

## How much “surgical effort” should be added to HIPEC?

Quanto esforço cirúrgico deveria ser associado à HIPEC?

Thales Paulo Batista<sup>1</sup>, Levon Badiglian-Filho<sup>2</sup>, Glauco Baiocchi<sup>2</sup>

Hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a main comprehensive treatment of malignancies on the peritoneal surface and thus, it has been considered a promising treatment option for a peritoneal-borne disease such as ovarian cancer. The rationale for using HIPEC is based on the direct cytotoxicity of hyperthermia for malignant cells, the enhancement of this cytotoxicity by anticancer drugs, and the pharmacokinetic advantages of the i.p. route for chemotherapy. It could also reduce the mechanisms of cellular chemo-resistance and induce an efficient anticancer immune response. This technique is delivered intraoperatively, avoiding the need for implantation of peritoneal access devices and thereby reducing catheter-related morbidity and tolerance issues. Despite these potential advantages of HIPEC, there was no clear evidence from randomized controlled trials to advocate this approach as a standard therapy for patients suffering from advanced ovarian cancer.

Recently, van Driel et al.<sup>(1)</sup> presented the first well-designed study addressed to provide some clarity to this issue. In this multicenter, open-label, phase III trial, 245 patients with at least stable disease after three cycles of neoadjuvant chemotherapy (NACT) were randomly assigned to undergo interval cytoreductive surgery with or without HIPEC (i.e.: CDDP 100mg/m<sup>2</sup>, for 90 minutes at 40°C). Three further cycles of carboplatin and paclitaxel were given postoperatively. With this comprehensive approach, the authors found a median RFS of 14.2 vs. 10.7 months favoring the HIPEC group (HR= 0.66, 95% CI 0.50–0.87; p=0.003). Median OS was 45.7 months in the HIPEC group and 33.9 months in the non-HIPEC group (HR=0.67, 95% CI 0.48–0.94; p=0.02). Also, the incidence of major adverse events was similar in the two groups and no significant differences in health-related quality-of-life outcomes over time were observed.

1. Department of Surgery/Oncology, Instituto de Medicina Integral Professor Fernando Figueira, Recife, PE, Brazil; Department of Surgery, Universidade Federal de Pernambuco, Recife, PE, Brazil.

2. Department of Gynecology, A.C. Camargo Cancer Center, São Paulo, SP, Brazil.

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**Corresponding author:** Thales P. Batista. Rua Pio IX, 435, Ap. 701/B - Recife, PE, Brazil. Phone: +55 (81) 98886-1203, Zip code: 50710-265.

E-mail: t.paulo@outlook.com

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As pointed by Spriggs and Zivanovic in an accompanying editorial survival outcomes in that trial were consistent with previous trials such as the EORTC55971 study, but were shorter than currently expected. No matter what this may result from enrollment of high tumor burden patients, the “surgical effort” appeared to be low based on the duration of procedures. Herein, the median duration of surgery was 192 minutes (IQR, 153 to 251) vs. 338 minutes (IQR, 299 to 426), despite surgery has been extended by about 2 hours due to addition of HIPEC.<sup>(1)</sup> These lengths of surgeries were lower than what were reported in the NACT group of the SCORPION and JCOG0602 trials (i.e.: median duration of 275 and 302 minutes; respectively), for example;<sup>(3)</sup> whereas the survival outcomes were quite similar to those reported in the feasibility study of NACT followed by interval cytoreductive surgery named JCOG0206 trial (i.e.: PFS and OS of 14 and 45 months, respectively), in which the median operative time was 330 (130–735) minutes.<sup>(4)</sup> In our ongoing trial exploring HIPEC as a short-course (i.e.: 30 minutes) regimen in a similar study design,<sup>(5)</sup> the current operative time is 430 (235–865) minutes, with a median time spent during perfusion of only 50.5 minutes. Previously, our experience with NACT (including patients with suboptimal CRS) had reached median PFS and OS of 17.6 and 41.6 months, respectively.<sup>(6)</sup>

Despite all the enthusiasm arising from the publication of this very important study,<sup>(7)</sup> we feel that a further “surgical effort” should be added to a comprehensive treatment involving HIPEC, since the surgical component of the *binomium* CRS plus HIPEC is the well-known element that most contributes to improve outcomes in ovarian cancer.<sup>(8)</sup> Additional skepticism from us involves the possibility of increased morbidity and mortality with the use of a 90 minutes in length regimen of HIPEC in less experienced centers.

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## Current status and future of peritoneal surface diseases

Estado atual e futuro das neoplasias peritoneais

Victor J Verwaal<sup>1</sup>, Mette Møller Sørensen<sup>1</sup>

In the last 20 years the treatment of peritoneal surface malignancies gained a special attention of the medical and surgical world. Previously peritoneal surface malignancies were seen as metastasized disease which could not be surgically removed due to technical difficulties and wouldn't be treated with systemic chemotherapy because of the leak of measurable disease. In 2003 the first randomized trial was published on the treatment of colorectal peritoneal metastasis in a more active way.<sup>(1,2)</sup> This trial showed a survival benefit of cytoreductive surgery with hyperthermic intra peritoneal chemotherapy followed by systemic chemotherapy when compared to systemic chemotherapy alone. This study was followed by a large number of studies which showed an even further improvement of the survival than published in the randomized trial. Most recently another randomized trial comparing systemic chemotherapy followed by cytoreduction and hyperthermic intraperitoneal chemotherapy to systemic chemotherapy followed by cytoreduction without hyperthermic intra peritoneal chemotherapy doubted the additional effect of hyperthermic intra peritoneal chemotherapy in patients with peritoneal metastasis of colorectal origin.<sup>(3)</sup> Whatever way one looks at these results it is clear from both trials that a complete cytoreduction is the cornerstone of the treatment of peritoneal metastasis.

Ovarian carcinoma is probably the most classic tumour with spreading to the peritoneum. Traditionally this disease is treated with debulking and systemic chemotherapy. Several studies showed that the completeness of the cytoreduction determines the outcome.<sup>(4)</sup> This year a randomized trial was published showing a benefit of adding hyperthermic intra peritoneal to the cytoreduction when combined with systemic chemotherapy.<sup>(5)</sup>

1. Department of Surgery, Colorectal Surgical Unit, Aarhus University Hospital, Aarhus, Denmark

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**Corresponding author:** E-mail: v.verwaal@nki.nl.

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In both above described situations it is clear that cytoreduction, thus the complete resection of all visible disease is key to success. Hyper thermic intra peritoneal chemotherapy give an extra benefit in ovarian cancer patients with peritoneal metastasis and give a benefit in colorectal cancer effected with peritoneal metastasis in the med range disease load. Probably the difference between the two diseases is that ovarian cancer is much more chemo sensitive to the current known chemotherapy agents and we are leaking really effective chemotherapy for colorectal cancer.

Systemic chemotherapy might help to improve the survival combined with cytoreduction, but we are leaking a trial comparing cytoreduction with and without systemic chemotherapy. If we compare this situation to liver metastases surgery one should doubt whether chemotherapy give a benefit to resection of metastatic disease because most studies of adjuvant chemotherapy after liver metastasis do not have a overwhelming result.<sup>(6)</sup>

To conclude, surgical resection of peritoneal metastasis is the key, all treatment around it is whether it is intra peritoneal chemotherapy or systemic chemotherapy has not established it final position. However it is mostly likely that the combination of everything is give the best results for the patients.

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