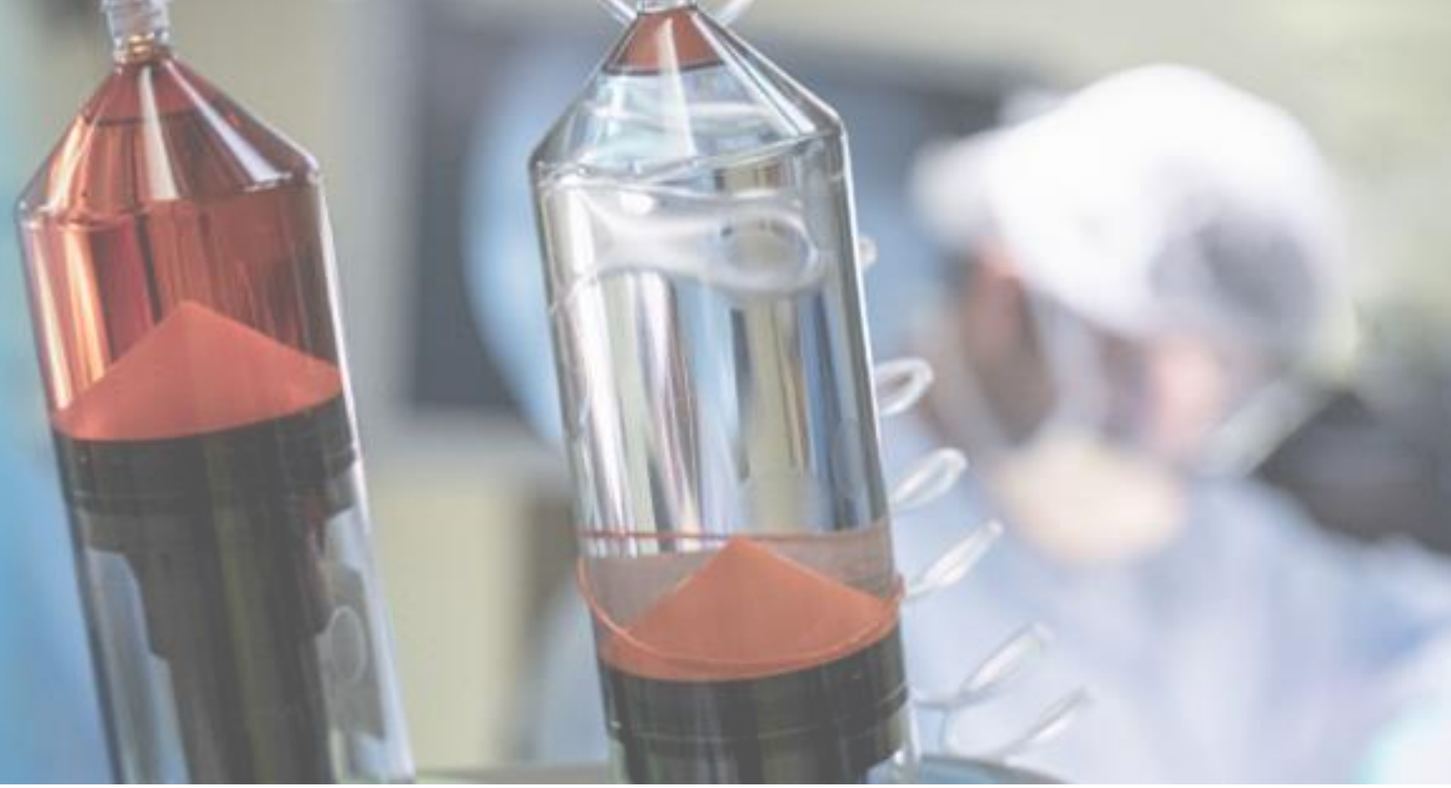
First U.S. PIPAC Training Workshop



Multimodal therapy and PIPAC

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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 and Oxaliplatin will be addressed.

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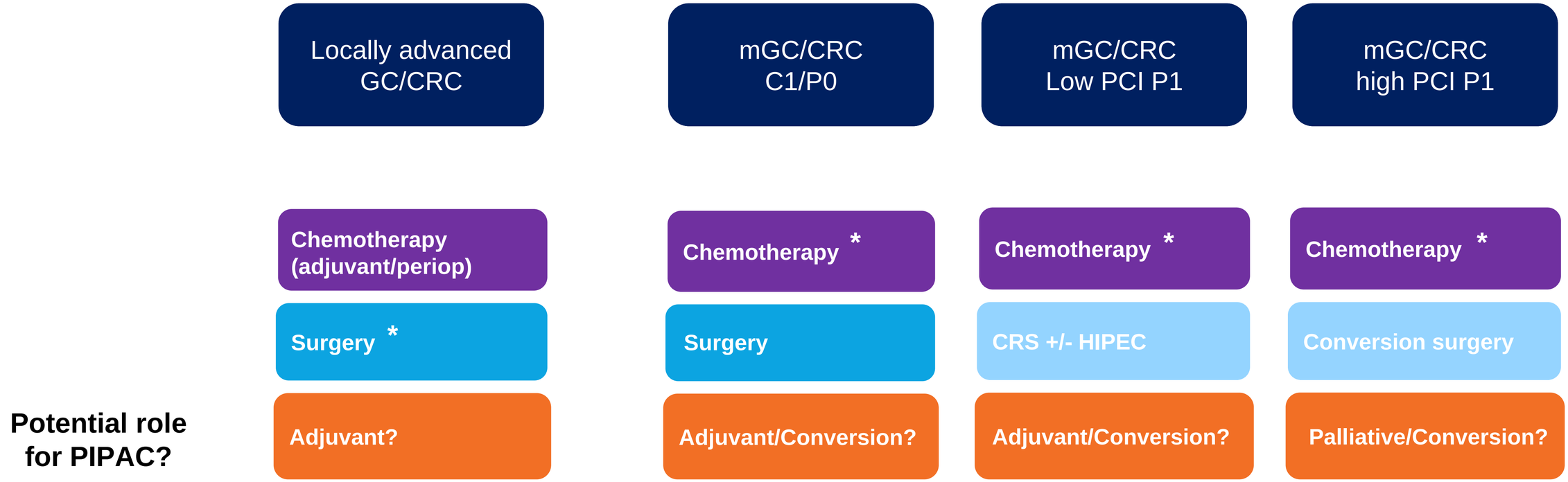
Multimodality therapy with PIPAC



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Why multimodality treatment?

- Systemic chemotherapy is the SOC in early and advanced in most cancer.
- In potentially resectable cancer that is biologically aggressive with high propensity for extra-peritoneal spread eg. gastric or pancreatic cancer, effective systemic chemotherapy prior to and after surgery is a necessity.
- Delay in administration of the effective upfront systemic treatment component may negatively affecting survival in the surgery population with C1 or P1 disease.
- Help test biology - exclude patient that lack systemic control and worse prognosis.

Bidirectional therapy in palliative setting

Bidirectional treatment of peritoneal metastasis with PIPAC and systemic chemotherapy: a systematic review

Author	Malignancies	PIPAC Chemo	Systemic Chemo	Interval between PIPAC
Alyami et al. [27]	Gastric, Colon, Ovarian, Mesothelioma, Pseudomyxoma and others	Oxa, C/D or mito-c	NR	NR
Demtröder et al. [28]	Colorectal	Oxa	NR	6 weeks[a]
Falkenstein et al. [29]	Biliary tract	C/D	NR	6 weeks[a]
Graversen et al. [30]	Pancreatic	C/D	Gem + S-1	4–6 weeks[a]
Hilal et al. [31]	Gynecological	C/D	NR	4–6 weeks[a]
Khomyakov et al. [24]	Gastric	C/D	XELOX	6 weeks[a]
Khosrawipour et al. [32]	Pancreatic	C/D	Gem+nab-Pax Folfirinox Gem	6 weeks[a]
Nadiradze et al. [33]	Gastric	C/D	NR	6 weeks[a]
Reymond et al. [34][a]	CUP, Pancreatic and Gallbladder	C/D	Cis + Gem	6 weeks[a]
Robella et al. [26]	Mesothelioma, Ovarian, Colorectal, Pseudomyxoma and Gastric	C/D or Oxa	Topotecan Folfox+cetuximab Folfoxiri Paclitaxel Folfiri Paclitaxel+Ramcirumab Xelox Paclitaxel Pemetrexed	6 weeks[a]
Farinha et al. [35]	Gynecological, Colorectal, Gastric, Small bowel, Appendix, Pseudomyxoma and Mesothelioma	NR	NR	6 weeks[a]
Hübner et al. [36]	Gynecological and Digestive	C/D or OXA	NR	6 weeks[a]

C/D Cisplatin/Doxorubicin, *CUP* cancer of unknown primary, *gem* Gemcitabine, *mito-c* Mitomycin c, *nab-pax* nab-Paclitaxel, *NR* not reported, *Oxa* Oxaliplatin,
[a] Pursued rather than actual interval

Ploug M. BMC Cancer 2020

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Bidirectional treatment of peritoneal metastasis with PIPAC and systemic chemotherapy: a systematic review

- Bidirectional treatment approach is practiced and feasible.
- “The studies were very heterogeneous including multiple malignancy types, different time-points of the diseases, varying disease extent and varying degrees of pre-treatment. Taken together, we were not able to draw any conclusions or perform a meta-analysis.”
- Recommend reportable endpoints: OS, PFS, QOL, CTCAE toxicity, OTR

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Ploug M. BMC Cancer 2020

What is the optimal scheduling for bidirectional chemotherapy + PIPAC?

Several studies has indicated that it is feasible to allow

- 1-4 weeks washout before PIPAC
- 0-2 weeks after PIPAC

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Robella M. World J Surg Onc 2016, Demtröder C. Color Dis 2016, Alyami M Eur. J. Surg. Oncol. 2017, Hilal Z. J Gynecol Oncol. 2017

What is the optimal scheduling for bidirectional chemotherapy + PIPAC?

General Principles:

Washout period is ~5 half-lives or 2-4 weeks for most drugs, but 6 weeks for drugs with delayed toxicity eg. mitomycin and nitrosoureas

Adequate marrow/liver/renal function; recovery to ≤G1 treatment toxicity

Consider staggered administration or Phase I evaluation if there are potential overlapping toxicity

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Meeting Abstract | 2020 Gastrointestinal Cancers Symposium

ESOPHAGEAL AND GASTRIC CANCER

Palliative systemic chemotherapy with or without pressurized intraperitoneal aerosol chemotherapy with cisplatin and doxorubicin (PIPAC C/D) for gastric cancer with peritoneal metastasis: A propensity score analysis.

Vladimir Khomiakov, Christoph Meisner, Andrey Ryabov, Larisa Bolotina, Anna Utkina, Ilia Kolobaev, Dmitry Sobolev, Anna Chayka

- The HR adjusted for PS for PIPAC vs. control was 0.396 (CI 5- 95% = 0.224-0.700, p-value 0.001).
- mOS control group was 7.0 months (CI: 4.51 - 9.49) and in the PIPAC group 14.0 months (CI: 11.46-16.54).
- These promising results need to be confirmed in a randomized trial.

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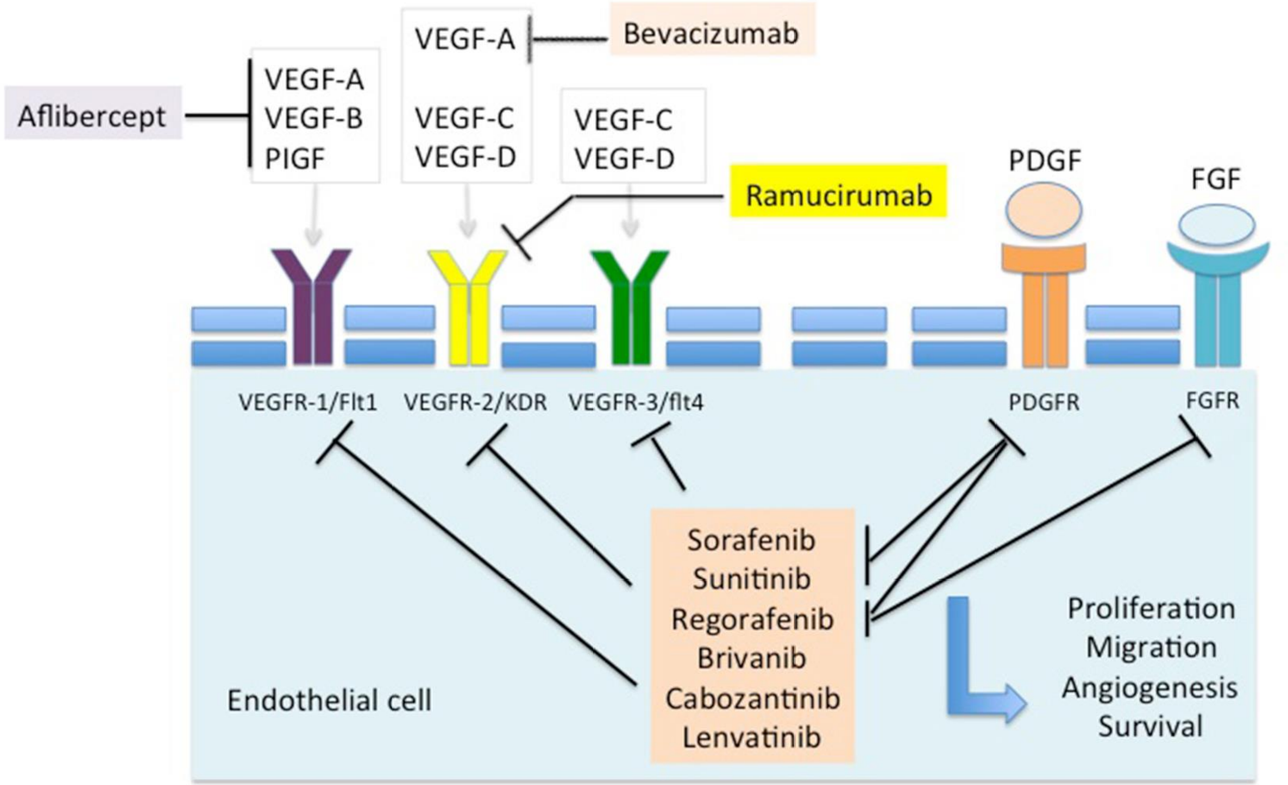
PIPAC with anti VEGFR therapy



- Bevacizumab, an anti-VEGF antibody, approved treatment for mCRC, ovarian and primary peritoneal cancer in combination with chemotherapy.
- Ramucirumab, an anti-VEGFR2 antibody, approved for 2L treatment for GC as monotherapy or in combination with paclitaxel.
- Angiogenesis inhibitors may affect wound healing, increase risk of perforation (1.5-2.5%) and bleeding.
- Current recommendations that suggest to withhold ramucirumab at least 28 days before surgery.

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PIPAC with anti VEGFR therapy

- Registry data of BEVA (n=26) vs non-BEVA (n=108) where bevacizumab without interruption before and after PIPAC as planned with a delay of 2 weeks between each cycle and PIPAC:
  - No difference in overall 30-day morbidity (BEVA: 13 (14.8%) vs non-BEVA: 29 (9.4%); p = 0.147).
  - No difference in grade III-IV complications (BEVA: 4 (4.5%) vs non-BEVA 10 (3.2%); P = 0.521).
  - Major complications from BEVA group were as follow, 2 bowel obstructions, one hematoma and one severe hypersensitivity reaction to platinum compound.
  - There was no 30-day mortality in BEVA group compared to 6 (5.5%) in NON-BEVA group.

"PIPAC associated with bevacizumab is safe, feasible and well tolerated. The potential oncologic benefit of the bevacizumab and PIPAC association remains to be evaluated by further prospective study."

My take:
Small sample size, difficult to pick up increase perforation rate.
Agree with author conclusion.

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Siebert M. Eur J Surg Oncol 2019

PIPAC with Ramucirumab-based therapy

- Retrospective cohort with median washout of 18 days
- overall postoperative morbidity was 11% with 6% (n=5) severe complications including surgical site infection*, small bowel perforation*, tracer site hernia, and acute abdomen/UTI*. *ramucirumab

	CTx - RAM (n = 42)	CTx + RAM (n = 35)	p-value
Overall morbidity	4 (10%)	3 (9%)	1.000
Severe complication	2 (5%)	3 (9%)	0.654
LOS (median, min-max)	3 (2-6)	3 (2-43)	0.211

Severe complications are classified as Clavien-Dindo ≥3a.

My take:
Generally safe!
But severe complication almost double
Perforation rate 2.9%
Small sample size, difficult to definitively conclude if treatment-free <28 days is safe

"Ramucirumab, even with a treatment-free interval as short as 2 weeks before PIPAC, does not increase the risk of postoperative complications "

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Feldbrugge L. Front in Oncol 2021

On-going randomized palliative study

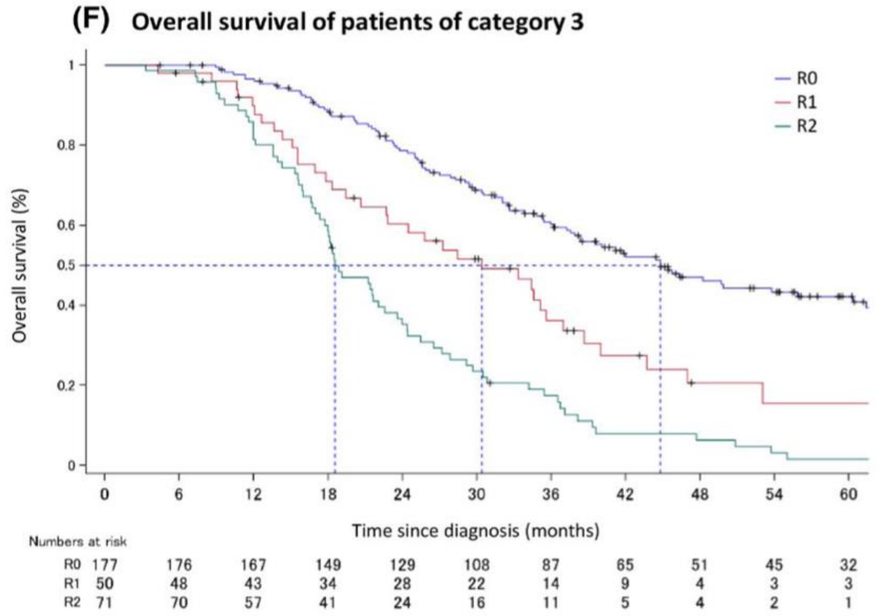
- Second Line Oxaliplatin Based Chemotherapy Alone Versus Oxaliplatin Based PIPAC and Chemotherapy in Colorectal Peritoneal Carcinomatosis : A Phase II Randomize Mutli-centric Study : OPAC Study - ClinicalTrials.gov Identifier: NCT04734691
  - Primary endpoint: PFS

- Phase II Multicenter Randomized Trial Evaluating the Association of PIPAC and Systemic Chemotherapy Versus Systemic Chemotherapy Alone as 1st-line Treatment of Malignant Peritoneal Mesothelioma: MESOTIP - ClinicalTrials.gov Identifier: NCT03875144
  - Primary endpoint: OS

Bidirectional therapy for conversion or neoadjuvant setting

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



Yoshida K Ann Gastroenterol Surg 2021, Bonnot P-E. J Clin Oncol 2019

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Rationale for bidirectional chemotherapy to convert GCPM for surgery

- PIPAC + systemic chemotherapy can lead to reduction in Peritoneal Carcinomatosis Index (PCI).
- Report of unresectable peritoneal metastasis treated by PIPAC leading to CRS and HIPEC.
- Surgery aiming at R0 operation after induction chemotherapy + regional therapy is a promising strategy for GC and CRC with PM.

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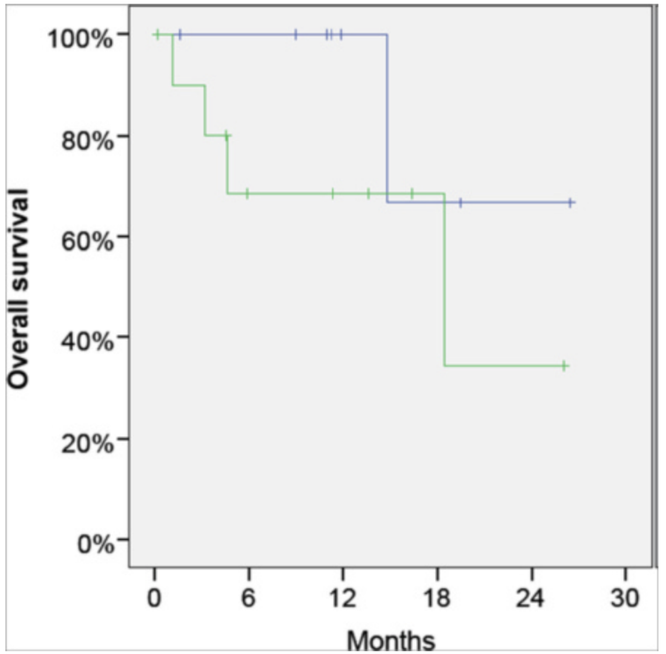
Alyami M. Eur J Surg Oncol 2019

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) as a neoadjuvant therapy before cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Ramy Girshally[1,2], Cedric Demtröder[1,2], Nurettin Albayrak[1], Jürgen Zieren[1,2], Clemens Tempfer[1,2] and Marc A. Reymond[3*]

- Registry data reported 21 patients (5.2%) undergone CRS + HIPEC after PIPAC.
- Low PCI (mean 5.8 ± 5.6) in 12 pts and advanced PCI (mean PCI 14.3 ± 5.3) in 9 pts at initial laparoscopy.
- After repeated PIPAC (mean number of cycles 3.5 ± 0.9), radiological tumor regression was observed in 7/9 patients and major histological regression was observed in 8/9 patients, so that secondary CRS and HIPEC became possible.



My take:
No information of prior or current systemic therapy; heterogenous tumour types; definition of respectability not predefined. However, provide signal of possible to convert inoperable PM to eligible for CRS + HIPEC.

On-going randomized neoadjuvant study

- Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) in Multimodal Therapy for Patients With Oligometastatic Peritoneal Gastric Cancer: a Randomized Multicenter Phase III Trial: **PIPAC_VEROne** - ClinicalTrials.gov Identifier: NCT05303714

  - Primary resectable gastric cancer with positive peritoneal cytology and/or low burden peritoneal metastases (PCI ≤6) confirmed by laparoscopy

  - Primary endpoint: Rate of radical intent surgery (cytoreductive surgery and HIPEC)

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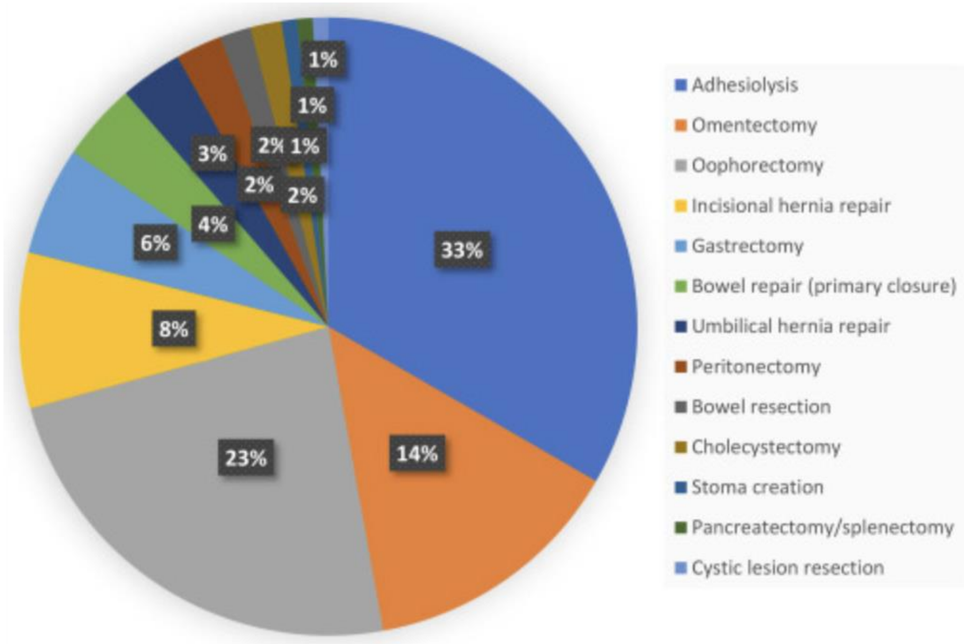
Adjuvant PIPAC in locally advanced PM

European Journal of Surgical Oncology
Available online 7 May 2022
In Press, Corrected Proof

Feasibility and safety of PIPAC combined with additional surgical procedures: PLUS study

Manuela Robella [a], Martin Hubner [b], Olivia Sgarbura [c, d], Marc Reymond [e], Vladimir Khomiakov [f], Andrea di Giorgio [g], Aditi Bhatt [h], Naoual Bakrin [i], Wouter Willaert [j], Mohammad Alyami [i, k], Hugo Teixeira [b], Andrey Kaprin [f], Federica Ferracci [g], Guillaume De Meeus [c], Paola Berchialla [l], Marco Vaira [a]
ISSPP PIPAC study group



- High rate of complications in the initial experience of PIPAC treatment following surgical procedure .
- PLUS study demonstrated that PIPAC associated increase of surgical time ($p < 0.001$), length of stay ($p < 0.001$) and medical complication rate ($p < 0.001$); the most frequently complications were abdominal pain, nausea, ileus and hyperthermia.
- “PIPAC can be safely combined in expert centers with additional surgeries. Widespread change of practice should be discouraged before the results of ongoing prospective studies are available.”

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Hübner M. Eur J Surg Oncol 2017, Giger-Pabst U J Gastrointest Surg 2018

On-going randomised adjuvant study

- Single-center Randomized Study Evaluating of Oncological Benifits of Pressured Intraperitoneal Aerosol Chemotherapy (PIPAC) in Patients With Locally Advanced Gastric Cancer in Patients With Cyt-ve - ClinicalTrials.gov Identifier: NCT04595929

  - 304 participants, primary endpoint: mOS

Objectives

- Why multimodality therapy?
- How to combine PIPAC with systemic chemotherapy?
- Median survival of PC has improved for ovarian, CRC and gastric cancer over past decades.
- Systemic therapy works in PC.
- Systemic therapy and regional therapy may improve outcome of patients with PC.

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Conclusions

- PIPAC C/D or Oxaliplatin can be administered safely as part of bidirectional therapy with systemic chemotherapy.
- Multimodality treatment appeared most promising in palliative and conversion/neoadjuvant setting.
- PIPAC use post major surgery should be discouraged before the results of ongoing prospective studies are available.
- Carefully designed prospective studies with appropriate endpoints, patient selection to minimize heterogeneity in disease types, stage, extent and prior treatments is needed to help define the role of PIPAC.