



Staging Videolaparoscopy and Peritoneal Cytology in the Colorectal Carcinomas for the Preoperative Selection of the HIPEC Treatment

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Abstract

The authors report their preliminary results about preoperative videolaparoscopy staging of colorectal cancer cases. The examination for peritoneal cytology, performed during preoperative staging could thus be used to plan since the first surgical operation in case of positive cytology (even more in presence of evident carcinosis which was not revealed through CT), the combination with Intraperitoneal Chemo-Hyperthermia (HIPEC). Realizing this procedural hypothesis requires a preoperative performance of a staging videolaparoscopy, in order to explore the peritoneal surface, exclude the macroscopic presence of carcinosis (in this case it is indicated to perform peritonectomy and HIPEC) and detect the cytologic study (through washing or aspiration of potential ascitic effusion). The expected results aim to see a significant reduction of the peritoneal recurrence, but till now our proposal is a medical hypothesis: in fact results should be considered temporarily because the reduced observation time.

Keywords: Colorectal cancer metastasis and treatment; HIPEC; Peritoneal carcinosis

Introduction

Colorectal carcinomas is a tumor age dependent that increases exponentially after 40 years: the average affected age is around 63 with range between 50 and 70, although in the 8% of cases it can develop under 40 years old with sporadic cases also around 20 years old. Urban areas of countries with high socio-economic and industrial level are more affected; in fact the diet consists in low residue of fibers and rich in animal fat and carbohydrates, that's why it plays an important role on the intestinal carcinogenesis [1-5]. In western countries it constitutes the 2nd cause of death after lung cancer. As for the incidence, it is third, after lung and breast cancer in women and lung and prostate cancer in men. Generally, 15% of all cancers in both genders start in the colorectal tract. The evaluation of the single prognostic factors of colorectal carcinomas [6-19], hereby reported, is necessary for the patient's selection, in order to chose the treatment, formulate the prognosis and guide the follow-up:

1. Age
2. Performance Status
3. Comorbidity
4. Geriatric evaluation
5. Stage of the tumor
6. Peritoneal cytology
7. Histological evaluation on the removed anatomical part (grading, ploidy, surgical resection edges, number of removed lymph nodes, histogenesis, etc...)
8. CEA, Ca 125, LDH, Fibrinogen
9. Expression EGFR, Oncogen Kras, Oncoprotein p53
10. New molecular prognostic factors
11. HIV positivity

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Figure 1: Closed HIPEC after gastrectomy, transverse colectomy and ileostomy.

12. Evaluation of the proliferative activity in the crypt cells (microadenomas)

The stage of the tumor at the moment of the diagnosis constitutes one of the most important elements for the prognosis and the planning of the treatment:

- pT parameter (prognosis worsens in relation to the depth tumor penetration in the wall of the bowel and to the blood vessel invasion)
- pN parameter (number of lymph nodes identified in surgical specimen, number of positive nodes; more 3 nodes involvement worsens prognosis)
- pM parameter
- the hepatic metastases have a worse prognostic meaning than the lung ones
- the peritoneal carcinosis has an unfavorable prognosis in regards to respective surgery and anastomosis execution

High preoperative levels of CEA foresee a higher risk of recurrence after surgery (CEA levels are related to vascularization of the tumor; in the less vascularised pelvic recurrence often there is not an increment of the marker); also important is the level of Ca 19.9. High preoperative levels of Ca 125 are probative for peritoneal carcinosis. High preoperative levels of LDH, or during the follow-up, are probative of hepatic metastasis. Preoperative hyperfibrinogenemia, with no sign of an inflammatory pathology in act (negative PCR), is related to a major incidence of recurrence; this allows to select a subgroup of patients who, no matter the other prognostic factors, could be started to the adjuvant chemotherapy [20-22]. Preoperative peritoneal cytology, when positive, is a negative prognostic indicator, which reduces survival up to 5 years. This last parameter (peritoneal cytology) in case of positivity could be used to combine first operative approach with intraperitoneal chemo-hyperthermia (HIPEC), although randomized studies are needed to confirm this hypothesis and, first of all, verify the incidence of false negative results.

Peritoneal Carcinosis from Colorectal Cancer

The first attempts to curatively treat peritoneal carcinosis date back to the pioneering studies by Sugarbaker et al. [23,24] which performed intraperitoneal chemotherapy in recidive carcinosis of ovarian carcinomas. The latter, more than the others, has the

tendency for peritoneal diffusion. After the first promising results, techniques evolved until the recent HIPEC procedure (Hyperthermic IntraPERitoneal Chemotherapy) combined with peritonectomy, either in the carcinosis from ovarian cancer or in the one from colorectal and gastric carcinomas, though it gave results for the latter, at least until now, which is by far less favorable [25-35]. Peritoneal carcinosis – still considered a disease with severe prognosis and with a mortality up to six months in the 100% of non-treated cases [36,37] represents one of the evolutive possibilities for the abdominal viscera malignancies, even though, at a minor level, can manifest as terminal stage in the extra-abdominal tumors; cases of primitive carcinosis are rare (mesothelioma).

The implant on the peritoneal surface is one of the three different ways for spreading of cancer together with the blood and the lymphatic vessels dissemination.

The condition of carcinosis became relatively frequent due to the increase of colorectal and ovarian cancer and, at a minor level, of the stomach. Approximately 10% of patients who are affected by colorectal carcinomas (about 50,000 new cases every year in Italy) present a peritoneal carcinosis at the moment of the diagnosis of the primitive tumor. Peritoneum, after liver, is the most frequent site for neoplastic diffusion after an apparently curative treatment of colorectal carcinomas and from 10% to 35% of the patients with recurrence is affected with peritoneal carcinosis. In this regards, the accomplishment of preventive oophorectomy in the digestive carcinomas [38] responds to the requirement of prevention for the development of ovarian micrometastases, being this one of the most affected sites in women for the implantation of tumoral cells, which are initially microscopic and then frankly evident in the form of Krukemberg' tumor. As far as colorectal carcinomas is concerned, the progress in secondary prevention of this tumor (early diagnosis) and in oncologic treatments (systemic chemotherapy, molecular target agents), significantly improved the results for patients' survival. A further and important contribution came from the use of local therapies in the cases of metastatic tumor when confined in specific organs such as liver and lung [39,40].

With regards to peritoneal spreading of digestive carcinomas, it was considered until approximately ten years ago a terminal stage of the disease, that had to be cured with supporting palliative treatments, even chemotherapy if necessary; whereas surgery, presenting an high incidence of morbidity, has been employed only to treat acute complications, such as occlusion or perforation [41,42]. In the last ten years of the past century the progress on knowledge's of natural history and diffusion modalities of colorectal carcinomas led to reconsider the meaning of peritoneal carcinosis, particularly when it manifests as only site of primitive tumor spreading, in absence of hematogenous metastasis; in fact, in these cases, Sugarbaker [43] introduced the new concept of locoregional disease, formulating the new term "peritoneal metastasis" instead of "carcinosis", which would imply the concept of systemic disease. In this way and also thanks to the development of new surgical and anesthesiological technologies, new horizons were discovered and led to treat peritoneal carcinosis (first just in the cases of ovarian carcinomas) with aggressive surgical procedures by removing all the affected organs that are not necessary for survival, including peritoneum: the well-known "cytoreduction with peritonectomy". During surgery, a locoregional treatment of intraperitoneal chemo-hyperthermia is associated (CIIP or HIPEC in the Anglo-saxon terminology).

Intraperitoneal chemotherapy gives an high percentage of response, also because the “plasmatic-peritoneal semipermeable barrier” allows to tolerate intensive doses of chemotherapy: drugs at an high molecular weight are administered, such as mitomycin C, 5-fluorouracil, cisplatin or gemcitabine [44-49]; by recurring to the peritoneal way, the exposition time of the peritoneal surface at pharmacologically active molecules can be notably increased, which go gradually through the peritoneum; however, the procedure is not free from toxic effects, but less than what happens intravenous administration, so that active collaboration with the oncologist is needed, from the perspective of a modern multimodal approach to the oncological disease [50].

The association hyperthermia-chemotherapy works in synergism, as demonstrated by many studies [51-56]; it potentiates local cytotoxic activity and promotes the tissue diffusion of the drugs; other than this, the heat itself performs a harmful action on tumoral cells. The optimal selective effect on tumoral cells is reached with temperatures between 41°C and 45°C. The chemotherapeutic penetrate more easily neoplastic cells when temperature reaches 42°C and when metastatic nodes are smaller than 2.5 mm. In cases of diffuse peritoneal carcinosis with a massive involvement on mesentery, there is no indication for a radical surgical treatment or chemo-hyperthermia; on the other hand, when mesentery is reasonably circumscribed, it can be treated by resecting the affected intestinal tracts. Baratti et al. [40] suggest to perform intestinal anastomoses always before HIPEC because heat and drug-induced bowel edema can make anastomosis completion technically difficult and at a risk of dehiscence. Although HIPEC procedure is still preserved to few specialized centers, more and more favorable results are reported, in terms of survival and recurrence reduction, most of all for the ovarian and colorectal carcinomas [57-59]. Therefore, in the light of this different point of view on carcinosis and as outlined above, aggressive and cytoreductive rather than palliative surgery was introduced in order to remove all the visible macroscopic lesions: diaphragmatic, pelvic and abdominal peritonectomy, great and small omentum exeresis and removal if possible of the visceral localizations except from liver and capsulectomy of pancreas (cholecystectomy, splenectomy, partial gastric resection, appendectomy, hysterosalpingo-oophorectomy and, if necessary, also right/left or total colectomy and limited tracts of small intestine). Obviously, colic or colorectal resection for the primitive tumor takes place before cytoreductive surgery and follows the rules of lymphadenectomy.

That said, here below are the current indications for HIPEC procedure:

- Patients affected by peritoneal carcinosis who were subjected to optimal surgical cytoreduction (peritonectomy) and radical exeresis of the primitive tumor
- Patients affected by peritoneal mesothelioma who were subjected to optimal surgical cytoreduction
- Patients affected by peritoneal pseudomyxoma who were subjected to optimal surgical cytoreduction
- Patients affected by perforated carcinomas of the digestive tract (so that dissemination of neoplastic cells in peritoneum is considered inevitable), after the exeresis treatment of the primitive tumor and the surgical cleaning of the peritoneal tract
- Patients affected by gastric or colorectal adenocarcinomas

with positive cytology.

As far as colorectal carcinomas is especially concerned, Glehen et al. [58,59] published interesting results in regards to a retrospective study led on 506 patients, who were subjected to peritonectomy and HIPEC; the most important Italian centers contributed to the study. Average global survival was of 19.2 months; patients, who obtained a complete cytoreduction, got a better prognosis with an average survival of 32.4 months. The completeness of cytoreduction was revealed to be a statistically significant variable ($p < 0.01$). Verwaal et al. [60] led a prospective study in 105 patients affected by peritoneal carcinosis from colorectal carcinomas: the research arm concerned surgical cytoreduction associated to HIPEC and was followed by systemic chemotherapy, while the control arm concerned standard therapy with systemic chemotherapy (5-fluorouracil-leucovorin) with or without palliative surgery. The research group presented a survival advantage compared to the control group. HIPEC in colorectal carcinomas, with the appropriate indications, hence constitutes an extremely important therapeutic treatment. In parallel with the colic resection procedure, the potential treatment for hepatic metastasis with resection procedures or through thermal ablation with radiofrequency is also performed [61,62].

New Perspectives for HIPEC

In 2015 we started a research project addressed to identify during pre-operative staging of patients affected by gastrointestinal carcinomas, those at risk of carcinosis and we try to select the ones with positive peritoneal cytology. Peritoneal cytology positivity is in fact a negative prognostic indicator, which reduces survival up to 5 years, as it expresses peritoneal recurrence risk of the tumor and demonstrates a biologically aggressive and advanced-staged tumor. The examination for peritoneal cytology, performed during preoperative staging could thus be used to plan since the first surgical operation in case of positive cytology (even more in presence of evident carcinosis which was not revealed through CT), the combination with intraperitoneal chemo-hyperthermia (HIPEC).

Realizing this procedural hypothesis requires a preoperative performance of a staging video laparoscopy, in order to explore the peritoneal surface, exclude the macroscopic presence of carcinosis (in this case it is indicated to perform peritonectomy and HIPEC) and detect the cytologic study (through washing or aspiration of potential ascitic effusion). The expected results aim to see a significant reduction of the peritoneal recurrence, most of all for the colorectal carcinomas, which presents a good chemo-sensibility; expectations are lower in cases of gastric carcinomas. Moreover, a further potential innovation in the HIPEC field was analyzed by Seretis and Seretis [63], who proposed to add heparin in the chemo-hyperthermic peritoneal lavage, in order to improve the perfusion, reduce adhesions formation and dissolve the fibrin shell that tends to protect tumoral cells spreading from the action of chemotherapy. An even further application is reported by Valle et al. [64], who, with palliative intent and mini-invasive videolaparoscopic access, subjected to HIPEC procedure 12 patients affected by malignant non-responsive ascites and not suitable for surgery and obtained outstanding clinical results.

Conclusion

Nowadays, HIPEC procedure represents an extremely important treatment, essential when one is dealing with tumors of the gastrointestinal tract at an advanced stage that present macroscopically evident peritoneal carcinosis; it would be advisable

to be able to reveal the carcinosis also at a microscopic level. HIPEC is a complex procedure which, due to the high costs and the need of specialized professionals, can be performed only in a few referenced hospitals for every region. Peritonectomy is between the major surgical procedures and requires a notable quantity of time spent in the operating room, dedicated surgeons and anesthetist equips, intensive therapy availability and constant collaboration with the oncologist. The results of our current study cannot be analyzed yet because of the reduced observation time (last report dec. 2016). Therefore we are not able at the moment to confirm the validity and the false negative percentage of the procedure, but the idea of preoperative detection of microscopic carcinosis through the videolaparoscopy preoperative staging, is suggestive and conceptually correct. Of course further studies on the topic are necessary. The purpose is to improve the selection of patients affected by digestive tract cancer, in order to plan a more effective and personalized treatment, by using HIPEC both in macroscopic carcinosis cases and in cases where the microscopic spreading to peritoneum can be demonstrated; particularly our study addresses the cases of colorectal carcinomas: until now we performed the staging videolaparoscopy in 24 patients without detect yet positive cytology cases. On the contrary, we confirmed the presence of carcinosis in 6 cases, which we already had suspected with CT, but unapt for HIPEC. As a matter of a fact, 4 of them had a diffuse carcinosis with massive involvement of ileus mesentery, while in the remaining 2 cases there was the coexistence of diffuse miliary hepatic metastasis in both the lobes and lung metastasis. All 6 cases presented a histotype of mucinous adenocarcinoma with “signet ring” cells. On the other hand, we performed HIPEC in a gastric juxtacardial carcinoma case with macroscopic carcinosis (Figure 1). In no case we have found positive cytology for microscopic peritoneal spread. Therefore, we assume that, as far as we have studied up until now, our result should be considered temporarily, whose feasibility requests further research and of course a larger number of patients.

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