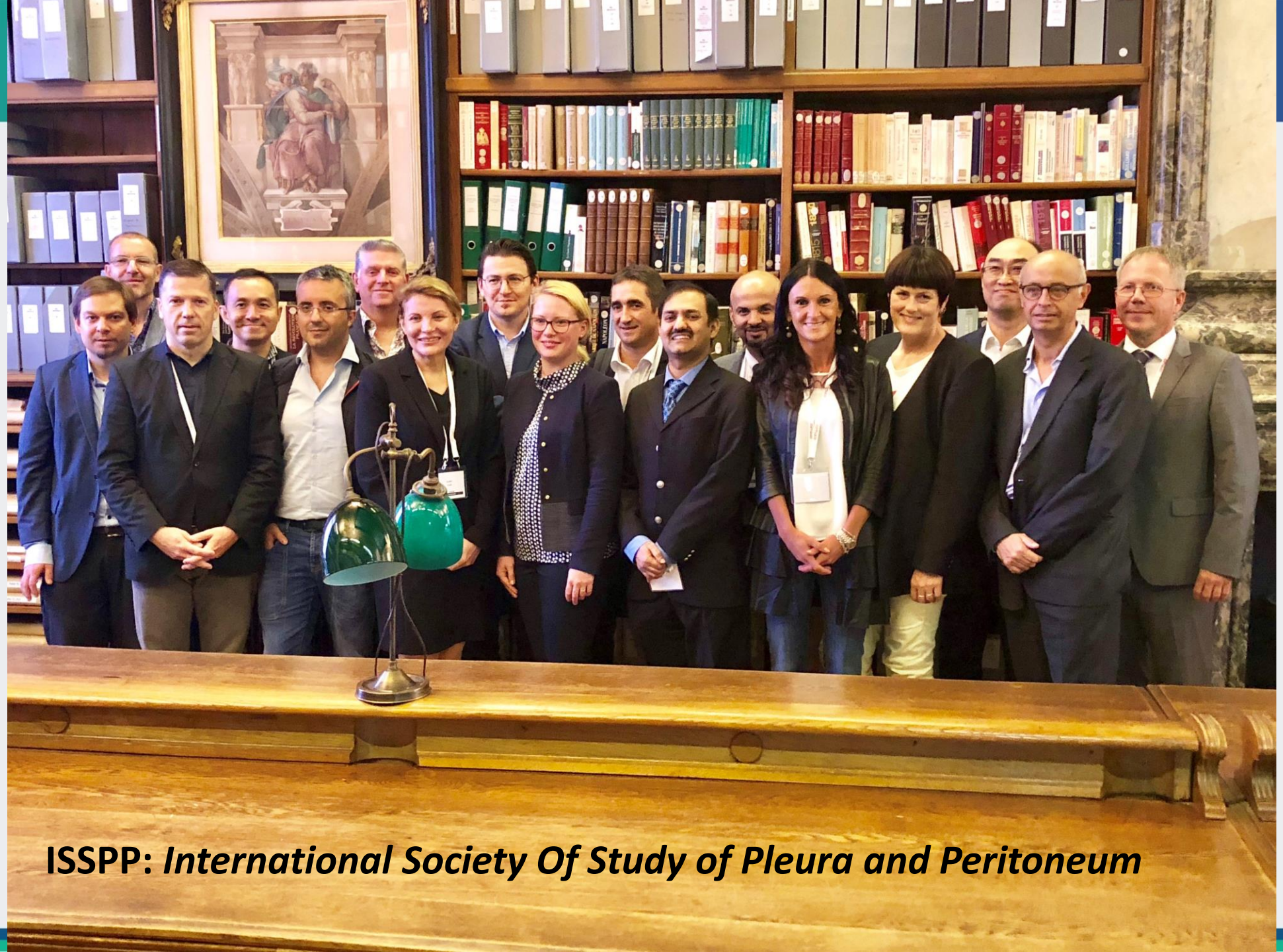

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