

# Prophylactic hyperthermic intraperitoneal chemotherapy can be considered in the management of advanced gastric cancer

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We read with interest the article by Dehal, Smith and Nash (1), intitled “Cytoreductive surgery and intraperitoneal chemotherapy: an evidence-based review—past, present and future” and, also congratulating them for the comprehensive review performed, we believe that, the role that hyperthermic intraperitoneal chemotherapy (HIPEC) can play in the prophylaxis of peritoneal carcinomatosis (PC) in patients with gastric cancer, should be emphasized.

The peritoneal surface is commonly involved in gastric cancer. It has been estimated that a percentage of patients ranging from 15% to 50% have a peritoneal disease at the surgical exploration, especially when there is serosal involvement by the tumor (2). PC, once established, is associated with poor survival, and, as reported by Dehal *et al.* (1), also the results of cytoreductive surgery (CRS) plus HIPEC aren't so promising as in other peritoneal malignancies, probably because gastric cancer have a more aggressive biological behavior than other malignancies. This concept can explain because, as reported by Canbay *et al.* (3), the cut off of peritoneal cancer index (PCI) to obtain an increased survival, in these patients, should not be higher than 6 and therefore lower than in the patients with PC of colorectal origin.

In a recent study (4) performed on 1,108 patients, 49.6% ( $\pm 5.4\%$ ) of the patients submitted to R0 D2 gastrectomy were diagnosed with tumour recurrence and 15.5% ( $\pm 1.8\%$ ) developed metachronous PC after a median time of 17.7 months (range, 15.1–20.3 months) after surgery, resulting in a tumour related mortality of 100% with a median survival of 3.0 months (range, 2.1–4.0 months).

Independent risk factors for the development of metachronous PC were serosa positive T-category, nodal positive-status, signet cell and undifferentiated gradings (G3/G4) (4).

This behavior can be explained with the “tumor cell entrapment hypothesis” (5), according to which, the manipulation of the cancer-bearing organ, transection of lymphatic channels, and blood loss from the cancer specimen result in free intraperitoneal cancer cells, that will be lethal in 100% of cases; the other way of peritoneal dissemination is the spontaneous exfoliation of primary tumor, event more frequent in tumors involving serosal surface. These concepts represent the rationale to use the locoregional approach, as CRS plus HIPEC, in the prevention of peritoneal diffusion of gastric cancer.

Many institutional reports have been carried out exploring the use of perioperative HIPEC as an adjuvant treatment for this subgroup of patients. Yan *et al.* in 2007 (6) have published a systemic review and meta-analysis that compared surgery for primary gastric cancer combined with intraperitoneal chemotherapy versus surgery alone. The meta-analysis showed that there was a significant improvement in survival with the use of HIPEC or HIPEC plus early postoperative intraperitoneal chemotherapy (EPIC), while there was no statistical significant improvement with normothermic intraoperative intraperitoneal chemotherapy (NIIC), EPIC alone or delayed postoperative intraperitoneal chemotherapy (DPIC).

A more recent meta-analysis (7), based on the evaluation of 280 studies, evaluated the benefits of HIPEC for patients

with serosal invasion in gastric cancer.

The results of this report indicated that HIPEC could potentially allow a better prognosis in patients who underwent resection for advanced gastric cancer compared to the control group, without statistically significant differences regarding adverse events.

We have published (8) the results of our initial experience in this topic, achieved in 12 patients with advanced gastric cancer (T3/4), having a minimal follow-up of 60 months. In all cases was performed a total gastrectomy with D2 lymphadenectomy associated in four cases to splenectomy. After intraoperative histologic examination, to confirm the serosal involved, all patients were submitted to HIPEC with the closed-abdomen technique. We have recorded a good median survival (24 months), higher than historically reported in the literature (9). However we think that the most important result is the very small number of peritoneal recurrences that we have recorded, 8.3% *vs.* about 50% reported in the literature (10). This result can be attributed to HIPEC that perform a washing of the intraperitoneal free tumor emboli and damages the cancer cells or micrometastases thanks to the synergistic effect of the heat and chemotherapeutic drugs.

In light of our experience and supported by literature data (6,7), we retain that HIPEC has a potential role in the prevention of gastric carcinomatosis. Certainly further studies are needed on a large scale for validate this new but promising approach.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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