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EDITORIAL – PERITONEAL SURFACE MALIGNANCY

# Is PIPAC a New Summit for Peritoneal Disease Treatment or are we Lost in the Snowstorm?

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In this single-institution retrospective study of 144 patients with gastric cancer undergoing attempted pressurized intraperitoneal aerosol chemotherapy (PIPAC), the authors report short-term surgical and long-term oncologic outcomes and attempt to identify variables associated with overall survival (OS).[1] All the typical limitations regarding selection bias apply, but there are several findings of importance for this relatively novel procedure. First, the 8% inability to access the abdominal cavity is important for risk–benefit considerations in selecting PIPAC as a treatment option. Second, the procedure appears safe, with a low reported morbidity and mortality rate. Third, this operation is no panacea, with a median OS of 11 months, which is consistent with reports of OS in gastric cancer patients with peritoneal disease treated with systemic chemotherapy treatment alone. Notably, there are few reports of this size for PIPAC and an almost complete lack of clinical trials.

There are multiple animal study comparisons of pressurized versus non-pressurized intraperitoneal chemotherapy, suggesting better distribution and tissue penetration. The title of this editorial will be lost on those who have not seen the snow-storm appearance of a PIPAC procedure, but we should temper our enthusiasm for the newest and seemingly most technologically advanced surgery. Similar to other discussions of regional therapy, there are many theoretical benefits, including the potential for repeated administration, a minimally invasive approach, coordination with systemic therapy, and limited systemic exposure. PIPAC was first reported in humans in 2014, and the short answer is that the benefits to date remain theoretical. Phase I data exist helping establish appropriate dosing of cisplatin and doxorubicin.[2] There are multiple retrospective reviews with median OS rates extending up to 19 months.[3] The clinical trials are less favorable and in a single-arm phase II study of PIPAC administered every 6 weeks, median OS was only 7 months.[4]

Most retrospective studies are susceptible to criticism based on the selection of patients with favorable outcomes. However, patients in this study had high-volume disease, with 64% having a peritoneal carcinomatosis index (PCI) score of $\geq$12 and a median ascites volume of 750 mL. Ten percent of patients did not receive systemic chemotherapy before PIPAC. We are all looking for a procedure to reduce peritoneal disease prior to embarking on gastrectomy, with or without cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC); however, only 7% of the patients in this study were candidates for gastrectomy and HIPEC.

The safety of this procedure, in combination with the reported low complication rate, could allow for PIPAC as a safe platform to incorporate targeted or immunotherapy in combination with systemic therapy. A phase I multi-institutional trial of oxaliplatin PIPAC in combination with nivolumab is ongoing.[5] In recognition, and perhaps frustration, the authors strongly acknowledge both the limitations of their retrospective review and also the urgent need for randomized trials against standard of care systemic chemotherapy. A randomized phase II trial of PIPAC in combination with systemic therapy compared with systemic chemotherapy only is attempting to address PIPAC as a potential treatment standard.[6] The authors have provided an update in the discussion that unfortunately enrollment on this trial has not commenced.



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Rather than accept the limitations of retrospective reviews, and in recognition of the slow improvement in survival with systemic therapy, we should persist in calling for randomized trials of regional versus systemic therapy. There are multiple candidates to choose from, such as laparoscopic HIPEC, intraperitoneal paclitaxel, bidirectional intraperitoneal and systemic chemotherapy, and, now, PIPAC.

The authors are to be congratulated for investigating the most common site of metastatic disease and the most common site of recurrence after potentially curative resection. Patients with peritoneal disease have inferior outcomes to other disease sites, perhaps due to limitations in chemotherapy penetration within the abdominal cavity. Regional therapy may or may not be the answer here, and the authors of the current study are sufficiently cautious in interpreting their results. There are also important quality-of-life issues as peritoneal disease can create a tremendous symptom burden with ascites and malignant bowel obstruction. Not every endpoint in a trial is a survival outcome and we should include quality-of-life measures focused on obstruction in our future trials. Regardless, the next step is clear and we will all need to continue calling for a comparative study with standard of care systemic therapy.

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