Preoperative criteria of incomplete resectability of peritoneal carcinomatosis from non-appendiceal colorectal carcinoma

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SUMMARY

Objective — To analyse the causes of non resectability of peritoneal carcinomatosis (PC) of non-appendiceal colorectal carcinomas, discovered only at the time of the laparotomy.

Summary background data — The combination of a maximal cytoreductive surgery (resecting tumor deposits > 1 mm in diameter) with intraperitoneal chemohyperthermia results in cure a significant number of patients. Complete resection of the PC is the determining factor of this time-consuming and resource-consuming therapy. Unfortunately, it has not been possible, so far, to safely predict complete resectability before carrying out the laparotomy.

Methods — All patients with colorectal PC who had undergone a laparotomy in order to receive this new treatment, but who finally presented a non completely resectable PC were included in our study. Their preoperative parameters were retrospectively studied and compared to matched number of patients who had successfully undergone this treatment.

Results — 29 patients had incomplete resection PC at laparotomy. They were compared with 29 matched patients who underwent a complete resection of the PC. The factors predicting non resectability were, in decreasing order of frequency: presence or persistence of an ascitis just before the laparotomy (P = 0.0008), progression of the PC while on neo-adjuvant chemotherapy (P = 0.01), abnormal CT-imaging (P = 0.03), and sub-occlusive syndrome (P = 0.05). These parameters were partially inter-related.

Conclusion — The persistence of ascitis and any progression of the disease while on chemotherapy are important predictive factors of incomplete resectability of non-appendiceal colorectal PC.

RÉSUMÉ

Critères préopératoires de non-résécabilité complète des carcinoses péritonéales d’origine colorectale (appendice exclu) — Dominique ELIAS, Emmanuel BENIZRI, Déwy VERNEREY, Hany ELDWENY, Daniela DIPETRANTONIO, Marc POCARD (Gastroenterol Clin Biol 2005;29:1010-1013)

Objectif — Analyser les causes de non résécabilité des carcinoses péritonéales (CP) d’origine colorectale (appendice exclu), découvertes seulement au moment de la laparotomie pour exérèse.

Rationnel — La combinaison d’une résection optimale de la CP (de tous les nodules de plus de 1 mm de diamètre) à une chimiohyperthermie intrapéritonéale immédiate permet de guérir un nombre significatif de malades. Cette résection « complète » de la CP est le facteur déterminant de ce procédé long et onéreux. Jusqu’à maintenant, personne n’a pu prédire avec fiabilité cette résécabilité avant la laparotomie.

Méthodes — Tous les malades laparotomisés dans le but de recevoir ce traitement combiné mais chez qui la résection complète était impossible ont été étudiés. Les paramètres préopératoires de tous les malades ont été comparés rétrospectivement à ceux d’un nombre similaire de malades appariés chez qui la résection complète a été possible.

Résultats — Vingt-neuf malades avaient une CP non résécable complètement lors de la laparotomie. Ils ont été comparés à 29 malades similaires qui ont bénéficié du traitement combiné. Les facteurs prédictifs de non résécabilité complète étaient, selon une importance décroissante : la présence ou la persistance d’une ascite juste avant la laparotomie (P = 0,0008), la progression de la CP sous chimiothérapie (P = 0,01), des anomalies radiologiques sur le TDM (P = 0,03) et un syndrome subocclusif (P = 0,05). Ces paramètres étaient en partie liés entre eux.

Conclusion — La persistance d’une ascite et/ou une progression sous chimiothérapie sont des facteurs prédictifs forts de non résécabilité complète d’une CP d’origine colo-rectale.

Introduction

Peritoneal carcinomatosis (PC) is generally considered as a preterminal stage in patients with colorectal adenocarcinoma [1, 2]. It was recently proven that complete resection of PC, when feasible, significantly increases the survival rate of these patients [3-7]. Based on experimental data [8], it is probable, even if not undoubtedly proven for human beings, that the addition of intraperitoneal chemohyperthermia (IPCH) increases the survival rate, and results in cure in some patients [4, 9-11]. It is also clear now that using IPCH is logical only after complete cytoreductive surgery of PC or, at least of all the tumor deposit greater than 1 mm in diameter, because the depth of penetration of IPCH is very limited [12, 13]. In this way, predicting the completeness of the PC resectability is a determining factor.

To be able to predict non resectability of PC would have two major consequences: to avoid a laparotomy and false hopes for the patient, and savings in hospital resources (loss of preliminary-booked long operative time, beds and other resources for the hospital).

Actually, this package combining complete cytoreductive surgery with IPCH is costly and represents a heavy treatment for patients and clinicians. It requires booking a prolonged operative time span, a specific device for IPCH, specific prescription for the intraperitoneal use of chemotherapy, a bed in the intensive care unit during the initial postoperative course, and all the
related personnel. When we discover, after one to three hours of surgery, that complete cytoreductive surgery is not feasible, this has obvious implications for both patients and hospital resources.

The purpose of this study was to analyze the causes of non resectability of PC, which were discovered only when performing the laparotomy, in an attempt to predict them and to reduce in the future unnecessary laparotomies for patients, and major planning difficulties for our hospital.

Material and methods

Criteria of inclusion in the trial with IPCH

A laparotomy with the aim to perform complete cytoreductive surgery with IPCH was proposed to patients with colorectal PC who fulfilled the following conditions:

1) physiological status: under 65 years old and fit for major surgery (normal bone marrow indices, normal renal and liver functions), 2) absence of digestive occlusion, 3) no huge and fixed invasion in the pouch of Douglas on rectal examination, 4) no visceral or hepatic metastases on the CT-scan, 5) absence of extra-abdominal metastases, 6) no multiple, diffuse and huge tumor deposits on peritoneum on the CT-scan, 7) signed consent to participate in an on-going trial.

Definition of a complete resectability of PC

PC was considered as completely resectable when all tumor deposits greater than 1 mm could be entirely resected. This corresponds also to a macroscopically complete resection or R1 status of UICC.

Causes for non resectability of the PC

On laparotomy, unfortunately, miscellaneous causes of incomplete resectability can be discovered in some of these patients. They are: 1) too widespread PC: the extent of the required resections would not allow to preserve a normal nutritional status by oral feeding only, 2) numerous tumor deposits which are poorly situated at the junction between the small-bowel and its mesentery, with severe retraction of the tissues, precluding their complete resection, 3) large lesions fixed all around the pelvic walls, 4) fortuitous discovery of multiple liver metastases, 5) fortuitous discovery of multiple retroperitoneal lymph nodes, 6) fortuitous discovery of a pleural carcinomatosis after resection of part of the diaphragm which was deeply infiltrated by the PC. Non resectability contraindicating the performance of IPCH was assessed, after a laparotomy from xyphoid to pubis and after an extensive and complete exploration of the abdominal cavity. In some cases, it appeared only after many hours of debulking (like the discovery of a pleural carcinomatosis at the end of cytoreductive surgery).

Evaluation criteria of the study

The patients who took part in this trial, but who did not receive this combined treatment due to incomplete resectability, were studied on the basis of the following three preoperative parameters, which represent the assessment criteria of this study: 1) Historical: synchronous or metachronous appearance of the PC with the primary tumor. 2) Clinical: chronic subocclusive symptoms (Koenig’s syndrome), presence of ascitis just before surgery, and the progression of PC during chemotherapy and/or chronic subocclusive pain) allowed moderate predictive information on resectability. The presence of increased CEA, as the presence of chronic subocclusive pain, gave moderate predictive information on resectability. The detection of any kind of abnormality on the CT-scan is more informative, but the two most significant parameters were the presence of ascitis just before surgery, and the progression of PC during systemic chemotherapy.

Control group

To allow analysis, the unresectable patients were compared with the same number of patients with colorectal PC, who had undergone the combined treatment with IPCH after complete cytoreductive surgery (colonic technique with oxaliplatin 460 mg/m², in 2 L/m² of 5% dextrose, at 43 °C during 30 min). These patients were selected retrospectively and carefully matched for age, sex, site of primary, date of surgery, preoperative chemotherapy regimens, and pathological findings. The same types of biotherapy (5-fluorouracil, leucovorin, oxaliplatin or CPT11) were preoperatively delivered in both groups of patients.

Statistics

Patients were prospectively registered, but the analysis of the assessment criteria was done retrospectively. No data were missing. Qualitative variables were compared using the exact Fisher test which is more precise than the chi2-test when the sample group is small. Quantitative variables (the delay between the primary and the discovery of the PC) were compared using the Mann Whitney test. Statistical significance was defined as P < 0.05. All statistical tests were two-sided. Statistical calculations were done with SAS version 8.2 (SAS Institute Inc., Cary, NC).

Results

Over 10 years, from January 1995 to December 2004, 131 patients were operated on for colorectal PC in order to receive the combined treatment with a curative intent. In 29 of them (22%), the disease was not completely resectable, and they underwent only a laparotomy, possibly associated with partial and palliative resection of the disease when symptomatic. PC of non-appendiceal colon cancer was histologically proven in the 29 patients of both groups. The causes of non resectability are reported in figure 1. The main causes were, in decreasing order of frequency: 1) diffuse extent of PC throughout the abdominal cavity, 2) a particular pattern of poorly located tumor deposits, at the junction between the small-bowel and its own mesentery (in spite of a moderate extent of PC), 3) complete fixation of a tumor mass in pelvis, and 4): discovery of multiple liver metastases or multiple retroperitoneal lymph nodes, or pleural carcinomatosis.

The same number of 29 matched but resected patients (control group) selected retrospectively on the criteria described above had the same preoperative characteristics as the non resectable patients, as shown in table I.

The comparison of the preoperative parameters of these two groups is presented in table II. These parameters are listed in decreasing order of significance in the table. The synchronous appearance of PC, like the presence of a partially fixed mass at rectal examination, was not predictive of non resectability. The presence of increased CEA, as the presence of chronic subocclusive pain, gave moderate predictive information on resectability. The detection of any kind of abnormality on the CT-scan is more informative, but the two most significant parameters were the presence of ascitis just before surgery, and the progression of PC during systemic chemotherapy. Finally, the presence of any of the three following parameters (presence of ascitis and/or progression of PC during chemotherapy and/or chronic subocclusive pain) allowed predicting non resectability in 72% (21/29) of the patients.
Discussion

In this study, we do not consider the advantages and disadvantages of palliative surgery for non-appendiceal colorectal PC. The treatment combining maximal cytoreductive surgery with IPCH is delivered only with a curative intent. In this way, to be able to predict the non resectability of PC in patients with colorectal cancers should have two major consequences: to prevent laparotomy for patients, and to avoid the loss of preliminary booked operative time, space and resources.

In this comparative non-randomized study (randomization is impossible in this situation), we show that two preoperative parameters were highly predictive of unresectability i.e., the presence of persisting ascitis, and the progression of the PC while on neoadjuvant chemotherapy. In a less obvious manner, the presence of any kind of abnormality on the CT-scan (excluding ovarian metastases) was also informative.

We could not find any similar study in literature relating to the preoperative criteria of PC resectability. One study underlines the negative impact of bowel obstruction and ascitis on survival, but not directly on resectability [7]. In their randomized study comparing the standard treatment of colorectal PC with IPCH, Verwaal et al. [9] concluded that they have not been successful in predicting the extent of the diseases based on preoperative findings. In their experimental arm, only 37% of the patients underwent complete resection with no macroscopic residual disease, 43% had residual deposits smaller than 2.5 mm, and 20% had residual tumor deposits greater than 2.5 mm.

We chose to compare patients with similar pathologic patterns. This had the advantage of increasing the similarity of the two groups, but did not allow obtaining any predictive analysis.
from histology. We considered that histological patterns could not be a reliable preoperative parameter, because they can come either from the primary tumor (but different patterns can be observed between primary and metastases) [14, 15], or from a preoperative biopsy of the PC (but there is a frequent genetic heterogeneity between different tumor deposits as well as within one tumor deposit) [15].

It is interesting to consider, that in our study, neither classical imaging with CT-scan, nor CEA (when increased) were sufficiently informative to safely predict complete resectability of the PC. CT-scans of abdomen, pelvis and thorax are mainly useful to eliminate visceral metastases and extra-abdominal localization. The FDG-positron emission tomography is useful in diagnosing colorectal PC [16], but gives very little information about its real extent and its resectability (personal data on 30 recent cases, not published). CEA level was increased in 35% of resected patients, and in 62% of unresectable patients (P = 0.06), at the limit of the statistical significance.

The two most potent informative factors of non resectability were the presence of ascites, and the progression of PC while on chemotherapy. When applied to our study, these two selection factors allow for a contraindication to surgery in 72% of the non resectable patients. There exists a correlation between these two factors when considering that, in patients responding to chemotherapy, the ascitis, if initially present, progressively disappears. In addition, these factors have the advantage of being simple to assess. Finally, persisting ascitis appears to reflect the particular aggressiveness of this cancer and/or of its resistance to chemotherapy.

Because of the extent of the disease within the abdominal cavity, these patients are at high risk for occult metastases and for recurrence after surgery. Therefore, our policy has been to combine surgery with pre- and postoperative chemotherapy.

In our study, resistance to chemotherapy appears as a primary prognostic factor of incomplete resectability, and consequently, of poor survival. The importance of the response to preoperative chemotherapy was demonstrated for resected colorectal liver metastases in the study of Adam et al. [17], with a 5-year survival rate of only 8% in the group progressing under preoperative intravenous chemotherapy, contrasting with 37% in the group responding and 30% in the group with tumor stabilization while on chemotherapy. In a similar way, response to neoadjuvant chemotherapy has been associated with improvement outcome following resection in breast cancer [18], esophageal cancer [19] and soft tissue sarcomas [20], but there has not been any precise analysis of its impact on resectability.

In the particular logic of a “package” combining systematically complete cytoreductive surgery to treat the macroscopic peritoneal deposits and IPCH for treat the remaining microscopic deposits, the status of resectability conditions its feasibility. It is the “all or nothing” principle. In this specific context, response to neoadjuvant chemotherapy has a very specific significance.

In conclusion, it appears that the persistence of ascites, and any kind of disease progression while on chemotherapy are important predictive factors of incomplete resectability of non-appendiceal colorectal PC. So, in the near future, our policy will be to cancel cytoreductive surgery plus IPCH, initially programmed, in such cases, after preoperative chemotherapy.

REFERENCES