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Efficacy and safety of intraperitoneal chemotherapy for pancreatic cancer

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Abstract

Pancreatic cancer is a highly aggressive cancer with unfavorable prognosis despite the therapeutic interventions. Intraperitoneal chemotherapy has recently shown potential outcomes in the presence of peritoneal metastases. However, a consensus is still lacking on different methods for intraperitoneal chemotherapy in pancreatic cancer. A variety of drugs and doses via three types of intraperitoneal chemotherapy have been studied. The prognosis and treatment strategies for pancreatic ductal adenocarcinoma (PDAC) will be significantly influenced by peritoneal dissemination and resectability of the macroscopic disease. Normothermic intraperitoneal chemotherapy (NIPEC) has been used for the treatment of peritoneal metastases of pancreatic carcinomas. Intraperitoneal chemotherapy is often combined with systemic therapies or surgical procedures which may lead to favorable combination therapies such as cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC). Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a relatively new approach that provides a homogenous and deep penetration of the chemotherapy into the peritoneum by producing aerosols. The present study aims to review the literature for recent evidence on intraperitoneal chemotherapy in pancreatic cancer.

Keywords Pancreatic cancer, Peritoneal metastasis, Intraperitoneal chemotherapy (IP chemotherapy), Cytoreductive surgery (CRS), Hyperthermic intraperitoneal chemotherapy (HIPEC), Pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Background

Pancreatic cancer ranks as the third leading cause of cancer-related mortality in the USA [1]. Almost half of the diagnosed pancreatic ductal adenocarcinomas (PDACs) develop metastasis prior to diagnosis, leading to a median survival time of less than six months [2]. after the liver, peritoneum is the second most frequent site of metastasis for pancreatic cancer [3, 4]. Peritoneal metastases occur before being detectable on imaging. Therefore, in some centers, diagnostic laparoscopy is employed for the detection of hidden intraabdominal metastases at the initial diagnosis of selected patients with pancreatic cancer [5]. Staging laparoscopy is considered positive in the presence of gross metastases or positive peritoneal lavage and cytology.

A multivariate analysis of 1,004 patients who underwent diagnostic laparoscopy revealed that young age, increased serum carbohydrate antigen (CA) 19−9, and several tumor-related factors are associated with positive peritoneal involvement. Therefore, diagnostic laparoscopy could be considered in the presence of these elements and is best to precede neoadjuvant chemotherapy since systemic therapy might reduce the sensitivity of laparoscopic assessment [6]. Approximately 20% of the patients may benefit from cytology for the detection of

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peritoneal metastases in the absence of any macroscopic disease [5]. Peritoneal dissemination in pancreatic cancer is multifactorial (e.g. through venous or lymphatic invasion), and there has been limited research on random sampling of the peritoneum to detect occult disease in patients with otherwise normal-appearing peritoneum. Consequently, such cases may not be detected at the time of diagnosis.

In the existence of peritoneal metastases, PDAC patients would have a median overall survival (OS) of 7.6 months despite systemic chemotherapy [7]. Poor blood supply of the peritoneum and elevated interstitial fluid pressure of the metastatic tumor prevent systemic therapy from adequately entering and influencing peritoneal carcinomatosis [8]. Moreover, in the presence of peritoneal involvement, receiving and continuation of systemic chemotherapy is restricted due to cancer-related signs and symptoms including malnutrition and ascites [9, 10]. Thus, intraperitoneal therapies have emerged for managing pancreatic cancer with peritoneal metastases [5, 11, 12].

Liquid intraperitoneal chemotherapy (L-IPC) for peritoneal metastases is limited due to variable distribution of the solution into the peritoneum and inadequate drug penetration into the tumor tissue [13]. Such limitations have been mostly conquered by pressurized intraperitoneal aerosol chemotherapy (PIPAC), which nebulizes the solution into the abdominal cavity [14]. Conversion surgery which is defined as adding surgical resection to chemo- or chemoradiotherapy in patients with primary unresectable PDAC, has been commonly used for locally advanced tumors [15].

In the presence of peritoneal metastases, intraperitoneal chemotherapy significantly increases the rate of conversion surgery in comparison to systemic chemotherapy; hence provides promising clinical improvements [16], while decreasing systemic exposure [17]. Hyperthermic intraperitoneal chemotherapy (HIPEC), which is often accompanied by surgical resection, has shown favorable oncologic outcomes in cases with PDAC and peritoneal dissemination [5]. Yet, the optimal intraperitoneal chemotherapy regimen and method of delivery are undefined for pancreatic cancer [3, 18]. Here, we reviewed the current literature on intraperitoneal chemotherapy for the management of pancreatic cancer.

Liquid intraperitoneal chemotherapy (L-IPC)

Normothermic intraperitoneal chemotherapy (NIPEC)

This type of intraperitoneal chemotherapy has been referred to as NIPEC by Frassini and colleagues [18]. Liquid-based intraperitoneal chemotherapy is a proven method, particularly in the setting of multimodal treatment regimens for managing peritoneal metastases [19]. Recently, Öman et al. administered intraperitoneal 5-Fluorouracil (5-FU) for resectable PDAC tumors the day before pancreatic resection and observed that 5-FU and its active metabolite were absorbed by pancreatic tissue, lymph nodes, and hepatic tissue [20]. Several studies investigated the outcomes of NIPEC in pancreatic cancer (Table 1.). Cytology of peritoneal washing is currently the gold standard method for the assessment of response to intraperitoneal chemotherapy in the presence of peritoneal dissemination [16].

Combination of intraperitoneal (i.p.) with intravenous (i.v.) regimen

A phase I trial on 12 patients with pancreatic cancer and peritoneal metastases did not reach the maximum tolerated dose but recommended the dose of 30 mg/m^2 for i.p. paclitaxel. Combination of i.p. paclitaxel with systemic gemcitabine and nanoparticle albumin-bound (nab)-paclitaxel showed a response rate of 25% [12]. A phase I clinical trial with the previously mentioned drugs determined the recommended dose of 20 mg/m^2 for i.p. paclitaxel, which revealed a response rate of 21/43 patients in phase II of the study. Additionally, the study reported that 8/46 (17%) patients became eligible for conversion surgery with a median OS of 12.4 months after the operation [21]. A report of two cases with pancreatic metastases to both liver and peritoneum, presenting with massive ascites, indicated that combination of systemic and intraperitoneal chemotherapy following the concentrated ascites reinfusion therapy (CART) might be a promising palliative management for such patients [22].

Combination of i.p., i.v., and oral regimens

Intraperitoneal paclitaxel of 20 mg/m^2 has also been used in combination with oral S-1 (a fluoropyrimidine-derived medication) and i.v. paclitaxel in a phase II study. Following the treatment, patients with peritoneum-isolated metastasis had a response rate of 36% [11]. Intraperitoneal plus i.v. paclitaxel and S-1 have been employed in a group of patients with gemcitabine resistance with malignant ascites and remote metastasis. It has indicated a median progression-free survival (PFS) of 2.8 months and a response rate of 8% [23]. Yamada et al. conducted a trial with a combined treatment protocol which allowed for 20% of the patients to undergo conversion surgery following the effective treatment. After the conversion surgery, the median PFS was reported to be 9.2 months [24]. Yamamoto et al. designed a phase III trial to compare the combination of systemic and intraperitoneal therapy with systemic chemotherapy alone in PDAC with peritoneal metastasis, which is still ongoing [25].

Comparing i.p. and systemic therapy

A retrospective study, comparing conventional systemic therapy and intraperitoneal paclitaxel, showed improved

Table 1 NIPEC for pancreatic cancer

Author, Year	Study design	Country	*N*	Age (median)	Tumor status	Chemotherapy agent, dosage	Median OS (months)	Note
Meguro, 2023 [22]	Case report	Japan	1	57	Unresectable peritoneal and liver metastases	I.p. PTX (30 mg/m^2) + i.v. nab-PTX (125 mg/m^2) + i.v. GEM (1000 mg/m2)	4.7 after start of therapy	Both patients underwent CART before combined chemotherapy
			1	58	Unresectable peritoneal and liver metastases	I.p. PTX + i.v. nab-PTX + i.v. GEM	9 after start of therapy	
Yamamoto, 2022 [16]	Retrospective cohort	Japan	101	69	Unresectable with PM	I.p. PTX + oral S-1 + i.v. PTX Or I.p. PTX + oral S-1 + i.v. GEM Or I.p. PTX + i.v. nab-PTX + i.v. GEM	17.9	Treatment responders (26%) underwent conversion surgery. The median OS of 27.4 months in the conversion surgery group
Yamada, 2021 [24]	Clinical trial	Japan	79	69	Unresectable with PM	I.p. PTX (20 mg/m^2) + i.v. PTX (50 mg/m^2) + oral S-1 (80 mg/m^2) Or I.p. PTX + i.v. GEM + i.v. nab-PTX	32.5	16 (20%) patients underwent conversion surgery PFS = 9.2 months
Takahara, 2021 [12]	Phase I clinical trial	Japan	12	56	Unresectable with PM	I.p. PTX (30 mg/m^2) + i.v. GEM (1000 mg/m^2) + i.v. nab-PTX (125 mg/m^2)	Median PFS 5.4	8 (66%) patients became cytology-negative after peritoneal lavage
Öman, 2021 [20]	Case series	Sweden	22	65	Radiologically Resectable without PM	I.p. 5-FU 1250 mg/m^2	~11	Followed by pancreatic surgery
Yamada, 2020 [21]	Phase I/II clinical trial	Japan	46	-	Unresectable with PM	I.p. PTX (20 mg/m^2) + i.v. GEM (800 mg/m^2) + i.v. nab-PTX (75 mg/m^2)	14.5	8 (17%) patients underwent conversion surgery
Satoi, 2017 [11]	Phase II clinical trial	Japan	33	69	Unresectable with PM	I.p. PTX (20 mg/m^2) + oral S-1 (80 mg/m^2) + i.v. PTX (50 mg/m^2)	16.3	8 (24%) patients underwent conversion surgery
Satoi, 2017 [26]	Retrospective cohort	Japan	49	69	Unresectable with PM	I.p. PTX (20 mg/m^2) + oral S-1 (80 mg/m^2) + i.v. PTX (50 mg/m^2)	20	-
Takahara, 2016 [23]	Phase II clinical trial	Japan	35	66	Malignant ascites caused by PM	I.p. PTX (20 mg/m^2) + i.v. PTX (50 mg/m^2) + oral S-1 (80 mg/m^2)	4.8	8 (22%) patients achieved negative peritoneal cytology

N, Number of patients; PM, Peritoneal metastases; OS, Overall survival; I.p., Intraperitoneal; I.v., Intravenous; GEM, Gemcitabine; PTX, Paclitaxel; Nab-PTX, Nanoparticle albumin-bound-paclitaxel; PFS, Progression free survival; CART, Concentrated ascites reinfusion therapy; 5-FU, 5-Fluorouracil

survival in patients with PDAC and peritoneal metastases who underwent intraperitoneal therapy (17.9 months vs. 10.2 months). Responders to treatment who underwent conversion surgery had a median OS of 27.4 months in the i.p. group versus 11.3 months in the systemic therapy group. However, in multivariate analysis, intraperitoneal paclitaxel did not show any positive effect on survival. Whereas, conversion surgery was significantly more applied in the group with intraperitoneal versus systemic chemotherapy group (23% vs. 4%) [16]. Satoi et al. carried out a retrospective cohort study, with intraperitoneal paclitaxel in a combination regimen that has shown decreased ascites development (25% vs. 62%), increased chance of conversion surgery (30% vs. 7%), and improved OS (20 months vs. 10 months) compared with systemic therapy alone in patients with PDAC and peritoneal dissemination [26].

Adverse events

Adverse events reported in phase II studies were mostly hematologic toxicities such as neutropenia, leukopenia, and anemia. Non-hematologic events included appetite loss, nausea, vomiting, and diarrhea. Peritoneal access-related complications include infection and device dislocation [11, 21, 23]. Yamada et al. [21] reported that 76% (35/46) of the cases developed grade 3–4 hematologic toxicity which is particularly high but comparable to standard systemic chemotherapy [27]. A summary of the 2021 Japanese guideline for clinical practice in PDAC with peritoneal metastases stated a weak recommendation regarding NIPEC for patients who do not have massive ascites [10].

Hyperthermic intraperitoneal chemotherapy (HIPEC)

It has been shown that hyperthermia (40–43℃) enhances the cytotoxicity of the chemotherapy agents [28]. There is evidence suggesting that an increase of HIPEC pressure to 20–34 mmHg would not be associated with postoperative complications or prolonged hospital stay, but elevated core body temperature would be [29]. In the published literature, HIPEC has been implemented through a closed or open procedure that lasts 30 to 90 min [5, 30, 31]. A new HIPEC technology (PRS Combat) employs an additional catheter to recirculate the drug and CO2, enhancing intraperitoneal chemotherapy distribution. It also uses a gas exchanger that controls intra-abdominal pressure following the circulation of CO_2 in a closed HIPEC procedure [32] (Fig. 1). Cytoreductive surgery (CRS), which is performed to clear all the macroscopic disease, is often combined with HIPEC to eliminate micrometastases [33]. It is suggested that different dimensions of quality of life such as cognitive, social, emotional, physical, and functional health recover or surpass the baseline by the first year after CRS/HIPEC [34].

Frassini and colleagues have found that completeness of surgical cytoreduction is associated with a survival advantage in patients with pancreatic adenocarcinoma. In fact, the study emphasizes that in cases with borderline resectable and locally advanced pancreatic cancer, in which CRS and surgical resection are possible after neoadjuvant chemotherapy, HIPEC could improve survival without adding to the morbidity [18]. Table 2. summarizes the studies using HIPEC for pancreatic cancer.

CRS/HIPEC in pancreatic cancer with peritoneal metastases

The application of CRS and HIPEC in pancreatic cancer with peritoneal metastases was first reported in 2018 by Tentes et al. who indicated that selected patients with tumors located in the tail of the pancreas may benefit from this approach [35]. Peritoneal carcinomatosis index (PCI) is a parameter that characterizes the extent of peritoneal carcinomatosis preoperatively [36]. Patients with a low volume of peritoneal metastasis (PCI < 7) who received induction systemic therapy and underwent CRS plus HIPEC had a three-year OS of 59% compared to systemic therapy alone with the three-year OS of 8% in a cohort study of 61 individuals [5]. However, a systematic review demonstrated that CRS and adjuvant HIPEC are possibly unsafe for patients with pancreatic cancer and peritoneal metastasis due to overall 34% morbidity and 8.5% mortality [37]. A recent systematic review revealed no significant survival benefit in resection of isolated liver metastases of PDAC compared with standard chemotherapy [38]. However, a case report offered the possible benefit of CRS/HIPEC for the synchronous liver and peritoneal metastases of pancreatic cancer [39].

Currently, CRS/HIPEC is not regarded as the standard of care for PDAC with peritoneal metastases due to the lack of sufficient evidence in the literature [3]. Treatment with CRS/HIPEC has also been successful in patients with pancreatic malignancies other than PDAC such as a Pancreatic solid pseudopapillary neoplasm with peritoneal dissemination [30]. Moreover, a case of Pseudomyxoma peritonei (PMP) originating from a perforated intraductal papillary mucinous neoplasm of the pancreas has been treated with CRS/HIPEC, which was considered safe and feasible [40].

Combination of intraoperative radiotherapy (IORT) with CRS/HIPEC

Grotz et al. conducted a prospective pilot study of 18 patients with only peritoneal metastasis of pancreatic cancer who have had at least six months of multiagent systemic chemotherapy. Pursuing systemic therapy, patients underwent neoadjuvant laparoscopic HIPEC and then a group with resectable tumors underwent CRS

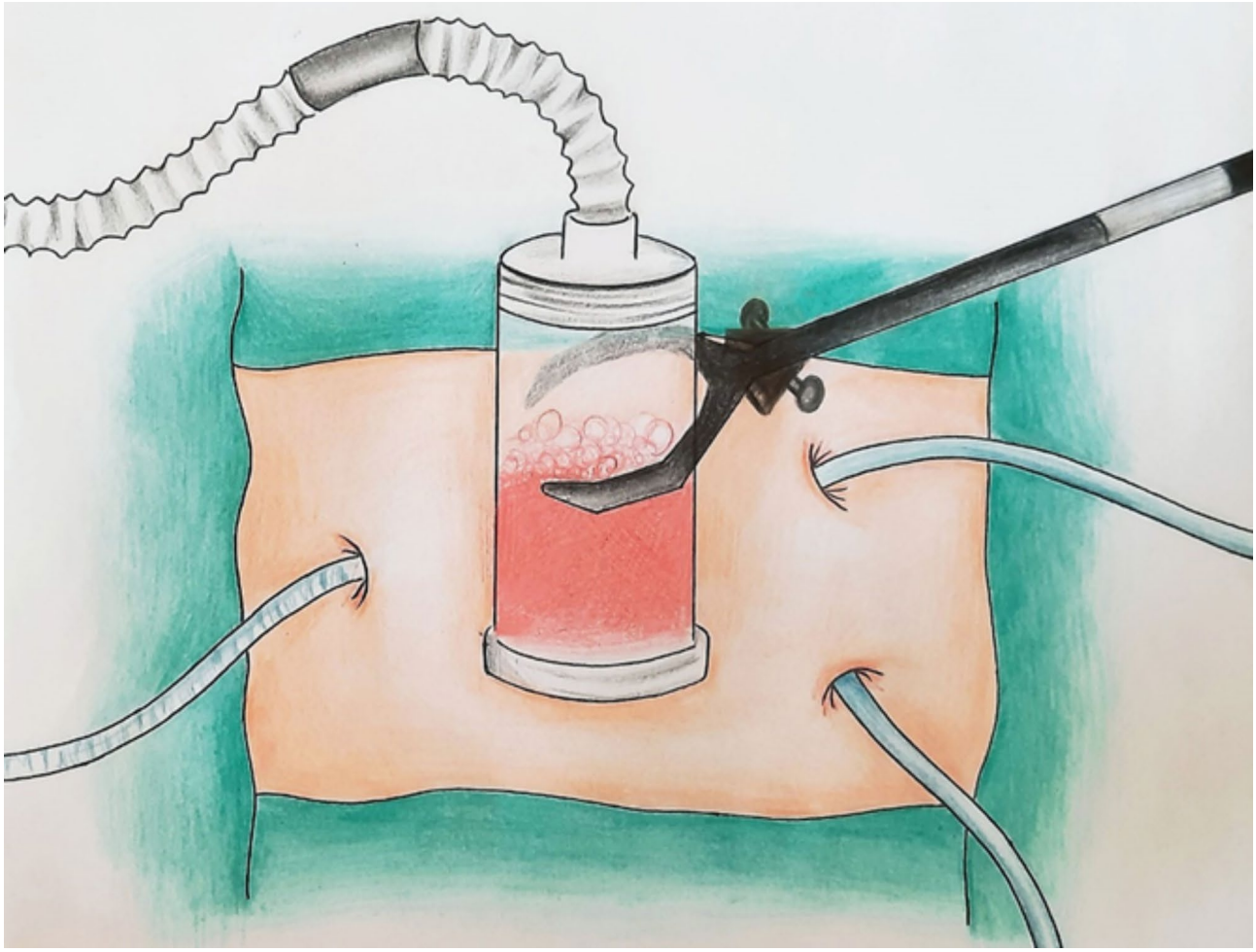

Fig. 1 HIPEC using a CO_2 recirculation system. HIPEC, Hyperthermic intraperitoneal chemotherapy

and HIPEC. Due to the lack of safety evidence on pancreatoduodenal resection in cases with locally advanced or borderline resectable primary tumors, a combination of irreversible electroporation (IRE) or intraoperative radiation therapy (IORT) with HIPEC was employed. After a median follow-up of 16 months, the median OS was reported to be 26 months [3]. Azzam and Amin retrospectively studied patients with resectable pancreatic cancer who underwent CRS followed by IORT and then HIPEC. They reported that this combination of procedures increases the advantages of each one alone, without adding to the perioperative complications [41].

Morbidity and mortality regarding CRS/HIPEC

A multicenter collaborative study of 2,364 patients with peritoneal malignancies of different origins who underwent CRS plus HIPEC demonstrated a postoperative morbidity of 56% and 30-day mortality of 3% [42]. These results were consistent with a study on pancreatic cancer patients with peritoneal invasion who received CRS/HIPEC and had a 30-day mortality of 4.3% and grade 3–4 complications of 43% [5]. Grotz et al. reported a 30-day mortality of 5.5% and a major complication rate of 44% in PDAC patients with limited peritoneal dissemination who underwent laparoscopic HIPEC induction followed by CRS/HIPEC and indicated that these are safe approaches with minimal complications [3].

A study from the United States HIPEC Collaborative included patients with peritoneal metastases of various sources with a median PCI of 13 who underwent CRS with/without HIPEC. The investigation demonstrated that over 17 years Clavien III/IV adverse events were similarly high (55% vs. 57%) while the 90-day mortality has decreased significantly (5% vs. 3%) as time passed [42]. These results were confirmed by a study evaluating distal pancreatic resection and HIPEC [43] and a phase I/II pilot trial of CRS/HIPEC [44]. Application of CRS/HIPEC followed by NIPEC has also shown favorable outcomes since just 1/12 patients developed class III morbidity [45]. Yurttas et al. in a pilot phase I/II trial of patients who underwent CRS and HIPEC reported that 3/13 patients had pancreatic fistula as a key adverse

Table 2 HIPEC in pancreatic cancer

Author, Year	Study design	Country	*N*	Mets	Mean Initial PCI	Age	Method	Time (min)	Tem (℃)	I.*p.* chemotherapy agent, dosage	Note	PFS (mo)	OS (mo)
Padilla-Valverde, 2024 [32]	Phase II/III randomized clinical trial	Spain	21	No	-	Median 68	Close	30	41–42	GEM (120 mg/m2)	CRS/HIPEC followed by adjuvant therapy	Median 14	Median 17.1
Zimmermann, 2024 [49]	Case report	Germany	1	No	-	~60	Close	60	42	GEM (1600 mg)	Left-sided pancreatic resection followed by HIPEC and six cycles of adjuvant systemic chemotherapy	65	65
Elhariri, 2023 [50]	Case report	USA	1	PM	9	74	-	90	41–42	MMC (30 mg/m^2) + CIS (171 mg/m^2)	Chemotherapy and pancreatoduodenectomy followed by CRS/HIPEC then adjuvant therapy	36	72
Sugarbaker, 2023 [31]	Case report	USA	1	No	-	55	Open	60	42	GEM (1000 mg/m^2)	Additional 6 cycles of NIPEC	60	120
Gudmundsdottir, 2023 [5]	Cohort	USA	23	PM	< 7	Median 57	Close	60–90	42.5	MMC (30 mg) + CIS (200 mg) Or PTX (175 mg/m^2) + CIS (100 mg/m^2)	≥ 6 mo of effective chemotherapy before CRS/HIPEC	17	41
Grotz, 2023 [3]	Prospective pilot study	USA	18	PM	2	Median 57	Close	60	42.5	MMC (30 mg) + CIS (200 mg)	≥ 6 mo of effective chemotherapy before neoadjuvant HIPEC and CRS/HIPEC or IRE/IORT and HIPEC	20	26
Nogueiro, 2022 [30]	Case report	Portugal	1	PM	5	43	-	30	43	Oxa (360 mg/m^2) + irinotecan (360 mg/m^2)	Complete CRS/HIPEC Pancreatic solid pseudopapillary neoplasm	24	24
Sugarbaker, 2021 [45]	Phase I/II of a pilot protocol	USA	12	No	-	Median 56	Open	60	Median 41.8	GEM (1000 mg/m^2)	CRS/HIPEC followed by 6 mo of long-term NIPEC	-	29 (in 8 patients)
Yurttas, 2021 [44]	Phase I/II pilot trial	Germany	16	No	-	Median 62.5	Close	60	42	GEM (1000 mg/m^2)	-	-	16.1 after surgery
Azzam, 2020 [41]	Case series	Saudi Arabia	5	No	4.2	Median 51	Open	60	40–42	GEM (1000 mg/m^2)	CRS followed by IORT and then HIPEC. No death until a median follow-up of 8 months	-	-
Tentes, 2018 [35]	Case series	Greece	6	PM	12	Mean 51.8	-	-	-	GEM (1000 mg/m^2) Or CIS (50 mg/m^2) + MMC (15 mg/m^2)	CRS/HIPEC followed by adjuvant chemotherapy with gemcitabine	-	> 12 (in 4 patients)
Tentes, 2016 [48]	Case series	Greece	33	No	-	Mean 67.8	Open	60	42.5–43	GEM (1000mg/m^2)	Complete surgical resection followed by HIPEC and for stage-3 patients additional systemic chemotherapy	9	13

N, Number of patients who underwent HIPEC; Tem, Temperature; PM, Peritoneal metastases; Mets, Metastases; Mo, Months; OS, Overall survival from diagnosis; PFS, Progression-free survival; IRE, Irreversible electroporation; IORT, Intraoperative radiation therapy; GEM, Gemcitabine; MMC, Mitomycin C; CIS, Cisplatin; PTX, Paclitaxel; Oxa, Oxaliplatin

effect. This study supported that HIPEC with PDAC surgery has a mortality rate of less than 10% [44].

The application of HIPEC for curative purposes in PDAC has been recently reported in a phase II/III randomized trial of 42 patients. This study demonstrated that the group who underwent CRS/HIPEC had similar perioperative Clavien-Dindo complications, duration of hospital stay, and cost compared with the CRS group [32]. A retrospective cohort study comparing CRS alone and CRS/HIPEC demonstrated that adding HIPEC to CRS did not raise the likelihood of pooled major adverse events or deaths from major complications at 30 days postoperatively [46]. Downs-Canner et al. have found that the incidence of postoperative pancreatic fistula is the same comparing CRS/HIPEC with distal pancreatectomy alone, although the severity of the fistula is increased when CRS is accompanied by HIPEC [47].

Prophylactic role of CRS/HIPEC in resectable pancreatic cancer

Recently, a systematic review and meta-analysis by Frassini et al. demonstrated that prophylactic treatment with HIPEC in borderline resectable and/or locally advanced pancreatic cancer leads to a three-year survival rate of 25.5%. However, this rate drops to 6.2% in the presence of peritoneal metastases. Therefore, they considered HIPEC as a promising method for prophylactic and curative intents [18]. A 55-year-old man with pancreatic cancer without evidence of any metastases who underwent pancreatic resection plus intraoperative HIPEC followed by six cycles of NIPEC postoperatively survived 10 years after diagnosis of pancreatic cancer [31]. A series of 33 patients with resectable pancreatic carcinoma indicated the potential influence of complete cytoreduction plus adjuvant HIPEC on locoregional recurrence [48]. A case with locally advanced PDAC was treated with oncological resection, HIPEC, and six cycles of adjuvant systemic chemotherapy and did not show any signs of recurrence in CT scan or serum CA 19−9 levels after five years of follow-up [49]. In a phase II/III randomized clinical trial, Padilla-Valverde et al. demonstrated that CRS/HIPEC for resectable PDAC is associated with lower locoregional recurrence but comparable OS, disease-free survival (DFS), and distant recurrence compared to resection alone after a median follow up of 18 months [32]. Nevertheless, the available evidence is insufficient to definitely suggest the use of HIPEC for prophylactic treatment of resectable PDAC, and further controlled studies are required to conclude [10, 37].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Intraperitoneal chemotherapy has gained attention for 30 years and PIPAC has become of interest for Peritoneal carcinomatosis over the past decade [8, 17]. The application of PIPAC for palliative therapy was initiated in 2011 for patients with peritoneal dissemination of various malignancies [14, 51]. A systematic review confirmed the safety, tolerability, and effectiveness of PIPAC for the treatment of peritoneal dissemination in a variety of malignancies [52]. A retrospective study of 118 patients with primary or metastatic peritoneal malignancies who underwent high-pressure/high-dose PIPAC at least once demonstrated that perioperative complications are equivalent to standard pressure/dose PIPAC, but therapeutic effects have yet to be evaluated [19].

Characteristics of the PIPAC procedure

Performing a standardized PIPAC procedure and using safety checklists, the procedure would have a minimal learning curve [53]. PIPAC provides the opportunity to increase the drug concentration of the aerosols by only decreasing the volume of the carrier solution without adding to the administered dose [19]. A minimum flow rate of 25 mL/min is required for stable aerosol formation during PIPAC, while volumetric rise only contributes to faster aerosol formation [54].

Newly developed PIPAC devices with diverse manufacturing properties and costs have been launched. Differences in droplet sizes, diffusion angles, and the pressure required for droplet formation may have variable impacts on patient safety and therapeutic effectiveness [55]. It is advised that new PIPAC nozzles with properties different from the original technology should undergo preclinical testing with regard to spatial distribution of chemotherapy drugs, tissue permeation, and concentration before being used clinically [56]. Despite the common belief that PIPAC causes widespread peritoneal drug delivery, Göhler et al. claimed that with standard microinjection pump operation in PIPAC, homogenous drug distribution into the abdominal cavity is not achieved. Therefore, it may lead to inadequately treated tumoral tissue and therapy failure [54].

Using a conventional PIPAC nebulizer, a 12 mmHg of CO_2 pneumoperitoneum at 37℃ is applied and lasts for 30 min [14]. Following the achievement of a desirable pneumoperitoneum, a high-pressure injector is attached to a nebulizer and placed into the abdominal cavity via a trocar [10]. Administration of PIPAC can be repeated two to five times with four to six weeks intervals [10, 17].

Various PIPAC regimens and outcomes

On a recent consensus for PIPAC in peritoneal carcinomatosis both the drug regimens cisplatin/doxorubicin and oxaliplatin have been validated by the experts [57]. Lately, in another consensus on PIPAC protocol for peritoneal disease, doxorubicin (2.1 mg/m^2) and cisplatin (10.5 mg/m^2) combination has been suggested by 90% of the experts, 72% approved oxaliplatin (90–120 mg/m^2),

and 77% supported combination of 5-FU with PIPAC oxaliplatin [51]. A phase I clinical trial reported that patients tolerated the high dose (120 mg/m^2) of oxaliplatin administered via PIPAC for different gastrointestinal cancers with peritoneal metastases [58]. However, adding systemic chemotherapy to PIPAC cycles would lead to a maximum safe dose of 90 mg/m^2 for oxaliplatin [33, 59].

In a phase II controlled trial, cisplatin and doxorubicin were administered for pancreatic cancer with peritoneal metastases through PIPAC which resulted in a median OS of 15.6 months [8]. Di Giorgio et al. demonstrated the safety, feasibility, and antitumor activity of PIPAC with oxaliplatin or cisplatin-doxorubicin in a retrospective study on patients affected by peritoneal metastases of pancreatic and biliary origins. They also found a pathological regression in 50% of the patients [60]. Ceelen et al. conducted a phase I clinical trial to study PIPAC with nab-paclitaxel in patients with unresectable peritoneal metastases from various cancers. They reported a maximum tolerated and recommended dose of 140 mg/m^2 for future phase II study, a median OS of 10 months, and a one-year survival rate of 50% [61]. Table 3. provides recent evidence on PIPAC for pancreatic cancer.

Evaluation of PIPAC response

At present, response to PIPAC in patients with peritoneal metastasis is mostly evaluated based on histopathological methods such as peritoneal regression grading score (PRGS); whereas, a variety of invasive and non-invasive modalities have been reported such as serum biomarkers, radiology, PCI, and cytology of peritoneal lavage fluid or ascites [62]. In 2021, next generation sequencing (NGS) was first used to evaluate the frequency of *KRAS* mutations in peritoneal quadrant biopsies and peritoneal fluids following the PIPAC for pancreatic carcinoma with Peritoneal involvement. NGS may be utilized particularly when there is access only to post-PIPAC peritoneal biopsies or fluids [63].

A systematic review and meta-analysis on peritoneal malignancies of different origins showed a one-year survival rate of 37% in patients with pancreatic cancer who were treated with PIPAC. Furthermore, the pathological response appeared to be the most reliable outcome for evaluating the anticancer activity of PIPAC with a permissible heterogeneity (I^2 28.41%, $p=0.09$). However, the correlation of pathological, radiological, and macroscopic response with patient survival has yet to be investigated [64]. Graversen et al. discovered that PRGS < 2 at the third PIPAC was the only independent prognostic factor in a multivariate analysis of age, sex, and bidirectional treatment [8]. A retrospective study by Kryh-Jensen et al. revealed that combination of PIPAC and systemic chemotherapy allows for 63% of the patients with pancreatic peritoneal carcinomatosis to reach long-term survival, which was defined as the minimum survival of 15 months [65].

PIPAC-related complications

Di Giorgio et al. systematically reviewed 10 years of PIPAC and revealed that severe complications (grade 3–4) had been reported in 4% of the procedures and death occurred in 1.3% of the patients mostly due to disease progression [64]. Generally, adverse events associated with PIPAC are considered acceptable [8]. A retrospective international cohort study has shown the safety of combining PIPAC with additional surgical procedures

Table 3 PIPAC for pancreatic cancer

Author, Year	Study design	Country	*N*	Age (Median)	Tumor status	Technique	Time (min)	Chemotherapy agent, dosage	MOS (months)	Note
Graversen, 2023 [8]	Phase II trial	Denmark	21	63	Unresectable with PM	Close	30–35	CIS-Dox (7.5 mg/m^2- 1.5 mg/m^2)	8.2	MOS since PM diagnosis = 15.6 months
Nielsen, 2021 [63]	Case series	Denmark	16	Mean 59	Unresectable	Close	30	CIS-Dox (7.5 mg/m^2- 1.5 mg/m^2)	9.9	-
Di Giorgio, 2020 [60]	Case series	Italy and France	14	64	Unresectable with PM	Close	30	CIS-Dox (7.5 mg/m^2- 1.5 mg/m^2) Or Oxa (92 mg/m^2)	9.7	MOS since PM diagnosis = 16.2 months Pathological regression rate = 50%
Graversen, 2017 [67]	Case series	Denmark	5	62	Unresectable with PM	Close	30–35	CIS-Dox (7.5 mg/m^2- 1.5 mg/m^2)	6	MOS since PM diagnosis = 14 months
Khosrawipour, 2017 [68]	Case series	Germany	20	Mean 64.9	Unresectable with PM	Close	30	CIS-Dox (7.5 mg/m^2- 1.5 mg/m^2)	9.1	Pathological regression rate = 35%

N, Number of patients; MOS, Median overall survival from first PIPAC; PM, Peritoneal metastases; CIS, Cisplatin; Dox, Doxorubicin; Oxa, Oxaliplatin

since it does not affect surgical complications or deaths but increases hospital stay, operation length, and minor medical complications [66]. However, based on a recent consensus on PIPAC, a combination of PIPAC with other surgical procedures was controversial among the expert panel [57]. Through PIPAC, Platin-based drugs are highly absorbed into the systemic circulation which may cause neurotoxicity in multiple PIPAC cycles or with prior platin-based chemotherapy [33, 59].

Comparison of different methods of intraperitoneal chemotherapy

At the end of the PIPAC, chemotherapy droplets are left in place; however, considering HIPEC the chemotherapy solution is pulled out. The brief exposure of chemotherapy in HIPEC results in lower absorption as well as decreased systemic toxicity. Moreover, unless HIPEC, PIPAC is performed by a minimally invasive method that can be repeated [33].

A systematic review of preclinical studies on peritoneal dissemination of different origins revealed that PIPAC is safe and provides better drug distribution and concentration into the peritoneum in comparison with traditional intraperitoneal chemotherapy by lavage [69]. Regardless of the type, intraoperative chemotherapy is associated with potential complications. For instance, a meta-analysis of gastric cancer patients has shown that intraperitoneal chemotherapy is associated with intra-abdominal abscess formation, fever, and bone marrow suppression [70]. Frassini et al. systematically reviewed the complications following HIPEC, PIPAC, and NIPEC; based on the Clavien-Dindo classification, the occurrence of grade III and IV side effects was found to be 5.5%, 5.1%, and 6.2%, respectively [18].

Future of intraperitoneal chemotherapy for pancreatic cancer

An ongoing phase II-III clinical trial (NCT03251365) studying HIPEC with gemcitabine following the CRS for pancreatic cancer is estimated to be completed in December 2024 [18]. A phase III RCT (UMIN000027229/jRCTs051180199) is in progress which will address the controversies regarding the safety and therapeutic effects of intraperitoneal chemotherapy in PDAC with peritoneal dissemination [25]. Clinical studies have shown the advantages of intraperitoneal immunotherapy for patients with malignant ascites and peritoneal metastasis from various cancer types such as PDAC [71–73]. Recently, 3DNA nanocarriers have been used for more effective and selective intraperitoneal drug delivery in a mice model of PDAC [74].

Conclusions

Regarding pancreatic cancer, recent studies have examined the effectiveness and optimal therapeutic regimens of intraperitoneal anticancer treatments. Despite low safety concerns based on a small phase II/III randomized clinical trial, current evidence on the efficacy of HIPEC for pancreatic cancer is limited since most studies are case reports and case series with a low sample size. Therefore, intraperitoneal chemotherapy in the management of PDAC has unclear long-term outcomes [18]. Based on the recent phase II/III randomized clinical trial, CRS/HIPEC shows similar survival and complication rates in comparison with complete resection alone. However, there is still a lack of evidence on the benefits of these approaches for the overall survival of patients with pancreatic cancer. Well-designed Phase I and II studies should be conducted before a Phase III study to determine the safety and effectiveness of different intraperitoneal chemotherapies in pancreatic cancer to have more realistic perspective on the future of these approaches for pancreatic carcinomas.

Abbreviations

CRS/HIPEC	Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy
NIPEC	Normothermic Intraperitoneal Chemotherapy
PIPAC	Pressurized Intraperitoneal Aerosol Chemotherapy
PDAC	Pancreatic Ductal Adenocarcinoma
OS	Overall Survival
L-IPC	Liquid Intraperitoneal Chemotherapy
5-FU	5-Fluorouracil
I.p.	Intraperitoneal
I.v.	Intravenous
CA 19 – 9	Carbohydrate Antigen 19 – 9
PFS	Progression-Free Survival
PM	Peritoneal Metastasis
GEM	Gemcitabine
PTX	Paclitaxel
Nab-PTX	Nanoparticle Albumin-Bound-Paclitaxel
CART	Concentrated Ascites Reinfusion Therapy
PCI	Peritoneal Carcinomatosis Index
PMP	Pseudomyxoma Peritonei
DFS	Disease-Free Survival
IRE	Irreversible Electroporation
IORT	Intraoperative Radiation Therapy
MMC	Mitomycin C
CIS	Cisplatin
Oxa	Oxaliplatin
NGS	Next Generation Sequencing
Dox	Doxorubicin

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Declarations

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