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Patient Selection and Treatment of Peritoneal Carcinomatosis from Colorectal and Appendiceal Cancer

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Abstract. Colorectal cancer is a disease process that disseminates through lymphatic channels, through hematogenous routes, and by invasion through the bowel wall. These mechanisms result in lymph node metastases, liver metastases, and peritoneal seeding. Although lymphatic and venous dissemination requires an invasive local process, peritoneal seeding may occur with both high grade and low grade malignancies. Cancer dissemination that causes liver and lymphatic metastases occurs prior to surgical resection of the primary colorectal cancer. Peritoneal seeding and seeding of the resection site (local recurrence) may also occur as a result of the surgical trauma that accompanies resection of the primary lesion. Leakage of malignant cells from transected lymphatic channels may be the mechanism of this intraoperative intraperitoneal cancer dissemination. To limit the progression of peritoneal seeding and to treat large volume, low grade intraabdominal tumor deposits, combinations of cytoreductive surgery and intraperitoneal chemotherapy have been successfully employed. Selection factors that correlate with long-term benefit are (1) low grade of malignancy, (2) lack of lymph node or liver metastases, and (3) treatment of low volume disease. For patients with moderate or high grade colorectal cancer, only a low volume of disease can be treated successfully. For patients with low grade cancer, peritonectomy procedures are used to achieve minimal residual disease before initiating the intraperitoneal chemotherapy. In properly selected patients, peritoneal carcinomatosis from colorectal and appendiceal cancer is a treatable condition that may result in long-term disease-free survival.

For more than a decade clinical research efforts have been directed at the treatment of peritoneal carcinomatosis from colorectal cancer. Treatment may be indicated either at the time of surgery for removal of the primary malignancy or at the time of recurrence. The subset of colorectal cancer patients with peritoneal carcinomatosis may be large. As many as 20,000 patients per year in the United States have peritoneal carcinomatosis as a site of colon or rectal cancer dissemination. The clinical features used to select patients for treatment and the strategies used to date have become better defined as large numbers of patients have been studied.

Tumor Biology of Colorectal Cancer

Some oncologists argue from a historical perspective that it is unreasonable to try to cure peritoneal carcinomatosis with a combination of surgery and regional chemotherapy. However, there is a rationale for this therapy derived from tumor biology. One may theorize that it is just as reasonable to treat peritoneal carcinomatosis as it is to remove lymph nodes or liver metastases because colorectal cancer metastasizes in a stepwise fashion; that is, it progresses metachronously. Not all cancers disseminate in a stepwise fashion. For the sake of comparison, it would not make sense biologically to treat with curative intent, using these regional cancer treatments, patients with disseminated breast cancer. The only reasonable treatment for metastases from breast cancer is systemic chemotherapy.

An understanding of two major tumor biology principles is necessary in order to accept that curative treatment of peritoneal carcinomatosis from colorectal cancer is a viable option. These two principles are metastatic inefficiency and tumor cell entrapment.

Metastatic Inefficiency

As implied in Figure 1, treatment for peritoneal seeding may be as effective as treatment for liver or lymph node metastases. As metastases grow in size over time, there is a stepwise progression from liver to lungs and from lymph nodes to lungs in a large proportion of patients. This stepwise progression to other intravascular sites may not occur as frequently with peritoneal seeding. In other words, one can think of the implants on peritoneal surfaces as terminal sites of disease spread. Cancer progresses at this site and results in further intracoelomic spread but does not routinely disseminate to distant intravascular sites.

This phenomenon, which gives rise to stepwise cancer progression, is called metastatic inefficiency [1]. It may be demonstrated by a fairly simple hypothetic experiment (Table 1). We inoculated littermate animals having the same genetic makeup with 10 million cancer cells. The inoculum was given intravenously, portal venously, or intraperitoneally on the same day in a randomized fashion. When the animals began to look sick, they were sacrificed and the number of tumor implants quantitated. On average, a total of 10 lung implants were identified. The 10 million tumor cells resulted in only 10 tumor nodules in the lungs. It is because of this low incidence of tumor implantation that the term metastatic inefficiency is used.

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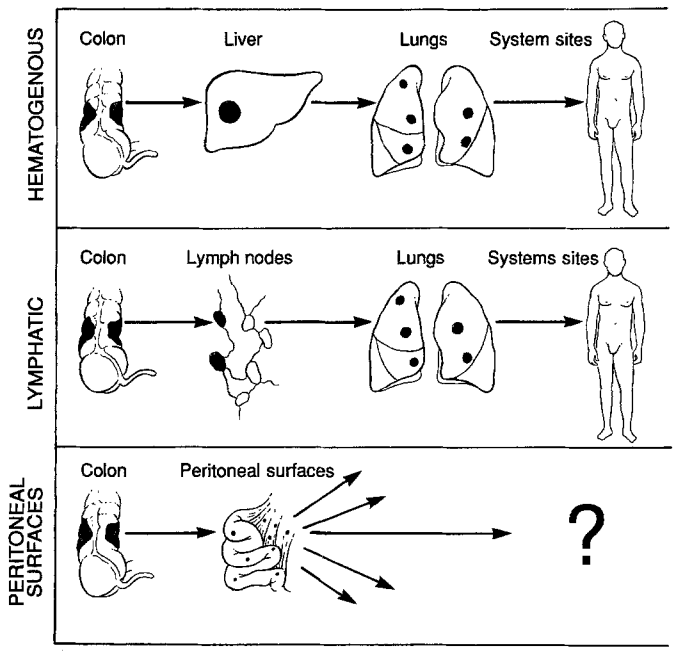

Fig. 1. Metastatic inefficiency helps explain the stepwise progression of primary colon cancer to liver, lymph nodes, and peritoneal surfaces.

Table 1. Simple experiment to show the variable metastatic inefficiency of cells inoculated intravenously, intraportally, or intraperitoneally.

Route	Inoculum	Implants	Efficiency
IV	10^7	10^1	10^{-6}
PoV	10^7	1	10^{-7}
IP	10^7	10^4	10^{-3}

Metastatic inefficiency is highest after portal vein injection. In a patient with a large primary colon or rectal cancer, tumor cells are potentially destroyed in the liver parenchyma at the rate of billions of cells daily. The experiment showed that cancer cells implant and grow in the peritoneal cavity with considerable metastatic efficiency: 10 million cancer cells resulted in 1000 peritoneal implants. This implantation on peritoneal surfaces occurs regardless of how badly traumatized the cancer cell is or its degree of biologic aggressiveness. For example, pseudomyxoma peritonei is a cancer of low malignant potential. It rarely metastases out of the peritoneal cavity to liver, lymph nodes, or lungs; yet it implants and grows efficiently on any surface.

Tumor Cell Entrapment

The tumor cell entrapment hypothesis suggests that cancers arising within the abdominal cavity differ from other malignancies. The difference can be attributed to the biologic forces of wound-healing, which play an important role in the progression of resection site recurrence and peritoneal carcinomatosis. As a result of these forces, the process of intraperitoneal cancer spread is highly complex. The surgically induced phenomenon of wound healing makes the natural history of gastrointestinal cancer different and especially virulent.

Full-thickness invasion of the bowel wall by cancer and intraoperative cancer cell dissemination result in intraperitoneal tumor emboli in a large number of patients. Intraperitoneal tumor cells implant extremely well within a matrix. The local conditions that occur as large volumes of fibrin are produced during the first phase of the healing process enhance tumor implantation. Cancer cells progress wherever fibrin deposition has occurred if intraperitoneal tumor cells are present. The inflammatory cells that enter the injured area do not destroy these tumor cells. Instead, they release growth factors that, in turn, further stimulate cell growth in the area. This sequence of events is called tumor cell entrapment and is outlined in Figure 2. It means that adhesions from prior surgical procedures are often involved by tumors. Because adhesions trap viable cancer cells and exclude regional chemotherapy it is important to use early postoperative intraperitoneal chemotherapy. The drug is easy to deliver and much more effective if it is given early postoperatively, when adhesions have not yet formed.

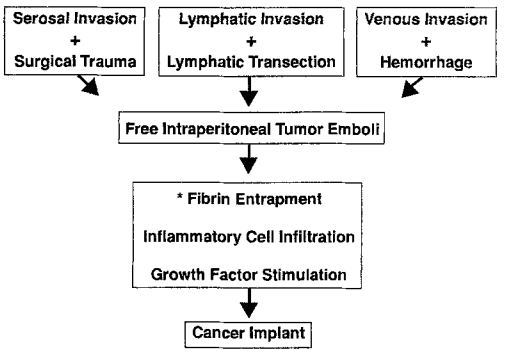

Fig. 2. Tumor cell entrapment hypothesis suggests that cancer implantation on traumatized peritoneal surfaces is an efficient process. *Occurs at the resection site, on abraded bowel surfaces, and underneath the abdominal incision.

Principles of Treatment

The cytoreductive approach to peritoneal carcinomatosis represents a new treatment strategy for cancer. It is a multimodality management plan that has curative intent in selected patients. The method is based on two requirements: (1) That dose intensity leads to an increased proportion of complete responses by avoiding the proliferation of drug-resistant cells. Sufficient dose response may eliminate the last cancer cell. (2) Surgery and surgically directed chemotherapy can be combined as a single treatment with acceptable morbidity and mortality. One does everything possible to temporally combine extensive surgery and aggressive regional chemotherapy as a single definitive treatment for peritoneal carcinomatosis.

Early Postoperative Intraperitoneal Chemotherapy

The major innovation of this new approach is the use of intraperitoneal chemotherapy during the early postoperative period for peritoneal carcinomatosis. There are several reasons why this new route and new timing of chemotherapy administration are particularly useful. (1) The resection site and peritoneal surfaces are at particularly high risk for cancer recurrence. During the early postoperative period, these surfaces are fully exposed to intraper-

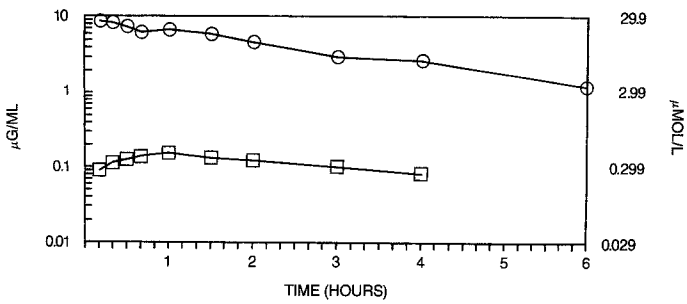

Fig. 3. Pharmacology of early postoperative intraperitoneal mitomycin C illustrates the peritoneal plasma barrier. ○: peritoneal fluid; □: plasma.

Table 2. Exposure advantage of peritoneal surfaces with four drugs commonly used with colorectal cancer.

Drug	Ratio IP/IV (AUC)
5-Flurouracil	91:1
Mitomycin C	22:1
Cisplatin	15:1
Doxorubicin	84:1

IP: intraperitoneal; IV: intravenous; AUC: area under the curve.

itoneal chemotherapy [2]. (2) Pharmacologic studies have shown a favorable therapeutic ratio for ablation of residual tumor microemboli on the peritoneal surface [3, 4]. (3) During the postoperative period the surgical techniques for drug delivery are simple and reliable. (4) Intraperitoneal chemotherapy (some drugs are exceptions) causes increased local effects without sacrificing systemic disease control; when chemotherapy is instilled into the peritoneal cavity it eventually becomes a systemic agent. Consequently, in many clinical situations one has everything to gain in terms of response and nothing to lose by using intraperitoneal chemotherapy [5].

To administer intraperitoneal chemotherapy, catheters are inserted so fluid can be introduced into the abdomen and drained by suction. The chemotherapy dwells for 23 hours in a large volume of fluid, drains for 1 hour, and then another instillation occurs. The physiologic rationale for intraperitoneal chemotherapy used during the early postoperative period is the peritoneal plasma barrier. The tissue located between the intraabdominal fluid and the nearest capillaries or venules acts as a barrier to the escape of large molecules. After instillation of chemotherapy in a large volume of fluid, the concentration of drug in the artificial ascites is many times greater at all points in time than in the plasma. The pharmacokinetics of intraperitoneal mitomycin is shown in Figure 3. The high concentrations of intraperitoneal chemotherapy over a long period result in a marked change in the regional effects of chemotherapy. The differences in chemotherapy exposure for four drugs used with colorectal cancer are itemized in Table 2.

An objection to the use of chemotherapy as part of a surgical procedure is the possible increase in morbidity and mortality. Surgeons fear that early postoperative intraperitoneal chemotherapy prevents wound healing and will result in an increased incidence of anatomic disruption. Among more than 300 anastomoses in 155 patients we found a 2% leak rate. In nonobstructed bowel without prior abdominal irradiation there was a fistula rate of approximately 2% [6].

Table 3. Changes in the use of chemotherapy for peritoneal carcinomatosis.

New route: intraperitoneal vs. intravenous
New timing: early postoperative vs. adjuvant
New target: peritoneal seeding vs. systemic disease
New selection criteria: metastatically inefficient vs. efficient
New surgical procedure: peritonectomy vs. resection
New results: benefit vs. prior failures

The most common major complication after cytoreductive surgery and intraperitoneal chemotherapy is fistula formation. Patients who have had prior intraabdominal treatments with either radiation therapy, intraperitoneal radioactive phosphorus, or intraperitoneal chemotherapy, and who then undergo extensive cytoreduction, are at an increased risk of complication [7]. We compared two groups. The first group of 24 patients had cytoreductive surgery first and then underwent intraperitoneal chemotherapy. The other group of 22 patients first underwent induction chemotherapy and then had the cytoreductive surgery. We saw a significant difference in the complication rate; virtually one-third of the patients from the second group had a serious enteric complication compared to only 4% in the first group. Consequently, it is evident that one must proceed carefully with induction intraperitoneal chemotherapy. The current recommendation is to wait 3 months after induction chemotherapy before proceeding with cytoreductive surgery.

A common misconception is that chemotherapy can be administered only by medical oncologists. Surgical oncologists have the opportunity to do things considerably differently. For gastrointestinal cancer there is a new route for administering chemotherapy. Intraperitoneal delivery is preferred to intravenous delivery for patients at risk of peritoneal seeding. Second, there is alternative timing—choosing early postoperative chemotherapy rather than an adjuvant approach. As a result of these different approaches, one may see benefits where in the past there were failures (Table 3).

Surgery for Peritoneal Carcinomatosis

To perform surgery for peritoneal carcinomatosis one must realize that not all gastrointestinal tissue is equally important in terms of survival. To maintain nutrition, the small bowel must be kept relatively intact, more so than either the stomach or the colon. Small volumes of grade I cancer on the small bowel are highly responsive to intraperitoneal chemotherapy. Long-term disease-free survival is recorded in many patients with peritoneal seeding, but no patients can be made completely free of disease by surgery alone. Because disease recurrence on small bowel is unusual, one must conclude that regional chemotherapy results in a high response rate with low volume disease.

There are six peritonectomy procedures. Each of these dissections takes about 2 hours to perform. If the entire abdomen is occluded by a tumor, surgery may take more than 12 hours. Although it has been called a superradical procedure by many, this cytoreductive approach is actually a minimally invasive way of stripping gross tumor from the abdomen. The peritoneum is removed only if implants are present. The cytoreductive surgery is

Table 4. Indications for early postoperative intraperitoneal chemotherapy in patients with resected pelvic cancer.

1. Large volume peritoneal surface malignancy from Grade I colorectal or appendiceal cancer
2. Cancer seeding of pelvic or peritoneal cavity
3. Tumor spill
4. Positive pelvic or peritoneal cytology
5. Perforated gastrointestinal cancer
6. Recurrent cancer resected with minimal or microscopically positive margins of resection
7. Cancer with direct extension to adjacent organs or structures

then followed by dose-intensive regional chemotherapy during the early postoperative period.

The following is a list of the six peritonectomy procedures that may be required [P.H. Sugarbaker, unpublished data]:

1. Greater omentectomy combined with splenectomy
2. Lesser omentectomy combined with cholecystectomy
3. Stripping the undersurface of the high hemidiaphragm
4. Stripping the undersurface of the left hemidiaphragm
5. Stripping the pelvis with hysterectomy and rectosigmodectomy
6. Antrectomy with gastrojejunostomy

Indications for the Cytoreductive Approach

Results of treatment to date suggest a definite salvage rate using cytoreductive surgery and early postoperative intraperitoneal chemotherapy for selected patients with peritoneal carcinomatosis who would otherwise die. As shown in Table 4 this group includes (1) patients with established peritoneal carcinomatosis from low grade colorectal or appendiceal malignancies, (2) those with perforated colorectal or appendiceal cancer, and (3) those with intraoperative dissemination of cancer cells. Tumor spill is a far more frequent problem than most surgeons would like to admit.

It is important to realize that adjacent organ involvement is only one step in a continuous process. The adjacent tumor had to move through the bowel wall, cause inflammation, and then invade an adjacent structure. Consequently, what appears as an adhesion between the primary tumor and the adjacent structures was at some point in time full-thickness invasion of the bowel wall by colon or rectal cancer.

During attempts to prevent peritoneal carcinomatosis one may investigate positive peritoneal cytology in a new way: While in the operating room, gently scrape the peritoneal surface of the primary colon cancer using a knife blade. The cells that are scraped away are placed on a slide, which is then given to the cytologist. This technique is the best way to determine a cytologically positive peritoneal cavity. Washing with large volumes of saline rarely produces the expected positive result.

It is important to establish that these combined treatments are not applicable to all patients with peritoneal carcinomatosis from colorectal or appendiceal cancer. Three treatment options exist for patients with peritoneal seeding. Selection of one of these option depends on the grade of cancer and the volume of peritoneal implants. For high grade, small volume adenocarcinoma, the current approach is to use three cycles of induction chemotherapy, a combination of systemic and intraperitoneal therapy. With this approach, we have had a high response rate; up

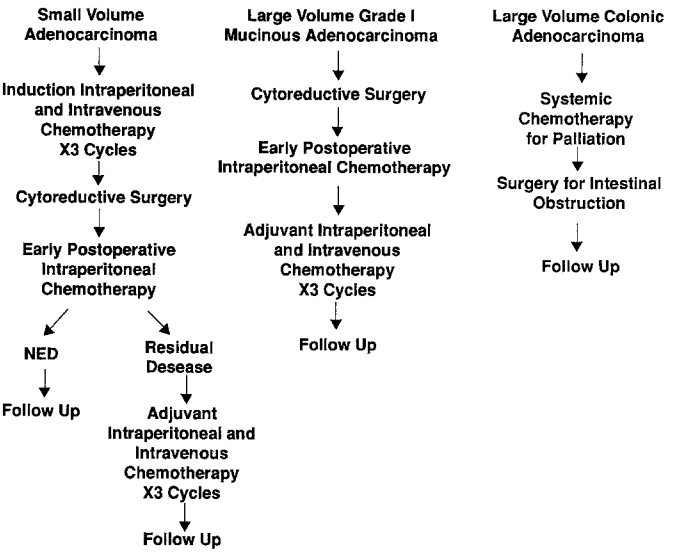

Fig. 4. Treatment plans for three groups of patients with peritoneal carcinomatosis.

to 50% of patients have a complete response in the abdomen after this treatment [P.H. Sugarbaker, unpublished data]. Patients then undergo complete resection of any residual tumor, followed by a final cycle of early postoperative intraperitoneal chemotherapy. Additional follow-up is needed before we know if the high complete response rates translate into prolonged survival (Fig. 4).

In general, intraperitoneal administration of chemotherapy for any large volume intraabdominal tumor is futile. Our greatest experience has been with pseudomyxoma peritonei, whether it is of appendiceal, colonic, or ovarian origin. For these types of large volume intraabdominal tumors one must start with cytoreductive surgery before proceeding to early postoperative intraperitoneal chemotherapy. The treatment is completed by three cycles of adjuvant intraperitoneal therapy combined with systemic therapy.

The major problem with high-grade adenocarcinoma is peritoneal seeding onto the small bowel. With low grade tumors that are basically noninvasive, one sees redistribution of tumor so small bowel surfaces are free of tumor. If low grade cancer is present, it can be peeled off the surfaces of the small bowel. However, such peeling cannot be done with higher grade invasive tumors. For high grade malignant tumors the goal is to treat small bowel surfaces definitively with chemotherapy before the adhesive process from surgery is well developed. That is the major reason for using the induction approach for the small volume, high grade disease.

Large volume, high grade disease should not be treated using the cytoreductive approach, as it does not respond. The options are no treatment, systemic chemotherapy, and surgery for palliation. Operating on all patients with intestinal obstruction is not recommended. Selectively is important for maintaining high levels of benefit and low morbidity and mortality with peritoneal carcinomatosis.

To summarize Figure 4, for small volume adenocarcinoma the treatment consists in three cycles of induction intraperitoneal and systemic chemotherapy followed by cytoreductive surgery and early postoperative intraperitoneal chemotherapy. For the large volume, low grade disease, we perform cytoreductive surgery and

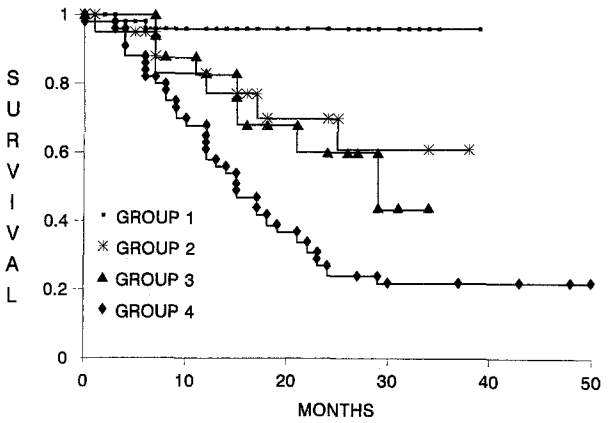

Fig. 5. Results of treatment of 155 patients with peritoneal carcinomatosis, by group (see text).

give early postoperative intraperitoneal chemotherapy, followed by three cycles of adjuvant intraperitoneal and systemic chemotherapy. Systemic chemotherapy is used for patients with large volume, high grade peritoneal carcinomatosis.

Results of Treatment

Our results after treating peritoneal carcinomatosis patients in a large phase 2 study of 155 patients are shown in Figure 5. An analysis of the clinical features of these patients was performed to determine which ones would favor a good prognosis. Four prognostic groups were identified in order to select the patients who were good candidates for the cytoreductive approach and those who should be excluded from this treatment strategy (Table 5). Group I patients have grade 1 histopathology, no lymph node or liver metastases, and complete cytoreduction. The latter was defined as removal of all visible tumor down to 2.5 mm diameter or less. Group II patients have any histopathologic grade of cancer, no lymph node or liver metastases, and complete cytoreduction. Group III patients have any histopathology, positive lymph node or liver metastases, and complete cytoreduction. Group IV patients have any histopathology, any nodal status, and incomplete cytoreduction.

Patients in group I do well. Those in groups II and III (lymph nodes positive for cancer) are metastatically efficient. The tumors in a large proportion of these patients will eventually progress outside the abdomen. Patients in group IV have a poor prognosis due to progression of the intraabdominal disease unless there is a remarkable response to chemotherapy.

Conclusion

Peritoneal carcinomatosis from colorectal or appendiceal cancer has traditionally been regarded as a uniformly lethal pattern of cancer dissemination. Through the use of intraperitoneal chemotherapy, peritonectomy procedures, and proper patient selection, some patients can be cured of this disease process. The patients who are likely to profit most frequently are those with metastatically inefficient peritoneal seeding with complete cytoreduction. In patients with higher grade adenocarcinoma, a curative approach is likely to succeed only if there is a low volume of peritoneal seeding. Patients with a large volume of high grade cancer are not usually candidates for the cytoreductive approach. Not only are selected patients with peritoneal carcinomatosis candidates for the cytoreductive approach, but these treatments can be utilized to prevent this lethal condition. Intraperitoneal chemotherapy used during the early postoperative period may be effective in preventing cancer recurrence at the resection site and on peritoneal surfaces. Additional clinical studies and pharmacologic investigations are needed to optimize the cytoreductive approach.

Table 5. Prognostic groups for patients with peritoneal carcinomatosis.

Prognostic group	Histology	Metastases	Cytoreduction	3-Year survival (years)
I	Grade I	No	Complete	90
II	Moderate	No	Complete	65
III	Any	Yes	Complete	35
IV	Any	Any	Not complete	25

Résumé

Le cancer colorectal est une maladie maligne qui s'étend à distance par des voies lymphatiques, des voies hématogènes et par invasion à travers la paroi intestinale. Ces mécanismes expliquent que l'on retrouve des métastases lymphatiques, des métastases hépatiques et enfin péritonéales. Alors que les deux premiers mécanismes exigent une invasion locale, l'ensemencement péritonéal peut se voir dans les cancers d'agressivité variable, de haut ou de bas degré de malignité. La dissémination responsable des métastases hépatiques et lymphatiques a lieu avant la résection de la tumeur primitive. L'ensemencement péritonéal et du site d'origine de la tumeur peut se produire par traumatisme lors de la résection chirurgicale. Une ≪fuite≫ au niveau des canaux lymphatiques est peut-être le mécanisme de cet ensemencement. C'est pour limiter l'évolution de l'ensemencement péritonéal et pour traiter les éventuels ensemencements péritonéaux, quel que soit leur grade de malignité, que la chirurgie ≪cytoréductrice≫ et la chimiothérapie intrapéritoneale ont été employées avec succès. Les facteurs de sélection qui sont corrélés avec un bénéfice pour le patient sont 1) un degré de malignité réduit, 2) l'absence de métastase lymphatique et/ou hépatique et 3) la réduction tumorale maximale lorsque le volume tumoral est limité. Pour les patients ayant un cancer colorectal à degré de malignité modéré ou élevé, le volume de cancer doit être réduit pour être traité avec succès. Si le cancer est de bas degré de malignité, des résections péritonéales (péritonectomie) sont nécessaires pour obtenir une réduction tumorale maximale avant d'initier la chimiothérapie intrapéritonéale. Chez des patients sélectionnés, la carcinose péritonéale à partir d'un cancer colorectal est traitable et peut donner des survies à long terme.

Resumen

El cáncer colorrectal es un proceso patológico que se disemina a través de los canales linfáticos, por vías hematógenas y por invasión de la pared del intestino. Estos mecanismos resultan en metástasis a los ganglios linfáticos, al hígado y, también, en siembras peritoneales. Aunque la extensión linfática y venosa

implica la existencia de un proceso invasor local, la diseminación peritoneal puede presentarse tanto en los tumores de alto grado de malignidad como en los de bajo grado. La diseminación del cáncer que causa metástasis hepáticas y ganglionares ocurre con anterioridad a la resección quirúrgica del neoplasma colorrectal primario. La siembra peritoneal, así como la siembra del lugar de la resección (recurrencia local), pueden también ocurrir como resultado del trauma quirúrgico asociado con la resección del neoplasma primario. La filtración de células malignas a partir de canales linfáticos seccionados también puede ser un mecanismo de este fenómeno intraoperatorio de diseminación del cáncer. Con el objeto de limitar la progresión de la diseminación peritoneal y de tratar depósitos tumorales de alto volumen/bajo grado de malignidad, se han empleado exitosamente combinaciones de cirugía citorreductora y quimioterapia intraperitoneal. Los factores de selección que se correlacionan con beneficios a largo plazo son: 1) bajo grade de malignidad, 2) ausencia de metástasis ganglionares o hepáticas y 3) tratamiento de enfermedad de bajo volumen. Para los pacientes con cáncer colorrectal de grado moderado o alto de malignidad, solamente se puede tratar con éxito un proceso neoplásico de bajo volumen. En pacientes con cáncer de bajo grado, se utilizan procedimientos de peritonectomía para lograr un mínimo de enfermedad residual antes de iniciar la quimioterapia intraperitoneal. En pacientes debidamente seleccionados, la carcinomatosis peritoneal por cáncer colorrectal es una entidad eminentemente tratable que puede resultar en prolongada sobrevida libre de enfermedad.

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