Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy in Patients with Appendix Mucinous Adenocarcinoma: Series of 43 Cases

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Cirurgia Citorredutora com Quimioterapia Intraperitoneal Hipertérmica em Pacientes com Adenocarcinoma Mucinoso de Apêndice: Série de 43 Casos

Cirugía Citorreductiva con Quimioterapia Intraperitoneal Hipertermal en Pacientes con Adenocarcinoma Mucinoso de Apéndice: Serie de 43 Casos

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ABSTRACT

Introduction: Primary appendix carcinoma is a rare condition. Many international retrospective reviews outline the experience of different centers in appendicular neoplasms. The cancer treatment in this location is complex and depends on the histological subtype and the extent of the disease. One of the most promising treatments is cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). In Brazil, there is no description of series of cases with this therapeutic approach. The purpose of this case series is to analyze the sociodemographic characteristics and the type of therapeutic intervention in patients with malignant diseases of the appendix in a High Complexity Care Center in Oncology III (Cacon III). **Case reports:** 43 cases of primary appendix tumors were included. Low-grade mucinous adenocarcinoma was the most diagnosed neoplasm. The main protocol used was one to two surgeries and application of mitomycin C at an average temperature of 40 degrees. There was great heterogeneity regarding the use of the protocol. **Conclusion:** The present report of 43 cases is important because it is a rare tumor with this location. The therapeutic modality described is promising, but there is no defined protocol for this purpose. It is necessary to update the therapeutic guidelines to standardize the conduct internally, especially in the case of a national reference unit.

Key words: hyperthermic intraperitoneal chemotherapy; appendiceal neoplasms; cytoreduction surgical procedures.

RESUMO

Introdução: O carcinoma primário de apêndice é uma condição rara. Muitas revisões retrospectivas internacionais delineiam a experiência de diferentes centros em neoplasias apendiculares. Por sua vez, o tratamento do câncer nessa localização é complexo e depende do subtipo histológico e da extensão da doença. Um dos tratamentos mais promissores é a cirurgia citorredutora (CCR) associada à quimioterapia intraperitoneal hipertérmica (HIPEC). No Brasil, não há descrição de séries de casos que tiveram essa abordagem terapêutica. O objetivo desta série de casos é analisar as características sociodemográficas e o tipo de intervenção terapêutica em pacientes com doenças malignas de apêndice em um Centro de Assistência de Alta Complexidade em Oncologia III (Cacon III). **Relato dos casos:** Foram incluídos 43 casos de tumores primários de apêndice. O adenocarcinoma do apêndice do tipo mucinoso de baixo grau foi a neoplasia mais diagnosticada. O principal protocolo utilizado foi de uma a duas cirurgias e aplicação de mitomicina C em temperatura média de 40 graus. Os casos apresentaram grande heterogeneidade quanto ao uso do protocolo. **Conclusão:** O presente relato de 43 casos é importante por se tratar de um tumor raro nessa localização. A modalidade terapêutica descrita é promissora, mas não há protocolo definido para essa finalidade. É necessário atualizar as diretrizes terapêuticas para normatizar a conduta internamente, especialmente em se tratando de uma unidade de referência nacional.

Palavras-chave: quimioterapia intraperitoneal hipertérmica; neoplasias do apêndice; procedimentos cirúrgicos de citorredução.

RESUMEN

Introducción: El carcinoma primario de apéndice es una entidad poco frecuente. Numerosas revisiones retrospectivas internacionales describen la experiencia de diferentes centros en neoplasias apendiculares. A su vez, el tratamiento de esta localización del cáncer es complejo y depende del subtipo histológico y la extensión de la enfermedad. Uno de los tratamientos más prometedores es la cirugía citorreductora (CCR) asociada a quimioterapia intraperitoneal hipertérmica (HIPEC). En Brasil, no hay descripción de series de casos que tuvieran este abordaje terapéutico. El propósito de esta serie de casos es analizar las características sociodemográficas y el tipo de intervención terapéutica en pacientes con enfermedades malignas del apéndice en un Centro Asistencial de Alta Complejidad en Oncología III (Cacón III). **Reporte de los casos:** Se incluyeron 43 casos de tumores primarios de apéndice. El adenocarcinoma mucinoso de bajo grado tuvo la mayor incidencia. El protocolo principal utilizado fue de una a dos cirugías y aplicación de mitomicina C a una temperatura promedio de 40 grados. Los casos mostraron gran heterogeneidad en cuanto al uso del protocolo. **Conclusión:** El presente informe es importante porque es un tumor raro. La modalidad terapéutica descrita es prometedora, pero no existe un protocolo definido para tal fin. Es necesario actualizar las pautas terapéuticas para normalizar la conducta internamente, especialmente en el caso de una unidad de referencia nacional.

Palabras clave: quimioterapia intraperitoneal hipertérmica; neoplasias del apéndice; procedimientos quirúrgicos de citorreducción.

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INTRODUCTION

Primary appendiceal cancer is rare and most commonly diagnosed post-surgery of appendicitis and alleged primary malignancy of the ovary or peritoneum and is the cause of 0.5%-1% of all appendectomies[1]. The main appendiceal tumors are mucinous adenocarcinoma, goblet cell adenocarcinoma and appendiceal primary neuroendocrine carcinoma (ANC)[2].

The treatment of appendiceal primary tumors is complex and depends on the histological type and extension of the disease. In the last three decades, a strategy called cytoreductive surgery (CRS) associated with hyperthermic perioperative chemotherapy – HIPEC has been described as an alternative treatment for appendiceal, peritoneum cancer and peritoneal metastases. It increases survival and improves its quality. The principle of hyperthermia is to potentialize the cytotoxicity and tissue penetration of the drug[3].

Given the rarity of appendiceal primary cancer, patients with advanced disease should be treated in specialized clinics with a multidisciplinary approach. However, no randomized prospective trials exist for these rare tumors, and management is oriented by retrospective data-based experts consensus guidelines[4]. Thus, this study aims to analyze the demographic characteristics and type of therapeutic intervention in patients with malignant appendiceal diseases in a High Complexity Oncology Care Center III (Cacon III). The Institutional Review Board of the National Cancer Institute José Gomes Alencar da Silva (INCA) approved the study, report 4.191.156 (CAAE 35048620.4.0000.5274).

CASES REPORT

Forty-three patients, 35 (81%) females and eight (19%) males were analyzed, primarily young adults below 50 years of age (42%), Whites (47%), non-smokers (79%), non-alcoholics (84%) and 5-year survivorship of 70%. Mean follow-up was 6.98 years (standard deviation, SD±4.20), and only 21% of the cases died because of the tumor. Time of follow-up was not significant among patients who died or survived (died 5.45±4.79 *vs.* survived 7.38±4.01; p=0.444).

Mucinous adenocarcinoma was the histological type diagnosed in all the patients. Forty-nine percent were classified as a low-grade type of differentiation, 47% were unspecific (no specification – NS), and two cases (4.6%) as a high and moderate grade of differentiation.

Most of the cases (93%) have information concerning tumor markers. However, only one case has information prior to the approach. In addition, there was no homogeneity in the markers, but nearly all of them were epithelial. The carcinoembryonic antigen (CEA) was the most requested in 58% of the cases. The cancer antigen (CA) 125 was tested in 48% of the patients and CA 19.9 in 14% of the cases. Only two cases had non-epithelial marker alpha-fetoprotein tested, and one case had information about CA 15.3.

The mean of interventions was 1.58 (SD±0.54) surgeries, mostly with one and two procedures. In only one case, there were three procedures. The mean temperature of hyperthermic chemotherapy was 40.21°C (SD±1.13), with an amplitude of 40°C to 42°C. Two procedures utilized different temperatures (36 and 38°C, respectively). Most cases were mitomycin C (49%) or cisplatin (33%). Three cases used oxaliplatin, and the other three had no record in the chart.

Table 1 synthesizes the data of all the cases evaluated.

DISCUSSION

CRS combined with HIPEC varies concerning survivorship when utilized to treat peritoneal surface disease (PSD), appendiceal and colorectal cancer[5]. This multimodal modality is the main recommendation for patients with primary or secondary spread because it has been instrumental to survivorship improvement. However, hyperthermia during HIPEC leads to an increase in the metabolic rate and, consequently, an increase in oxygen demand, cardiac frequency, expired carbon dioxide, lactatemia and worsening metabolic acidosis[6]. To be eligible to benefit from this therapy, it is required to evaluate the reliable prognostic indicators, peritoneal cancer index (PCI), level of surgical cytoreduction, and further individual aspects of the patients such as performance status, age and comorbidities. It applies to cases where the prognosis is sensitive. Eventually, preoperative parameters can define the patient who is able to benefit from CRS and HIPEC[7].

The results reveal that mitomycin C warmed at 41°C was the most utilized protocol. However, the literature is controversial regarding the chemotherapy protocol and level of hyperthermia. Kemmel et al.[8] suggest that mitomycin is the chemotherapeutic of choice in CRS and HIPEC for colorectal malignancies because its pharmacokinetic profile leads to rapid concentration in the residual tumor deposits. On the other hand, more recent randomized clinical trials show that with similar results of survivorship and complications, oxaliplatin should be considered as a chemoperfusion agent for patients with mucinous appendiceal cancer submitted to HIPEC[9].

Finally, the temperature appears to be a critical threshold for the effects of cytotoxicity of the neoplastic cell for global survivorship and progression-free survivorship of patients submitted to HIPEC. Schaaf et al.[10] showed that hyperthermia significantly potentialized the impact of

Table 1. Description of series of cases of patients with appendiceal primary tumors (n=43)

Identification	Histological type: mucinous adenocarcinoma	Surgery	Protocol HIPEC	T°C§ HIPEC	Tumor marker	Follow-up (years)	Death
1	Low grade	1	Cisplatin	40	CA 125/CEA	10.25	No
2	NS	2	Mitomycin C	42	CA 125/CEA/CA 19.9	6.1	No
3	Low grade	2	Oxaliplatin	42	Non-tested	2.5	No
4	Low grade	2	Cisplatin	41	CA 125/CEA	5.0	No
5	NS	2	Cisplatin	-	CA 125/CEA	5.1	No
6	NS	2	-	-	CEA	3.4	No
7	Low grade	1	-	-	CA 125/CEA	6.0	No
8	NS	1	-	-	CA 125/CEA/CA 19.9	10.1	No
9	NS	2	Mitomycin C	42	CA 125/CEA	6.25	Yes
10	NS	1	Mitomycin C	42	CA 125/CEA	10.4	No
11	Low grade	1	Oxaliplatin	40	CA 125/CEA	5.0	No
12	Low grade	1	Cisplatin	40	CA 125/CEA	4.75	No
13	High grade	2	Mitomycin C	40	CA 125/CEA/CA 19.9/α-FPT	2.75	Yes
14	NS	2	Mitomycin C	40	CA 125/CEA/α-FPT	7.9	No
15	Low grade	2	Mitomycin C	40	CA 125/CEA/CA 19.9	9.9	No
16	Low grade	1	Mitomycin C	41	CA 125/CEA	5.25	No
17	Low grade	1	Cisplatin	40	CA 125/CEA	4.6	No
18	NS	2	Cisplatin	40	Non-tested	2.1	Yes
19	Low grade	1	Mitomycin C	40	CA 125/CEA	9.5	No
20	Low grade	1	Cisplatin	38	CA 125/CEA/CA 19.9	3.5	No
21	Low grade	1	Cisplatin	40	CA 125/CEA	8.9	No
22	Low grade	1	Mitomycin C	42	CA 125/CEA	11.1	No
23	NS	1	Mitomycin C	41	CEA	9.5	No
24	NS	2	Mitomycin C	-	CEA	7.75	Yes
25	NS	3	Mitomycin C	40	Non-tested	9.25	No
26	NS	2	Mitomycin C	40	CA 125/CEA/CA 15.3	11.25	No
27	Low grade	1	Mitomycin C	41	CA 125/CEA/α-FPT	5.5	No
28	Low grade	1	Mitomycin C	40	CA 125/CEA	9.0	No
29	NS	2	Cisplatin/ Mitomycin C	-	CA 125/CEA/α-FPT	24.0	No
30	Low grade	1	Cisplatin	40	CA 125/CEA/CA 19.9	1.25	Yes
31	NS	2	Mitomycin C/Cisplatin	40	CA 125/CEA	12.0	Yes
32	NS	2	Cisplatin	-	CA 125/CEA/CA 19.9	4.0	No
33	Moderately differentiated	2	Unspecified	-	CA 125/CEA/CA 19.9	7.0	No
34	NS	2	Mitomycin C	40	CEA	9.5	No
35	NS	2	Mitomycin C	-	CA 125/CEA	6.0	No
36	Low grade	2	Cisplatin	40	CA 125/CEA	7.75	No
37	Low grade	2	Cisplatin	40	CA 125/CEA	4.25	No
38	Low grade	2	Oxaliplatin	41	CA 125/CEA	13.75	Yes
39	NS	1	Cisplatin	40	Non-tested	1.25	Yes
40	Low grade	1	Mitomycin C	-	CA125/CEA/CA 19.9	6.75	No
41	Low grade	1	Cisplatin	36	CA125/CEA/CA 19.9	0.25	No
42	NS	2	Mitomycin C	40	CEA/CA 19.9	2.0	Yes
43	NS	2	Mitomycin C	40	CA 125/CEA	8.0	No

Captions: HIPEC = Hyperthermic intraperitoneal chemotherapy; α-FPT = alpha fetoprotein; NS = no-specification; CA = cancer antigen; CEA = carcinoembryonic antigen.
(§) Temperature (Celsius).

chemotherapy only at temperatures above 40°C *in vitro*, making this threshold important for patients' survivorship. However, the collaborative study US HIPEC[11], with 921 patients with appendiceal mucinous carcinoma, concluded that both early postoperative intraperitoneal chemotherapy and HIPEC are seemingly associated with similar perioperative and long-term results. So, complete cytoreduction with perioperative intraperitoneal chemotherapy is promising whether hyperthermia is used or not.

CONCLUSION

HIPEC is an aggressive surgical procedure with good results and improves the prognostic of patients with abdominal, metastatic and non-metastatic peritoneal tumors. In addition, HIPEC is an oriented technique to fight abdominal cancer with more minor side effects than traditional chemotherapy.

The current primary challenge is the creation of specific protocols addressing its use, including early monitoring of tumor markers and follow-up progression. Further, it is essential to correlate chemotherapy modalities utilized according to the histological type and operation technique consistent with staging and location. Even at Cacon III, there is still significant intervention and follow-up conduct heterogeneity, which reveals its fragility. With increased experience and refinement of selection criteria, it is expected more effectiveness for this modality.

CONTRIBUTIONS

Both authors contributed to the study design/conception, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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