City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

HEPATIC PANCREATIC BILIARY (HPB)

Role of PIPAC in HPB Cancers

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Advancing Innovative Therapies for Cancers That Invade the Peritoneum and the Pleura

Disclosures

- I do not have any relevant financial relationships.

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

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

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HPB Cancers with Peritoneal Metastasis (PM)

- (Intra-)/extrahepatic bile duct cancer
- Periampullary cancer
- Pancreatic cancer

Pancreatic cancer with peritoneal metastasis (PM)

Synchronous PM

1/8 (population-based data)
1/4 (of patients referred for palliative treatment)

Metachronous PM

1/7 (following resection)

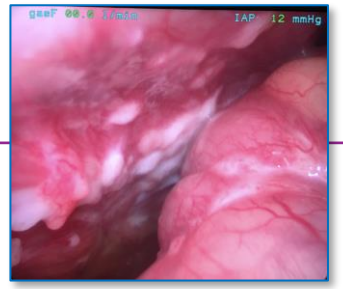
Underdiagnosis is a major problem

Median survival 6 weeks (CI 5-7)

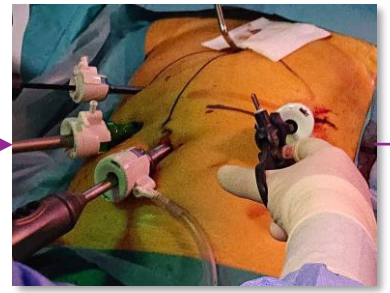
(Conroy et al. N Eng J Med 2011)
(Blastik et al. Pancreas 2011)
(Morizane et al. Pancreas 2011)
(Thomassen et al. Pancreas 2013)
(Takahara et al. Pancreas 2015)
(Solon et al. EJSO 2019)

HPB Cancers with Peritoneal Metastasis (PM)

1. PIPAC directed therapy in manifest HPB-PM

2. Adjuvant PIPAC directed therapy in (high risk) HPB cancers?



PIPAC Directed Therapy in Manifest HPB-PM

Safe (including ePIPAC)

(Reymond et al. Pleura peritoneum 2016)
(Graversen et al. Ther Adv Med Oncol 2018)
(Nielsen et al. J Clin Pathol 2020)

Tolerable and repeatable

(Graversen et al. Ther Adv Med Oncol 2018)
(Nielsen et al. J Clin Pathol 2020)

Out patient procedure

(Graversen et al. Pleura Peritoneum 2018)

Validated and reproducible scoring system (PRGS)

(Solass et al. Histopathology 2019)

IHC improves PRGS interobserver agreement

(Detlefsen et al. Hum Pathol 2022)

Combined progression index (Cyt + PRGS) and PRGS holds prognostic value

(Benzerdjeb et al. Histopathology 2020)

NGS Monitorering af PM before and after PIPAC

(Nielsen et al. J Clin Pathol 2020)

PRGS at PIPAC 1 and 3 holds prognostic value (cut-off at mean PRGS 2)

(Graversen et al. *Submitted 2022*)

PIPAC Directed Therapy in Manifest HPB-PM

Treatment response and survival

PM in Pancreatic adenocarcinoma			
Author/Year	**N**	**Response**	**mOS from first PIPAC (months)**
Reymond 2016	1	PRGS, 100%	8.6
Graversen 2017	5	PRGS, 80%	6.0
Khosrawipour 2017	20	TRG, 35%	9.2
Horvath 2018	6	PRGS, 50%	12.7
Di Giorgio 2020	14	PRGS, 50%	9.7
Nielsen 2021	16	PRGS, Regression 62%	9.9
Graversen 2022 (submitted)	*25*	*PRGS ≤ 2, 51%*	*8.2*

Clavien Dindo complications

- Grade 0-2: 46.2% (31-62)
- Grade >2: 5.1% (1-18)

(Frassini et al. Eur J Surg Oncol 2022)

PIPAC Directed Therapy in Manifest HPB-PM

Treatment response and survival

PM in Cholangiocarcinoma			
Author/Year	**N**	**Response**	**mOS from first PIPAC (months)**
Horvath 2018	6	PRGS, 40%	15.1
Falkenstein 2018	13	TRG, 80%, (4/5) (2/3 had one PIPAC, only)	3.0
Di Giorgio 2020	6	PRGS, 50%	10.9

Additional hypothesis-generating data may be provided within existing PIPAC registries
(e.g. bile duct cancer: 32 patients, pancreatic cancer: 60 patients)

(ISSPP PIPAC Database, July 2022)

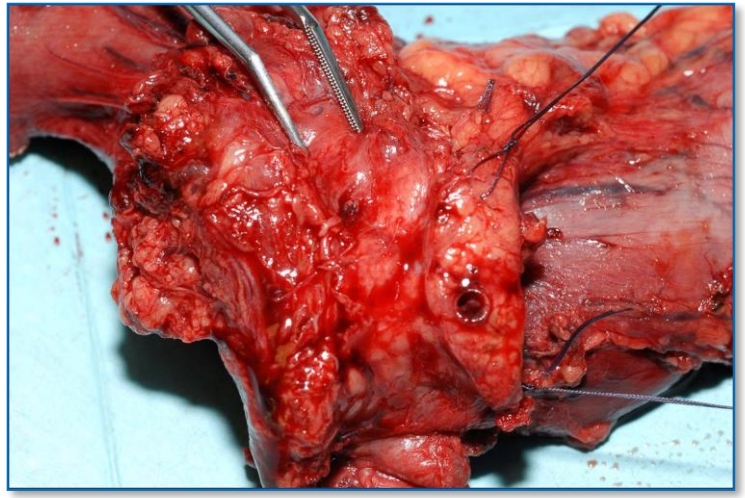
Bidirectional treatment (PIPAC + systemic chemo) is practised and feasible – also in HPB cancers, but data are limited..

(Ploug et al. BMC Cancer 2020)

Adjuvant PIPAC Directed Therapy in (High Risk) HPB Cancers?

High risk of positive cytology/PM in pancreatic cancer

- Cyt+ patients have a significant poorer survival than Cyt- patients (HR 3.18)
- Cyt+ most frequent in advanced resectable PC
- Surgical manipulation increases positive PLF from 10% to 54%
- *Cyt+ patients should not be resected (?)*



(Satoi et al. J Gastrointest Surg 2015)
(Cao et al. Review and meta-analysis, Oncotarget 2017)

PIPAC directed therapy to provide a ”clean peritoneum” before/after resection?

Adjuvant PIPAC Directed Therapy in (High Risk) HPB Cancers?

PIPAC directed therapy may convert Cyt+ and positive PLF

- Conversion malignant (PIPAC 1) → non-malignant (PIPAC 3) in 23%

(Graversen et al. Ther Adv Med Oncol 2018)

PIPAC directed therapy may convert Cyt+ and positive PLF

- *Conversion malignant (PIPAC 1) → non-malignant (PIPAC 3) in 13%*

(Graversen et al. Submitted 2022)

Conversion Surgery	N	Response	Resection (n)
Satoi 2017	33	RECIST: 36%	24% (8)

- Catheter based IP Paclitaxel
- PM (n=22), postive cytology only (n=11)

Phase I dose escalating trial: NAB-PTX was well tolerated, and the maximum tolerated dose was 140 mg/m^2

(Ceelen et al. eBIO Medicine 2022)

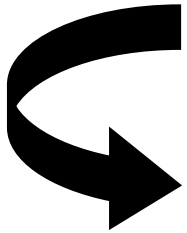
Adjuvant PIPAC Directed Therapy in (High Risk) HPB Cancers?

Adjuvant pressurized intraperitoneal aerosol chemotherapy (PIPAC) during laparoscopic resection in high-risk gastric cancer patients: A Multicentre Phase-I Study (*PIPAC-OPC4)*

(Graversen et al. Submitted 2022)

CONCLUSION

1. PIPAC directed therapy seems to provide regression/stable disease in at least half of HPB-PM patients
2. PIPAC directed therapy provides encouraging survival data in selected HPB-PM patients
3. PIPAC directed therapy should probably be integrated in the early treatment of manifest HPB-PM
4. Treatment may be bidirectional and outpatient based
5. ePIPAC can be used



Phase I, dose escalation trials
Improved aerosolizer, drug formulations, etc.
Phase II trials, new drugs for PIPAC directed therapy (e.g. nab-Paclitaxel)
Randomized phase II/III trial, standard *chemo* vs *chemo + PIPAC directed treatment*

1. HPB-PM incidence - and the detection of intraperitoneal cancer cells, may indicate a need for adjuvant PIPAC directed therapy
2. However, safety, timing, number of PIPAC's, drug(s),…, is unknown

5th Scandinavian PIPAC Workshop

June 8-9, 2023,

Odense PIPAC Center (OPC) (www.PIPAC.dk)
Odense University Hospital, Odense, Denmark

Region of Southern Denmark

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INTERNATIONAL SOCIETY FOR THE STUDY OF PLEURA AND PERITONEUM - 2018 -