

Sitilo Experience on Peritoneal Carcinomatosis From Colorectal Cancer: Clinical Prognostic Features

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A multicentric prospective study has been carried on 69 patients affected by peritoneal carcinomatosis from colorectal cancer. Patients have been treated by cytoreductive surgery and intraoperative hyperthermic chemoperfusion. CC 0-1 has been achieved in 82%. Major morbidity and mortality was 21.7% and 2.9% respectively. Three-yrs overall survival was 26.7% for all series. Difference in survival evaluating CC 0-1 vs. CC 2 pts and PCI ≤ 10 vs. >10 was statistically significant. Evaluating only patients CC 0-1 and PCI ≤ 10 4-yrs overall survival risen up to 44.7%. A smaller subgroup of patients with a disease-free interval to peritoneal carcinomatosis ≥ 2 -yrs showed a 5-yrs disease-free survival of 50%. Conclusions: PCI ≤ 10 , complete or optimal cytoreduction feasibility have to be considered for the patients selection to the integrate treatment. Disease-free interval seems to be a powerful prognostic indicator and deserve to be better outlined in further studies.

Key Words: Peritoneal carcinomatosis, Peritonectomy, Hyperthermic chemoperfusion

An high number of colorectal cancer patients experience a peritoneal recurrence often as the only site of relapse. Recent studies on natural history of peritoneal carcinomatosis from colorectal adenocarcinoma show a median survival that does not exceed 7 months (1,2).

The combination of fluorouracil and leucovorin has been widely used to treat metastatic colorectal cancer with disappointing results. New promising molecules have been introduced in the clinical practice and the association of irinotecan, fluorouracil and leucovorin has recently achieved a 7 months of median progression-free survival with an overall survival of 14.8 months, mostly in patients with liver involvement (3).

As a matter of fact, in the last years it has been realized that some peritoneal carcinomatosis have to be considered a locoregional disease to be treated with locoregional better than systemic therapy. Sugarbaker introduced a new therapeutic approach with curative intent that obtained a wide diffusion in the surgical setting. It is based on the surgical cytoreduction (peritonectomy) of all visible disease followed by intraop-

erative hyperthermic chemoperfusion (IHCP) or early postoperative intraperitoneal chemotherapy (EPIC). Encouraging results were obtained in many phase II studies (4-8), the 3-year survival ranging from 22% up to 65%. Moreover a prospective randomized study has been recently carried out in the Netherland Cancer Institute strongly demonstrating the benefit of peritonectomy plus IHCP plus i.v. 5-FU and leucovorin vs. the conventional palliative surgery plus i.v. 5-FU and leucovorin (9).

Despite the increased survival, the wide range of results obtained with the integrated treatment suggests still open questions regarding patients selection and prognostic factors identification.

The Italian Society of Locoregional Treatments in Oncology (SITIO) started in 1996 a prospective study, still ongoing, on the treatment of peritoneal carcinomatosis from various intra-abdominal malignancies by peritonectomy and perioperative chemotherapy. The purpose of the present study is to evaluate the SITIO experience on peritoneal carcino-

matosis from colorectal primary focusing the impact of prognostic indicators on survival.

Patients and Methods

Sixty nine consecutive patients, who had undergone peritonectomy for treatment of colorectal carcinomatosis from Gennuary 1996 to October 2002 in four Italian istitutions, made up the study population. The surgical technique was described in details by Sugarbaker (10) and can be summarized as follows:

- peritoneal stripping from the cephalic portion of the right hemiabdominal wall and right subdiaphragm, together to peritonectomy of the Morrison's pouch.
- peritoneal stripping from the cephalic portion of the left hemiabdominal wall and left subdiaphragm;
- removal of the falciform and triangular ligaments of the liver and Glisson's capsule on the entire liver surface and cholecystectomy with peritoneal removal from the porta hepatis and lesser omentum
- omentectomy in continuity with the superficial layer of the transverse mesocolon and the anterior surface of the pancreas, followed by splenectomy;
- peritoneal stripping from the right and left caudal portion of the abdominal wall, from the bladder and iliac fossa preserving the ureters; resection of the sigmoid colon and mesosigmoid from the origin of inferior mesenteric artery;
- pelvic peritonectomy dividing the subperitoneal rectum and vagina in women to remove "en bloc" all the neoplastic tissue in the peritoneal "cul de sac"; closure of the vagina and colorectal anastomosis using EEA stapler after mobilization of the entire left colon;
- the operation is completed removing every visceral disease, most frequently the cecum and the right colon where the tumor implants usually develop large neoplastic plate involving the right parietocolic peritoneum. Resection of the gastric antrum due to the presence of tumor deposits may be necessary.

As completion of peritonectomy and before performing intestinal anastomosis, IHCP was carried out for 60-90 minutes at a temperature of 41.5-42.5°C in the abdomino-pelvic cavity, introducing into the perfusion circuit mitomycin-C (3.3mg/m²/L) and cisplatin (25mg/m²/L).

Clinical data have been recorded in a standard database form and evaluated by the same author. To study relationships between variables Chi (2) has been used. Survival analysis was performed with Kaplan-Meier's method and comparison of curves with the Log-rank test. Standard probability cut-off, $p \leq .05$, was chosen as significance level.

Results

The median age was 52 years (range 19-76). Many patients (75%) had been previously treated with adjuvant or palliative systemic chemotherapy, most of them with 5-fluorouracil and leucovorin and then cisplatin, leucovorin, mitomycin-C, oxaliplatin and irinotecan alone or in various associations. Twenty-five percent of the patients showed subocclusive symptoms at the time of hospitalization. The peritoneal cancer index (PCI), as described by Sugarbaker, ranged between 11 and 20 in 47% and was more than 20 in 19% of the patients.

The cytoreductive surgery was synchronous with the resection of the primary tumor in 29 patients (42%); total peritonectomy was performed in 12 cases (18%). A complete cytoreduction (CC-0) was achieved in 75%, optimal (CC-1) in 7%, while in 18% of the patients peritonectomy resulted in macroscopic residual tumor with nodules larger then 0.5cm (CC-2).

The IHCP was routinely performed except in 4 cases because of the bulky residual disease. The technique was open (Coliseum) in 85% of the procedures and closed in 15%, lasting 90 minutes in 68% and 60 minutes in the remnant 32%.

Morbidity was 21.7% and was directly correlated with the extension of cytoreduction (Chi square for trend .04). The most important events were represented by anastomotic leak (4.3%), perforation (2.9%) and sepsis (2.9%). Surgery was required in 40% of the complicated cases. Locoregional toxicity evaluated according to modified Ozols classification (11) (Tab I) was G1 in 21.7% of the patients, G2 in 1.4%, G3 in 1.4% and G4 in 2.8%. The observed systemic toxicity (WHO) was only hematologic G1 in 2.8% and G2 and G3 in 1.4%. No G4 toxicity was registered. Perioperative mortality was 2.9%.

The 3-year overall survival for the entire series was 26.7% with a median survival of 19 months. Evaluating only the patients that could be cytoreduced to CC-0-1 the 3-year survival raised to 31.3%. Synchronous resection of primary adenocarcinoma did

Table I - Modified Ozols classification of locoregional toxicity after intraperitoneal chemotherapy

Grade	Description
1	Abdominal pain after third postoperative day that requires analgesic drug administration (nonsteroidal anti-inflammatory drugs).
2	Abdominal pain after third postoperative day that requires major analgesic drug administration (morphine).
3	Abdominal pain resistant to all analgesic drug.
4	Leak or perforation

not modify overall and disease-free survival ($p = ns$).

No differences either in survival or in recurrent rate have been registered performing IHCP with the “open” vs. “closed” technique ($p = .08$) or modifying the duration of chemoperfusion from 60 to 90 minutes ($p = .07$). A PCI cut-off of 10 had a significant impact ($p = .02$) on survival which was 42% at three years ($PCI \leq 10$) vs. 23% ($PCI > 10$).

Evaluating patients with a low PCI (≤ 10) and complete or optimal cytoreduction (CC-0-1) vs. patients with a $PCI > 10$ and residual disease larger than 0.5cm (CC-2) the 4-years survival was 44.7% and 0% respectively ($p = .008$). In the first group the median survival was 28 months.

Finally we analyzed the influence of the disease free interval (DFI) between resection of primary tumor and the onset of peritoneal carcinomatosis: at the DFI cut-off of 24 months we found that a subgroup of patients (20% of the evaluable patients) with a DFI longer than 24 months showed 60% 5-year overall survival ($p = .04$) and 50% 5-years disease-free survival ($p = .01$).

The analysis of recurrence distribution pointed out that the incidence of relapses is still locoregional in 80% of the patients.

Discussion

Recent reports indicate that the development of peritoneal carcinomatosis follows its own rules that differ from that proper of metastatization. Nishimori (12) found that different cell lines from human gastric adenocarcinoma have a different aptitude to peritoneal spreading or hepatic metastatization depending on their biomolecular features; in particular the latter

appears to be controlled by more complex mechanisms than the former. Kanellos (13) noticed that the finding of free peritoneal cancer cells in patients submitted to curative resection for colorectal adenocarcinoma was correlated to the tumor depth while was not correlated to nodal status, grading and vascular or neural invasion, indicating that peritoneal carcinomatosis has an independent pathway from hematogenous metastasis.

It seems presumable that cancer cells lacking of the biological factors promoting the metastatization show a natural history characterized by an early peritoneal spread and that in these cases the peritoneal carcinomatosis has actually to be considered a locoregional disease (14).

When peritoneal carcinomatosis is established, the main prognostic indicator is the extent of the disease but even with a limited extent the median survival does not exceed 10 months.

A very recent randomized study (3) evaluated progression-free survival in patients with metastatic colorectal cancer treated by irinotecan, fluorouracil and leucovorin vs. fluorouracil and leucovorin vs. irinotecan alone. In the entry criteria no prior therapy for metastatic disease was permitted and more than 80% of the patients had liver metastasis as the only site of disease. Progression-free survival was 7.0 months for the first arm, 4.3 for the second and 4.2 for the irinotecan alone arm.

Zoetmulder⁹ randomly allocated patients with colorectal peritoneal carcinomatosis in two treatment arms: the first consisted in cytoreductive surgery and IHCP with mitomycin-C followed by systemic fluorouracil and leucovorin weekly for 6 months, and the second consisted in palliative surgery followed by the same systemic fluorouracil/leucovorin treatment. Kaplan-Meier survival analysis showed a mean sur-

vival of 21 months in the first arm and 10 months in the second. The study was stopped for ethical reasons.

Despite favourable results obtained with the intent to cure treatment in a number of phase II trials, survival time differs in a wide range and several prognostic factors have been advocated.

Sayag-Beaujard (15) treated in a phase II study 21 patients with resectable colorectal cancer and peritoneal carcinomatosis by cytoreductive surgery and IHCP with mitomycin C obtaining an overall median survival of 1 year. Considering only patients with malignant nodules less than 5 mm in diameter median survival raised to 26 months.

Pilati (16) reported 34 patients with colorectal peritoneal carcinomatosis treated by complete cytoreductive surgery and IHCP with mitomycin C and cisplatin. Median survival time was 18 months. He pointed out that patients with well or moderately differentiated adenocarcinoma have a better outcome than patients with poorly differentiated adenocarcinoma with a median survival of 20 vs. 10 months.

Sugarbaker (17), on 64 colorectal carcinomatosis, obtained a median survival of 11.9 months and identified several significant clinical features. In particular patients with a lesion size ≤ 5 cm showed 68% 5-year survival vs. 4% in patients with larger lesions ($p=0.0001$) and patients with one or two abdominal regions involvement had 48% 5-years survival vs. 4% in those with more than two abdominal regions. On these bases he developed the peritoneal cancer index (PCI) that in further series showed a significant correlation to survival (18).

In the present series the median survival was 19 months with a 3-yrs survival of 26.7%, but 18% of the patients presented a CC-₂ residual disease. The difference in survival in CC-₀₋₁ vs. CC-₂ patients was statistically significant ($p<0.00001$) and evaluating only the CC-₀₋₁ group the 3-yrs survival raised to 31.3%. According to other Authors (19) we could not demonstrate any difference in survival related to duration and technique of IHCP. Pesteiau and Sugarbaker (18) reported the better prognosis of patients with colorectal carcinomatosis treated with concomitant management of primary tumor. We had an high rate of primary tumor synchronous to peritoneal carcinomatosis (42%), but we failed in demonstrating any survival advantage emerging from concomitant management.

Evaluating the group of patients with good prognostic factors ($PCI \leq 10$ and CC-₀₋₁) vs. the group characterized by $PCI > 10$ and CC-₂, 4-yrs overall survival was respectively 44.7% vs. 0% ($p=0.008$). Median survival of the former group, that represents one third of

the total series, was 28 months. It is a main point, because from a median survival of 19 months, that overlaps with the current literature results, a proper selection of patients will probably permit previously unbelievable results. This should be achievable as soon as it will be possible to evaluate, at the time of diagnosis, the real extent of the disease, its biological characteristics and the feasibility of the integrated treatment.

Disease-free interval has demonstrated to have a strong prognostic value in many malignancies and it seems not surprising that the delayed developing of a peritoneal carcinomatosis could also correlate with a better outcome, even if until today does not exist any previous report concerning the relationships between DFI and survival in carcinosis. In our series, about 20% of the evaluable patients had a disease-free interval between the colon resection and the onset of peritoneal carcinosis longer than 24 months and showed a 5-yrs disease-free survival of 50%. These results have obviously to be confirmed by a multivariate analysis on larger series, but patients with a long DFI are likely to have a good prognosis and should be considered with curative intent also when other prognostic indicator, as the PCI, seem to be unfavourable.

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