



## Don't Call It a Comeback—HIPEC for Gastric Cancer

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With the recent negative studies of hyperthermic intraperitoneal chemotherapy (HIPEC) in colorectal cancer, HIPEC may seem to be up against the ropes in terms of clinical efficacy. This boxer analogy, and HIPEC, reminds me of the 1991 music video “Mama Said Knock You Out,” which features LL Cool J in a boxing ring. The song famously, at least for my generation, begins with “don't call it a comeback, I been here for years”. HIPEC is not a new treatment modality for gastric cancer, being utilized and investigated for over 35 years. There are now dated reviews of HIPEC as adjuvant therapy for high-risk disease, and also for established peritoneal disease, with the finding of improved survival.<sup>1–4</sup> The systematic review and meta-analysis by Martins et al. provides a modern analysis of the potential benefit that HIPEC adds to cytoreductive surgery (CRS) with the inclusion of studies from 2011 and 2019, as well as studies from the 1980s and 1990s.<sup>5</sup> We do not need to reminisce about these older studies like the golden age of hip hop. There are a few recent and ongoing trials of intraperitoneal therapy for gastric cancer that we should highlight and discuss. The first is the recently reported GASTRIPEC trial from ESMO 2021, a randomized trial comparing CRS with CRS + HIPEC.<sup>6</sup> Although awaiting publication, the study was terminated early owing to slow accrual and limited by a dropout rate of 52% owing to tumor progression and unresectable disease. There was no difference in median overall survival (OS); however, there was a statistically significant increase in median OS

for those undergoing complete cytoreduction (CCR = 0) and in progression-free survival for those undergoing HIPEC in addition to CRS.

One strength of this systematic review, and the authors are to be congratulated for addressing an important yet controversial topic in gastric cancer treatment, may be the inclusion of 5-year OS as an outcome measure.<sup>5</sup> Median survival rates may not be the best outcome based on the small differences in many studies, but perhaps also based on patients' goals of care for this operation. Having consented many patients for this surgery, patients often state the goal of obtaining long-term survival. For an operation that probably takes 4–6 months to recover from, the potential for 3- and 5-year OS seems like a much better outcome measure than an improvement in median survival rates. Notably, the accompanying article reports a 5-year OS rate three times higher for CRS + HIPEC than for CRS alone.<sup>5</sup> In the GASTRIPEC study, although median OS was not significantly different, and certainly limited by the small patient numbers, the 5-year OS rate appeared to be approximately 10% in the HIPEC arm, and 0% in the non-HIPEC arm.<sup>6</sup> We have also recently reported a small phase II trial of CRS + HIPEC with a 3-year OS rate of 28%, and hope to report on the 5-year OS rate soon.<sup>7</sup>

Importantly, the authors also report no significant difference in complication rates with the addition of HIPEC to CRS.<sup>5</sup> Other studies that support this finding include the interim safety analysis of the GASTRICHIP trial and the results of the GASTRIPEC trial. Interim safety results of 200 patients enrolled in the GASTRICHIP trial, presented at the 2nd Congress of the International Society for the Study of Pleural and Peritoneum 2021, reported no difference in morbidity for perfusion with oxaliplatin over 30 min in combination with intravenous 5-FU-leucovorin. In the GASTRIPEC trial, there was no increase in morbidity and mortality with HIPEC using mitomycin and cisplatin for 60 min.<sup>6</sup>

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The authors are also correct in that there are no published national guidelines. The current National Comprehensive Cancer Network Guidelines comment that “HIPEC may be a therapeutic alternative for carefully selected stage IV patients in the setting of ongoing clinical trials and is under further investigation.”<sup>8</sup> In addition to the Peritoneal Surface Oncology Group International recommendations, there are also the Chicago Consensus Guidelines summarizing regional therapy for gastric peritoneal disease.<sup>9</sup> In Supplementary Table 3 from the current review, the authors provide a summary of the ongoing randomized controlled trials (RCTs) in this setting.<sup>5</sup> The much anticipated PERISCOPE II trial comparing standard of care systemic chemotherapy versus HIPEC is currently at 62 participants, and powered for 226. I would also like to highlight the GOETH Italian trial (NCT03917173) and, although not a HIPEC trial, the Phoenix-GC2 trial investigating adjuvant intraperitoneal paclitaxel for patients at high risk of peritoneal recurrence.<sup>10</sup>

Getting back to the LL Cool J analogy, the song supposedly was inspired by LL being challenged by several up-and-coming rappers. HIPEC for gastric cancer may need its own redemption song soon as recent challengers include intraperitoneal paclitaxel, laparoscopic HIPEC, PIPAC, hyperthermic PIPAC, and now electrostatic PIPAC. The most important take-home point, and one that is supported by studies such as the current review by Martins et al., is that surgery needs to be consistently reevaluated alongside improvements in systemic therapy. As immunotherapy and targeted therapy continue to provide improvement in survival, surgery should be included as the only known cure for gastric cancer and investigated to identify its appropriate place in the treatment of stage IV disease.

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