Editorial Commentary

Carcinomatosis in gastric cancer: the potential for cytoreductive surgery and intraperitoneal chemotherapy

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In gastric cancer, the finding of a positive peritoneal cytology is considered stage IV metastatic disease. Such patients behave similarly to patients with distant metastatic disease (1). Frank peritoneal carcinomatosis carries even a worse prognosis. In a recent randomized trial comparing up front surgery for patients with metastatic gastric cancer to treatment with chemotherapy alone without surgery, including patients with limited peritoneal disease or disease limited to retroperitoneal lymph nodes, initial surgery resulted in no survival benefit compared to chemotherapy treatment alone (2). Survival trended inferior with poorer therapy tolerance in patients undergoing surgery. The application of aggressive surgical intervention in patients with peritoneal confined metastases including cytoreductive surgery and gastrectomy remains a subject of considerable and ongoing controversy.

Cytoreductive surgery is done ideally to achieve either little or no residual disease remaining. Extent of peritoneal disease is most commonly measured by the peritoneal carcinomatosis index (3). Peritoneal disease is scored in 13 locations in the peritoneal cavity with lesions scored as 0–3. Lesions with a zero score indicate that none are visible, 1 are lesions up to 0.5 cm, 2 are lesions up to 5 cm, and 3 are lesions >5 cm. Scores can range from 0 to a maximum score of 39.

Hyperthermic intraperitoneal chemotherapy (HIPEC) attempts to exploit the potential enhanced direct tumor exposure to chemotherapeutic agents and may also lead to exposure to much higher levels of drug than achievable with systemic administration. Hyperthermia may also increase the tumoricidal effect of administered agents.

Bonnet and colleagues now report one of the largest retrospective series of patients treated with cytoreductive surgery for gastric cancer peritoneal disease with or without the administration of HIPEC (4). They observed a potential disease free and overall survival benefit for such therapy in appropriate patients with acceptable surgical morbidity. Of 277 patients studied, 180 underwent cytoreductive surgery plus HIPEC and 97 patients underwent surgery alone. Patients were treated from 1989 to 2014 at 19 French centers, and patients were required to have undergone surgery leading to either CC-0 (no residual disease) or CC-01 (<2.5 cm residual peritoneal nodules). The non HIPEC patients tended to be older, fewer received any chemotherapy prior to surgery, and had a lower baseline peritoneal carcinomatosis index. Median overall survival favored HIPEC (18.6 months) compared to no HIPEC (11.4 months) and 3- and 5-year overall survival also favored HIPEC (26% and 20%) over no HIPEC (11% and 6%). The authors concluded that cytoreductive surgery followed by intraperitoneal chemotherapy could be a therapy option in appropriately selected patients able to undergo complete or near complete surgical debulking therapy.

The strengths of this series include the mandate for consistent and high quality cytoreductive surgery, the comparison of a hyperthermic chemotherapy treated group to patients undergoing cytoreductive surgery alone, and the

attempt to overcome imbalances in demographics in the therapy groups using a weighted propensity score analysis. Weaknesses include the conduct of this analysis over several decades which could have impacted on patient evaluation including imaging technology; potential variation in the use of systemic chemotherapy regimens over time; and potential evolution over time of surgical techniques. Arguably more favorable patients were selected as it was required that cytoreduction be achieved to CC 0-1.

Although all subgroups seemed to benefit with the inclusion of hyperthermic chemotherapy, the greatest benefit appeared to be in the subset with baseline carcinomatosis index between 1–6, but any speculation about subset benefits is at best speculative and hypothesis generating.

Most series of intraperitoneal chemotherapy and cytoreductive surgery in gastric cancer are retrospective, and consequently are subject to patient selection bias and ideally require validation in controlled randomized clinical trials. A recent meta-analysis evaluated 21 retrospective series and 11 controlled trials indicated a potential survival benefit of cytoreductive surgery combined with HIPEC (5). The recent Phoenix-GC trial from Japan randomized 2:1 patients with carcinomatosis and the gastric primary in place to intraperitoneal chemotherapy with paclitaxel combined with systemic S-1 and paclitaxel, to chemotherapy alone with S-1 and cisplatin (6). There was no difference in overall median survival with (17.7 months) or without IP chemotherapy (15.2 months), but 3-year overall survival trended to favor of IP chemotherapy (21.9% *vs.* 6%). Ongoing randomized trials include PERISCOPE, randomizing patients with or without positive cytology or peritoneal disease to undergo chemotherapy alone or cytoreductive surgery plus HIPEC (NCT00348250); GASTRICCHIP treating resectable gastric cancer with or without positive cytology to surgery with or without HIPEC (NCT01882933); and GASTRIPEC, comparing patients with peritoneal carcinomatosis who undergo cytoreductive surgery with or without HIPEC (NCT02158988).

Who should undergo gastrectomy and cytoreductive surgery for limited peritoneal disease, or positive cytology? Some argue that chemo responsive patients may fare better, with selection of patients for aggressive therapy if there is either response or clearance of a peritoneal cytology and peritoneal disease after initial chemotherapy, or at least significant response to chemotherapy prior to considering heroic surgery. It is hoped that ongoing randomized trials will help clarify the role of gastrectomy, cytoreductive surgery, and use or not of HIPEC in managing these patients, as well as comparisons to conventional palliative systemic chemotherapy alone.

The results from CYTO-CHIP are provocative and suggest a benefit in patients with a favorable carcinomatosis index and in whom cytoreduction to CC 0-1 can be achieved. More effective systemic chemotherapy, however, may also question the approach of cytoreductive surgery. In ovarian cancer, despite survival benefits in randomized clinical trials, the use if intraperitoneal chemotherapy has largely not been adapted given improvements in survival with the development of more effective systemic chemotherapy regimens.

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Footnote

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