Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC)

For gastrointestinal tumors

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Topics

- Background
- Pharmacology an 3-D CRC cell line model
- PIPAC vs HIPEC: indications and contraindications
- PIPAC as salvage therapy
- PIPAC as neoadjuvant therapy
- Clinical studies
- Update on therapy centres
If anticancer drugs cannot reach all the cells within a tumour, their effectiveness is compromised.

Physical laws support the superior distribution of drugs within the abdominal cavity if they are administered in gaseous form, like during PIPAC.


Increased direct penetration of drugs

PIPAC directly delivers chemotherapy under pressure, increasing tissue penetration and can induce the regression of peritoneal tumour nodes of > 5 mm

This is a clear advantage over other delivery routes such as hyperthermic intraperitoneal chemotherapy (HIPEC)

Dosis reduction, less side-effects

High local disponibility and favourable therapeutic index allows 90% total dose reduction of chemo-therapeutics administered. Organ toxicity is minimal.

Decrease in the outflow of drug by capillary flow

PIPAC (laparoscopy) reduces blood outflow from the abdomen over the liver and the abdominal wall during the uptake phase.

This increases the pharmacokinetic advantage of regional delivery and limits toxicity.


Repeated application

PIPAC allows repeated local application of chemotherapy for up to a maximum of eight sessions.

At the beginning, therapy intervals are six weeks, in case of objective tumour regression this can be prolonged to three or six months.

This is another advantage over HIPEC

Tempfer C et al (submitted); Nadiradze G et al (submitted); Demtröder C et al (submitted)
Comparing biopsies obtained during repeated PIPAC allows objective tumor response assessment.

This is not possible after HIPEC.

Solaß W et al (submitted)
Less time, inconvenience and costs

• Although it is not yet possible to balance the patient benefits of PIPAC against the costs for the healthcare system, it is feasible to say that PIPAC is a minimally invasive procedure requiring a short hospital stay.

• The costs of chemotherapy are much lower than systemic palliative chemotherapy with biologicals and HIPEC.
PIPAC: Indications

5.11.2011 to 21.1.2015: 636 PIPAC + 11 PITAC in 328 patients
752 procedures (intention to treat)

Palliative indication in pretreated, platin-resistant peritoneal carcinomatosis, primary CRS and HIPEC not indicated

Therapy within the framework of regulatory studies PIPAC-OV1 (NCT01809379) and PIPAC-GA1 (NCT01854255) as well of as off-label use according to German AMG.
All patients had previous guideline-based therapy with approval of the IRB. All patients were presented at the tumor board of the Comprehensive Cancer Center, Marien Hospital, Ruhr-University Bochum.
A few questions*

• How many of your patients will be able to undergo systemic chemotherapy after CRS & HIPEC?

• Why shouldn‘t I use the information provided throughout the pre-OP treatment phase?
  – Response
  – How the patient does tolerate all procedures?

• ... and the pathology information after resection for further decision making?

*asked during the 9th HIPEC symposium in Amsterdam by P. Piso
Neoadjuvant treatment allows us to predict prognosis and to „learn“ about the individuals biology

YES!
Chemosensitivity assessment

• Many surgeons recommend systemic chemotherapy between staging laparoscopy and CRS & HIPEC, e.g. for 3 months

• In patients eligible for CRS & HIPEC:
  – Why not applying PIPAC at staging laparoscopy, and q6 weeks in order:
    • to determine chemosensitivity (repeat objective tumor response assessment) = prognostic chance
    • to increase the chances of CC-0 resection ? = therapeutic chance by reducing a diffuse disease to a focal disease ?
Indication 1: PIPAC as salvage therapy

- In patients not eligible for CRS & HIPEC:
  - What are you proposing to these patients?
  - Why not applying PIPAC q6w until disease progression?
    - ¾ objective tumor regression (histology) in platin-resistant PC of ovarian, gastric, colorectal cancers and mesothelioma?
    - Low risk, minimal invasive procedure
    - Improvement of QoL
Clinical Benefit Rate ($\Sigma$ histological CR + PR) is 84% (11 objective tumor regressions in 13 patients with $\geq$ 2 PIPAC) or 64% (out of all 17 patients).

Semi-quantitative analysis of regression grading after 1 PIPAC shows a significant drop of median TRG 5 à 2, $p=0.005$.)
Observed actuarial survival of 17 consecutive patients with peritoneal carcinomatosis of colorectal cancer (mean Peritoneal Carcinomatosis Index = 16) after PIPAC salvage therapy with oxaliplatin. Patients had previously received 2 lines of palliative systemic chemotherapy (median, min-max 1-3). All patients had previous surgery. Most patients received combined systemic palliative chemotherapy with PIPAC. One-year survival is 70%, 14/17 patients are alive after a mean follow-up of 237 days. Median survival has not been reached yet (dotted line). X-axis: survival in days. Y-axis: cumulated survival.
Quality of life preservation

Peritoneal carcinoma patients generally suffer gastrointestinal symptoms that deteriorate until death.

Quality of life data showed that gastrointestinal symptoms remained stable following PIPAC.

Global quality of life improved and disease-related symptoms were stabilised for at least 3 months in the majority of patients.

Odendahl K et al. (submitted). Tempfer C et al (submitted)
Indication 2: „neoadjuvant“ PIPAC

- In patients **not** eligible for CRS & HIPEC:
  - Why not applying repeated PIPAC until major tumor **regression** in order to perform secondary CRS and HIPEC?
    - Around 1/4 complete tumor response in platin-resistant PC of ovarian, colorectal, gastric cancer and mesothelioma
    - Secondary CRS and HIPEC possible in a significant number of patients
      - Colorectal cancer
      - Gastric cancer (incl. signet-ring)
      - Mesothelioma
      - Others?
In > 10 cases, secondary CC-0 cytoreductive surgery + HIPEC could be performed after repeated PIPAC in presence of diffuse small bowel involvement, suggesting a role for PIPAC as a „neoadjuvant“ therapy.
58 y.o. patient with metachronous peritoneal carcinomatosis of colorectal cancer 27 months after diagnosis and after systemic chemotherapy (XELOX, then capecitabin alone due to side-effects) (a) Abdominal CT-scan before PIPAC-therapy with extensive peritoneal carcinomatosis (arrows) (b) Complete radiological response according to RECIST criteria after 3 cycles of Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) q6w with oxaliplatin 92 mg/m^2 at a pressure of 12 mmHg and a temperature of 37 °C for 30 minutes, combined with systemic chemotherapy (FOLFIRI). Patient is alive 1 year after PIPAC #1 with excellent quality of life.
The patient underwent complete cytoreductive surgery (CC-0) and Hyperthermic IntraPeritoneal Chemotherapy (HIPEC) 7 months after PIPAC #1. (a) Macroscopy of the left upper abdomen showing limited PC (Peritoneal Carcinomatosis Index = 3) with diffuse scarring. (b1) Four suspect millimetric nodes on the surface of the small bowel were resected, all of them were tumor-free (+). (b2) Vital tumor cells (arrows) were found in 3/9 peritoneal biopsies and in the omentum, together with extensive fibrosis (#) and large mucous areas (&) as a sign of tumor regression.
Repartition of the pressurized therapeutic aerosol under clinical conditions. Intraoperative finding during secondary cytoreductive surgery and HIPEC after repeated PIPAC. **Panel a:** main abdominal cavity shows major regressive changes of the peritoneal surfaces and of the great omentum, with complete regression of small bowel nodes and development of a fibrotic sheet around the omentum. **Panel b.** Same patient. Active tumor can still be observed in the lesser sac (bursa omentalis) that was obviously not reached effectively by the pressurized therapeutic aerosol.
Sclerosis of large nodules

Macroscopy of the great omentum of a 64 y.o. colorectal cancer patient after repeated PIPAC with oxaliplatin 92 mg/m² body surface. Complete secondary cytoreductive surgery (CC-0) and HIPEC was possible. A fibrotic capsule of 2-3 mm thickness (arrows) had developed in the periphery/ at the outer invasion front of the tumor mass (8.4 x 7.4 x 4.6 cm). Patient is alive 11 months after salvage therapy with PIPAC with excellent quality of life.
HIPEC vs. PIPAC: Indication

CRS & HIPEC: curative intent
PIPAC: Palliative indication in pretreated, platin-resistant peritoneal carcinomatosis, not eligible for CRS and HIPEC

Blue: german HIPEC registry
Red: 5.11.2011 to 31.8.2014: 557 PIPAC + 10 PITAC in 284 patients
658 procedures (intention to treat)
## Contraindications: HIPEC vs. PIPAC

<table>
<thead>
<tr>
<th>Condition</th>
<th>HIPEC</th>
<th>PIPAC</th>
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<tbody>
<tr>
<td>Diffuse small bowel involvement</td>
<td>X</td>
<td></td>
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<td>Retroperitoneal Infiltration / pancreas</td>
<td></td>
<td>X</td>
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<tr>
<td>Mesenterial root infiltration (Class III Sugarbaker)</td>
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<td>X</td>
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<td>Infiltration of Ligamentum hepatoduodenale</td>
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<td>X</td>
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<td>Short bowel syndrome</td>
<td>X</td>
<td>?</td>
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<td>Non-resectable extraperitoneal metastases (e.g. liver)</td>
<td>X</td>
<td>?</td>
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<td>Extraabdominal metastases</td>
<td>X</td>
<td>X (?)</td>
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<td>Palliative 2nd cancer situation</td>
<td>X</td>
<td></td>
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<td>Karnofsky &lt; 70%</td>
<td>X</td>
<td>?</td>
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<td>Ileus, &gt; 3 stenosis</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Cardiac. Renal or Hepatic contraindications</td>
<td>X</td>
<td></td>
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<tr>
<td>Active infection</td>
<td>X</td>
<td>X</td>
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Adapted from A. Königsrainer, University of Tübingen, Germany
PIPAC will evidence HIPEC

- Choice of drugs in CRS & HIPEC is poorly evidenced
  - Study design difficult because of methodological barriers

- PIPAC can help HIPEC for determining the right drug in a particular indication
  - Comparative studies comparing drug A vs. drug B in various cancer types and histologies possible
  - Favourable methodological framework conditions
    - Objective response assessment
    - Procedure standardized
  - Results could be largely extrapolated to HIPEC


PIPAC: Clinical studies


PIPAC Hospitals: Europe (Feb. 2015)
PIPAC Hospitals: Worldwide

- Active
- Trained
- To be trained
Conclusions

- PIPAC is a highly effective drug delivery system in peritoneal carcinomatosis
- PIPAC can not be combined with CRS
- PIPAC can be proposed to many patients ineligible for CRS & HIPEC
- PIPAC might be a „neoadjuvant“ therapy before CRS and HIPEC
- PIPAC provides scientific evidence on intraperitoneal chemotherapy
- At current stage. there is no concurrence between HIPEC and PIPAC
It is good to know that today’s utopia is nothing else that the reality of tomorrow, and that today’s reality was the utopia of yesterday.

Le Corbusier