Preventive intraperitoneal chemotherapy in colon cancers with high risk of recurrence: outcome at 5 years from a prospective study

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OBJECTIVES

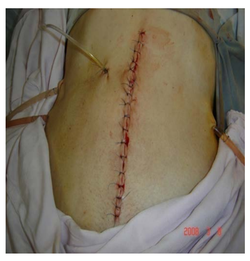
- The study evaluated the effectiveness of immediate postoperative adjuvant chemotherapy intraperitoneal (CIPPI) in the prevention of local and peritoneal recurrence in colon cancer at high risk of recurrence and the 5-year survival.
- On initial diagnosis of colorectal cancer, peritoneal localization is present in 10-15% of patients [1]. Furthermore, 50% of patients operated for colorectal cancer will present a local or locoregional recurrence in the first two years after surgery.
- The peritoneum is the second site of recurrence after radical surgery referred [2] after the liver. This is exclusively peritoneal recurrence in 10-35% of cases [1].

METHODS

- From November 2005 to April 2008, 105 patients (53 men and 52 women), mean age: 54 years (26-70 years) with a colon adenocarcinoma and high risk of local recurrence and peritoneal were randomized into two groups.
- The first group CIPPI (+), 53 patients received, after radical resection of the primary tumor, intra peritoneal chemotherapy immediate postoperative without hyperthermia. In the second group CIPPI (-), 52 patients received only a curative surgery.
- Inclusion criteria were: presence of macroscopic involvement of the serous or invasion of adjacent organ, presence of a tumor perforation or stenotic and occlusive tumor, the presence of localized peritoneal carcinomatosis or stage 1 classification Gilly or synchronous ovarian metastases and finally, the presence of malignant cells in peritoneal lavage fluid examined extemporaneous.

Conduct of the surgery:

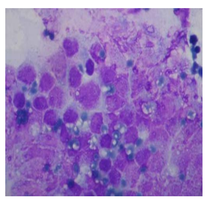
- After a median laparotomy, a thorough exploration of the abdominal cavity has to search at least one of the inclusion.
- Twenty (20) mL of the washing liquid is removed and the sample is immediately sent to the pathology department for cytological reading after centrifugation (3000 rpm for 10 minutes) and staining with May-Grunwald-Giemsa (MGG).
- In all cases, surgical treatment was with oncologic resection of the tumor and the adjacent mesocolon.
- The end of surgery, an implantable chamber of intraperitoneal chemotherapy in position and three drains:
- 2 in sub diaphragmatic position and one in Douglas' pouch was developed for patients ICPIP (+).



- Conduct of the intraperitoneal chemotherapy:
- At D0, intra peritoneal chemotherapy was started as early as possible in the following pattern: 1 liter per m2 infusion of normal saline containing Mitomycin C in doses of 10-15 mg / m2 and clamping drains for 23 hours.
- On D1, slurping recovering the intra-peritoneal fluid infused on day 0 followed by the infusion of 1 liter / m2 of saline in combination with 5-fluoro uracil at a dose of 650 mg / m2. This operation was repeated until J4.

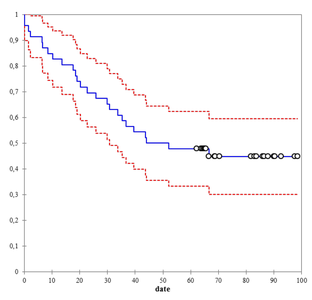
Graphs and tables

Type of resection	CIPPI (+)	CIPPI (-)
Segmental resection	12 (22,6%)	16(30,8%)
Right hemicolectomy	19(35,8%)	13(25%)
Left hemicolectomy	1(1,9%)	0(0%)
HARTMANN	10(18,9%)	6(11,5%)
Anterior resection	5(9,4%)	11(21,2%)
Total Colectomie	3(5,7%)	4(7,7%)
Total conservative Coloprotectomie	2(3,8%)	2(3,8%)
Total Coloprotectomie with ileostomy	1(1,9%)	0(0%)
Total	53	52



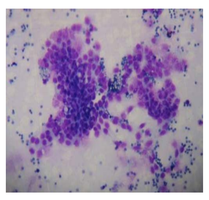
Clusters of epithelial cells with abundant cytoplasm, irregular nuclei

CIPPI + 54,7 months (95% CI, 43,95-65,61)



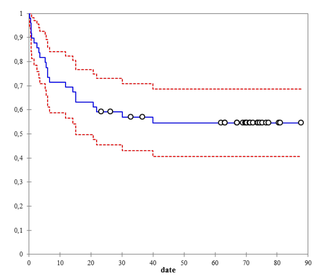
Comparison of relapses in the 2 groups

	CIPPI (+)	CIPPI (-)	P
Mortality	5 (9.4%)	2 (3.8%)	0.25 NS
Morbidity	30%	21%	0.29 NS
Local recurrence	4/53 (8%)	14/52 (27%)	0,008 S
Distant metastasis	9/53 (17)	9/52 (17%)	0,29 NS



Rich smear with atypical epithelial cells cupboards, signs of duplication

CIPPI - 48,7months (95%CI,38,37-59,19)



RESULTS

- Primary tumor was on the left colon in 67 cases (64%), the transverse colon in 7 cases (7%), the right colon in 33 cases (31.4%) and rectal localization was present in 3 cases. One patient had three tumor localization, and dual tumor localization was recorded in 3 cases.
- Sixty nine interventions (66%) were performed by the same surgeon.
- In 43 cases (81%), intra peritoneal chemotherapy was started in the operating room at D0. She was delayed on Day 1 in 8 cases (15.1%) and D3 in 2 cases (3.8%), due to hemodynamic instability, difficulty breathing or a disturbed renal function.
- The chemotherapy treatment was discontinued in 14 cases (26.5%) between D2 and D4. Side effects were observed in 29 patients (54.7%), however, no serious haematological toxicity (Grade 3) was observed. In most cases, they were nausea and / or vomiting. Note that leaks of goshawks clamped drains were observed in almost 19% of cases. No serious dermatitis was observed.

Results of cytology:

- Free and perennial neoplastic cells were found in 15 patients (18.7%).
- Peritoneal cytology was positive in 29.3% of tumors classified pT3 / T4 and only 7.7% of tumors classified pT1 / T2; however, this difference was not significant (P = 0.08).
- Similarly, a greater than 5cm tumor size was associated with a positive cytology in over 22% of cases compared to only 9.5% when the size of the tumor was less than 5 cm (p = 0.09 NS).

Oncologic results:

- Local or peritoneal recurrence was observed in 4 cases (8%) in the group treated by intraperitoneal chemotherapy versus 14 cases (27%) in the second group (p = 0.008 s). Seven patients died in the postoperative period (D0 to D30) in both groups.
- The immediate intra peritoneal chemotherapy was associated with a mortality rate 3 times higher in the CIPPI + group compared to the control group: 5 patients (9.4%) in the group treated with intraperitoneal chemotherapy versus 2 patients (3.8%) for the control group. This difference was not significant (P = 0.25 ns). Survival at 5 years was 54.7 months for group 1 vs 48.7 months (P = 0.812 ns)

CONCLUSIONS

- This study shows that intra peritoneal adjuvant chemotherapy after resection of locally advanced adenocarcinoma of the colon can be reduced by more than 3 times the rate of local recurrence and peritoneal (p = 0.008).
- The analysis of the literature shows that several clinical trials of Phase III have evaluated the benefit of intraperitoneal chemotherapy in adjuvant colon cancers considered at high risk of recurrence. [3]
- Sugarbaker [4] randomized 66 patients operated on for colorectal cancer at high risk of locoregional recurrence. After complete resection of the tumor, 36 patients were treated for 5 days, 5-fluoro-uracil intra peritoneal. In the control group (n= 30 patients), patients received only adjuvant systemic chemotherapy with 5-fluoro-uracil. Peritoneal recurrence observed in the second look, were significantly lower in the group of patients treated with intraperitoneal chemotherapy (2 peritoneal recurrence of 10 in the first group versus 10 of 11 in the second group) with a significant difference (p = 0.003).
- Scheithauer and al [5] randomized a total of 241 patients operated for colon cancer stage III (n = 196) and stage II with high risk of recurrence (T4N0M0). One group of patients received a standard regimen of systemic chemotherapy with 5-fluoro-uracil more Levamisole for 6 months while the second group received a protocol including, in addition to a systemic adjuvant chemotherapy, 6 based chemotherapy cures 5 fluoro-uracil more Levamisol administered intraperitoneally for 3 days, every 4 weeks.
- Disease-free survival and overall survival at 5 years were respectively 85% versus 66% and 78% versus 61% for the group treated with the combination of systemic chemotherapy and intraperitoneal.
- After a median follow-up of 4 years, the benefit of intraperitoneal chemotherapy was more significant for stage III patients with a reduction of the estimated mortality rate to 43%. No benefit was observed for patients classified as Stage II.

- In a prospective multicenter french study by Valiant [6], 267 patients with stage II and III colon adenocarcinoma (stage II= 151) were randomized into 2 groups after curative surgery .
- The first group (n = 133) was treated with intraperitoneal chemotherapy for 6 days (from J4 to J10) 5FU preceded by a bolus 5FU IV intraoperatively. The second group was treated with a single surgical resection.
- After 58 months of follow-up, the median overall survival was 74% in intra peritoneal chemotherapy treatment group versus 69% in the control group (P = 0.30), while disease-free survival was 68% versus 62%, always in favor of the arm who received intraperitoneal chemotherapy (P = 0.26).
- This study showed a benefit of disease-free survival for patients classified stage II, having received all the intraperitoneal chemotherapy treatment (89% vs 73%) (P = 0.05). Moreover, we must remember that several experimental studies have shown the efficacy of adjuvant intraperitoneal chemotherapy in preventing recurrences of peritoneal [7-8-9].
- In our study, the rate of digestive fistulas was equivalent in the 2 groups (7.6% vs 5.8%). However, we encountered more serious disunity requiring reoperation in CIPPI (+) group (5.7% vs 1.9%).
- Small fistula observed after CIPPI (+) were certainly aggravated by diffusion of the digestive contents throughout the peritoneal cavity, due to dilute ascites chemotherapy drugs. In CIPPI (-), fistulas have been properly drained to the outside of the abdominal cavity.
- This explains why the mortality rate was higher in CIPPI (+) group, although the difference was not significant (P = 0.25). In this study, the presence of malignant cells in the peritoneal lavage fluid was considered an inclusion criterion and therefore a predictor of peritoneal recurrence. Malignant cells were found in frozen section in 15 cases. However, the prognostic value of cytology in operated colorectal cancer remains controversial.
- In a meta-analysis, Rekhraj et al [10] analyzed nine studies published between January 1990 and July 2007 and suggested that patients positive cytology were a subgroup of high risk of local recurrence patients.

CONCLUSION:

- The intra peritoneal adjuvant chemotherapy after resection of colorectal cancer remains a logical therapeutic perspective for the prevention of local and peritoneal recurrence. Nevertheless, it is associated with increased morbidity and mortality imploring than conventional surgery.
- A real benefit can be obtained by careful selection of subgroups of patients with the risk of local recurrence and peritoneal important after surgical resection with curative intent. However, there is no significant benefit for overall survival at 5 years.

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