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Editorial

Radical Treatment of Peritoneal Carcinomatosis: Times Are Changing☆

Tratamiento radical de la carcinomatosis peritoneal. Tiempos de cambio

Since its first clinical application by Spratt in 1980,[1] the radical multidisciplinary treatment of peritoneal carcinomatosis (PC) has been the object of several and varying controversies.

The first obstacle to treatment was the fact that PC had been historically considered an incurable tumor presentation. However, new knowledge about the pathophysiology of tumor implantation and development on the peritoneal surface led to the change of this paradigm, and PC came to be considered a locoregional disease that is potentially curable with radical treatment, similar to what was proposed in the 1980s for the treatment of colorectal liver metastases. While the radical treatment of hepatic metastases (including lung metastasis) was accepted by the oncological community in a rapid and generalized manner, the integrated use of radical surgery, peritoneal chemotherapy±peritoneal hyperthermia generated distrust and fear among surgeons, even though both treatments shared a similar theoretical reasoning and nearly simultaneous technical development.

The multidisciplinary treatment of PC or peritoneal metastasis (the most appropriate term to define peritoneal dissemination) was immediately labeled as a complex, aggressive therapeutic procedure with an elevated economic cost that is disproportionate for a group of patients who are considered terminal. It was also associated with high rates of complications, negative effects on patient quality of life and prolonged periods of clinical recovery. In addition to all these objections, there was doubt about the reproduction of the good results achieved by Sugarbaker advocating the treatment.

The decade of the 1990s, the initial development period of multidisciplinary treatment, was marked by a combination of rejection, skepticism and indifference to treatment. In spite of this, the interest in peritoneal malignancies was maintained, especially among surgeons. Sugarbaker's new contributions on surgical treatment (peritonectomy procedures[2]) and on methods for the administration of perioperative peritoneal chemotherapy[3] were extensively communicated, which attracted the interest of new surgical teams who, in turn, promoted greater development of the treatment and the creation of several scientific societies and cooperative networks. All this led to rapid popularization of the multidisciplinary treatment, and radical cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) was established as the most universal application. In this process of diffusion, we must also highlight the studies by workgroups in France (led by Elias[4]), Netherlands (Verwaal[5]), Italy (Deraco[6]), Japan (Yonemura[7]) and many others. Spain has actively participated in the development, promotion and diffusion of CRS+HIPEC through the teams of the Spanish Group of Peritoneal Oncological Surgery (GECOP).

At the beginning of this millennium, almost all of the initially raised objections to CRS+HIPEC were refuted, to a large extent, by the increase in the level of scientific evidence provided by the studies of these international groups, which until then had been insistently criticized by oncologists. This formidable fight against the tide led to the recognition of CRS+HIPEC as the only treatment capable of offering the possibility of a 5-year survival in patients with PC of different tumor origins.

These results were reproduced in numerous studies and led to growing interest among professionals and hope among patients for multidisciplinary treatment. The creation of numerous emerging workgroups, together with the rapid expansion of the treatment, once again generated new objections, this time regarding the lack of homogeneity in the indications and in the execution of CRS+HIPEC.[8]

Several international health agencies identified the need to carry out CRS+HIPEC in the context of clinical studies, with indications approved by multidisciplinary committees and surgical teams to guarantee that the procedures are performed both homogenously and safely. Patients should receive

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accurate information about the expected risks and benefits, while the results should be transparent and evaluated periodically.[9–11] In the United Kingdom, Moran pointed out the need to create hospitals specialized in this treatment, similar to those existing in other complex oncological diseases/procedures.

The United Kingdom, France, Netherlands, Belgium, Germany, Australia and Italy, together with a few other countries, have incorporated part of these recommendations into their public health policy in order to ensure the proper use of treatment, its viability and universal access.

In Spain in 2006, Catalonia was one of the first regions to implement a specialized medical center (Hospital de Sant Joan Despí Moisès Broggi) and a regional peritoneal carcinomatosis program, as directed by the Agency for the Evaluation of Medical Technology and Research of Catalonia. The proposal emerged from the Oncology Master Plan included in the Catalonian Healthcare Plan, with the expectation that it would subsequently be applied to other autonomous communities.[12] The model established in Catalonia is based on the training and accreditation of specialized multidisciplinary teams and the promotion of tertiary referral centers in complex or low-prevalence diseases and treatments, together with the preparation of organizational instructions for the management of these diseases. The specialized medical centers are subject to periodic evaluations. Scientific societies participated in different phases of the process. Within the public healthcare sector, this care model seeks to guarantee universal access to treatment, reduce clinical-therapeutic variability and achieve maximum treatment efficiency.

The PC program recently exceeded 1000 CRS+HIPEC procedures. It is, in all likelihood, one of the most active PC programs internationally and one of the few monitored with an external evaluation process of the results.

The therapeutic efficacy achieved in these 1000 procedures has been comparable to the best survival (SV) data reported by other international reference groups. The median SV achieved by the program in PC of colorectal origin was 40.5 months, 45.4 months for peritoneal recurrence of ovarian cancer, 62.7 months in malignant peritoneal mesothelioma, 20.6 months in stomach PC and 109 months of mean SV for peritoneal pseudomyxoma. The complication rate of grades III/IV in this series was 17%, which is significantly lower than rates described in other complex oncological surgeries.[13] Mortality 90 days after treatment was 2 patients (0.2%), which corresponds to the lowest mortality rate described in such a numerous series of procedures.

The PC program results corroborate the clinical benefits of CRS+HIPEC and the safety of the procedure when indicated and performed following the recommendations described.

Very recently, results have been reported from the phase III PRODIGE 7[14] study, which aims to establish the role of HIPEC in the context of CRS+HIPEC. The unpublished results demonstrate that, in patients with PC of colorectal origin, CRS+HIPEC does not offer longer SV than CRS+CTx (without HIPEC), except in the subgroup of patients with moderate PCI, in which a significant increase in SV was observed after administering HIPEC. The study gives an unexpected value to CRS. It is premature to determine the scope of these results, since additional studies are necessary to contemplate all the variables that impact patients with PC and the treatment itself. Until these doubts are revealed, it seems reasonable to continue considering CRS+HIPEC the treatment of choice for selected patients with PC of colorectal origin.

CRS+HIPEC is evolving. The challenges currently faced by multidisciplinary treatment include 3 different scenarios:

1) In the therapeutic use of CRS+HIPEC, clinical variability should be avoided in the indications and application of the treatment. The scientific-technical training of professionals involved in the new workgroups must be guaranteed with directed and supervised training. Surgical team training is especially important given the transcendental role of CRS in the context of multidisciplinary treatment. Certification standards are required for the creation of specialized medical centers, and results should be evaluated periodically.
2) The prophylactic/proactive use of the multidisciplinary treatment of PC of colorectal cancer should currently be done in the context of clinical studies. There are solid conceptual bases that have motivated the initiation of several controlled studies in this field of application of CRS+HIPEC. The PROPHYLOCHIP study,[15] which analyzes the role of second-look surgery plus HIPEC in patients at high risk of developing PC, has not provided the expected benefits in the SV of these patients, but there are other ongoing studies that offer encouraging preliminary data.
3) The access of public healthcare users to multidisciplinary treatment must be guaranteed. Based on available evidence, public healthcare administrators should analyze the current needs of patients with PC and foresee future requirements in order to determine the number of specialized hospital centers needed. Although Spain is one of the countries with the greatest diffusion and development of multidisciplinary treatment, universal access to this treatment is currently limited.

Today, PC should not be considered, initially, an incurable disease. It does require, however, individual assessment of each patient. Medical professionals who treat cancer must understand CRS+HIPEC, the patient selection criteria and the risks and benefits of the procedure in order to refer potential candidates to specialized hospitals as early as possible and in the best possible clinical condition.

CRS+HIPEC treatment is a good example of the multidisciplinary approach to cancer in which CRS is the cornerstone of the treatment. Technical training in peritonectomy procedures is fundamental for surgical teams specialized in multidisciplinary treatment. Currently, as shown by the results of the PRODIGE 7 study, the role of surgery (CRS) is also significant for the treatment of PC. Therefore, knowledge about peritonectomy techniques should not be relegated only to surgery groups that administer HIPEC. Peritonectomy procedures are useful in several fields of oncological surgery, where they can provide technical advances; in addition, these capabilities prepare surgeons for the surgical requirements that may occur in patients with PC who do not require the simultaneous administration of other regional treatments. It is recommended to extend the training in these surgical techniques to include all surgeons who treat cancer patients.

It is evident that we live in times of change for the management of peritoneal tumor disease, as any expectation of cure would have been unrealistic in certain cases until a few years ago. CRS+HIPEC treatment has followed a period of development, establishment and expansion. In this process of continuous evolution, adaptations arise from the generation of new knowledge. The therapeutic value of HIPEC has been added to the transcendental role of CRS in patients with PC, which is still a significant technique even when it is not associated with HIPEC. Once again, surgery demonstrates its irreplaceable value in the treatment of cancer. This is not a reason to rejoice, but instead to increase our surgical training. We should understand these treatments and become well trained in them.

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