Role of aggressive surgery for peritoneal metastases

Dominique Elias *, *Frédéric Dumont, Charles Honoré, Diane Goéré*

Gustave Roussy, Cancer Campus, Grand Paris, France

1. Peritoneal cavity: a particular site of metastasis

The spatial conformation and the poor prognosis of peritoneal metastases (PM) make it an original entity. Once contaminated by tumour cells, disease spread is rapid and multidirectional over a surface that is equal to the body surface area in m^2. The prognosis of PM is poorer than that of metastatic spread elsewhere; patients with colorectal metastases treated with chemotherapy and targeted therapies have a median survival of 15 months with PM versus 21 months without PM ($P < 0.001$) [1]. The presence of PM is thus traditionally deemed a fatal event.

Complete cytoreductive surgery (CCRS) resects all visible peritoneal deposits, and the remaining invisible disease is subsequently treated with a high local concentration of chemotherapy potentiated by hyperthermia (HIPEC) in one session. This aggressive surgery can therefore be proposed only for disease confined to the peritoneum. According to the origin of the disease, such treatment is administered in two out of three colorectal carcinomas, one out of three gastric carcinomas, seven out of ten ovarian carcinomas, nine out of ten pseudomyxomas and eight out of ten mesotheliomas.

2. Aggressive surgery as a state of the art: pseudomyxoma and mesothelioma

CCRS + HIPEC is considered the gold standard treatment for these two peritoneal malignancies. In a retrospective multicentric registry, including 2298 patients with pseudomyxoma from 16 specialised units using this combined approach [2], median survival was 16.3 years and 10-year survival was 63%. Mortality was 2%, and major complications occurred in 24%. The main prognostic factors in the multivariate analysis were the histological subtype, a high extent score and no HIPEC. CCRS achieved the best outcome. Similar conclusions were drawn for malignant mesothelioma in a multi-institutional registry including 405 patients [3] in which only 46% underwent CCRS. Median survival was 53 months and 5-year survival was 47%.

3. Aggressive surgery as a new therapeutic approach: colorectal carcinoma

3.1. *Long-term results after CCRS plus HIPEC*

Ten years ago the results of a randomised study [4] – which included 105 patients treated for colorectal PM (systemic chemotherapy versus with surgery plus HIPEC) – demonstrated significantly prolonged survival in patients treated with surgery plus HIPEC, with a median survival twofold higher ($P = 0.03$), although CCRS was achieved in only 38% of cases. This was confirmed in another study [5] comparing two similar groups in terms of the main patient characteristics. All patients underwent a laparotomy and had resectable PM; 48 patients were treated with CCRS + HIPEC in one centre, and 48 were treated in five other centres without HIPEC. After a minimal follow-up of 63 months, 5-year overall survival was 51% in the CCRS + HIPEC group and 13% for patients in the no-HIPEC group ($P < 0.05$).

Long-term results of primary CCRS + HIPEC demonstrated that definitive cure of PM was possible in 16% of the 93 patients treated between 1995 and 2004 [6], a rate which is close to that obtained with a similar long follow-up after hepatectomy for liver metastases (LM). Median survival was 36 months at that time, but attained 48 months in 2011 [7], emphasising a learning-curve effect and better patient selection.

CCRS + HIPEC is wrongly reputed to cause excessive morbidity, but in specialised centres and in selected patients mortality is lower than 5% and grade 3–4 morbidity is lower than 30%.

Aggressive surgery plus HIPEC is also considered costly, but its clear superiority over the usual palliative therapies in terms of QALY (cost-efficacy) has been demonstrated.

Regarding prognostic factors, the results of the French Registry – which analysed 523 patients treated with CCRS + HIPEC – showed that the extent of PM (scored with the peritoneal cancer index, PCI) is the main prognostic factor [8]. There were no survivors when the PCI exceeded 20, and we now consider a PCI above 20 to be a contraindication.

* *Corresponding author:* Address: Gustave Roussy, 114 Rue Edouard Vaillant, 94807 Villejuif, France. Tel.: +33 1 42 11 40 85.
E-mail address: dominique.elias@gustaveroussy.fr (D. Elias).
1359-6349/$ - see front matter
http://dx.doi.org/10.1016/j.ejcsup.2013.07.036

3.2. *Role of complete cytoreductive surgery alone*

No randomised study has compared CCRS to systemic chemotherapy. The results of four retrospective series provide some elements of response: median survival was 28 months, with 5-year survival at 24%, showing clear but limited superiority over systemic chemotherapy alone. In contrast, an incomplete resection (R2) afforded no advantage, with survival rates similar to those reported with chemotherapy alone [8]. In conclusion, CCRS benefits patients with limited PM and a good general status.

3.3. *Role of hyperthermic intraperitoneal chemotherapy*

No randomised study has been published to date. We are awaiting the results of Prodige 7, the French randomised trial comparing the survival of patients treated with CCRS + HIPEC to that of patients treated with CCRS alone, whose accrual was recently completed ($n = 260$). This study will define the real impact of HIPEC.

3.4. *Future*

As this aggressive surgery gives far better results for limited PM, it should be used mainly to treat patients at a very early stage, but early diagnosis of PM cannot be done by clinical or imaging examinations. Only systematic second-look surgery (SLS) can detect PM early, but this aggressive approach should be proposed exclusively in patients at high risk of PM. In such patients (limited PM resected with the primary, a history of ovarian metastases and a perforated primary tumour) with no preoperative evidence of PM, SLS has allowed us to find macroscopic PM in 55% of cases [9], and to treat PM earlier with CCRS + HIPEC. A randomised multicentric trial (Prophylochip) comparing the standard treatment (follow-up) in these high-risk patients to the new one (second-look + HIPEC) is ongoing.

4. CCRS + HIPEC to treat PM of other origins

Indications are in progress for ovarian-, gastric-, NET- and rare disease-derived PM. The initial results of CCRS + HIPEC were disappointing, but progress in techniques and in indications in ongoing prospective trials is giving promising results.

5. Conclusion

CCRS + HIPEC yields long-term survival in patients with PM. No clear and widely accepted definition of resectable PM exists. However, we postulate that when the patient has a good general status and when the extent of PM is limited, without extraperitoneal disease, this approach is beneficial.

Conflict of interest statement

None declared.

REFERENCES

[1] Klaver YL, Simkens LH, Lemmens VE, Koopman M, Teerenstra S, Bleichrodt RP, et al. Outcomes of colorectal cancer patients with peritoneal carcinomatosis treated with chemotherapy with and without targeted therapy. Eur J Surg Oncol 2012;38:617–23.

[2] Chua T, Moran B, Sugarbaker P, Levine E, Glehen O, Gilly F, et al. Early and long-term outcome data on 2298 patients with pseudomyxoma peritonei of appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol 2012;30:2449–56.

[3] Yan TD, Deraco M, Baratti D, Kusamara S, Elias D, Glehen O, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 2009;27:6237–42.

[4] Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21:3737–43.

[5] Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol 2009;27:681–5.

[6] Goéré D, Malka D, Tzanis D, Gava V, Boige V, Eveno C, et al. Is there a possibility of cure in patients with colorectal peritoneal carcinomatosis amenable to complete cytoreductive surgery and intraperitoneal chemotherapy? Annals of Surgery 2013;257:1065–71.

[7] Quenet F, Goéré D, Mehta SS, Roca L, Dumont F, Hessissen M, et al. Results of two bi-institutional prospective studies using intraperitoneal oxaliplatin with or without irinotecan during HIPEC after cytoreductive surgery for colorectal carcinomatosis. Ann Surg 2011;254:294–301.

[8] Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63–8.

[9] Elias D, Honoré C, Dumont F, Ducreux M, Boige V, Malka D, et al. Results of a systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. Ann Surg 2011;254:289–93.