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En Bloc Resection in Peritoneal Carcinomatosis with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Appendiceal Cancer: Surgical Strategies, Oncologic Outcomes, and Epidemiological Insights

Luis Jorge Caldera Sanchez[1], Héctor Cisneros Pérez[2], Mario Hernandez Mancillas[3], Víctor Mario Ortega Valerio[4], Francisco Rico Fernández[5], Marina Gallegos Colón[6]

[1,2,3,4,5,6]Hospital del Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado Zacatecas. Zacatecas, Zacatecas, México. Servicio de cirugía general.

ABSTRACT

Appendiceal cancer with peritoneal carcinomatosis (PC) represents a complex oncologic condition with distinct biological behavior and therapeutic challenges. Unlike other gastrointestinal malignancies, appendiceal neoplasms often exhibit extensive peritoneal dissemination, particularly in mucinous subtypes such as low-grade appendiceal mucinous neoplasms (LAMN) and pseudomyxoma peritonei (PMP). Historically, peritoneal dissemination was associated with poor prognosis, but the advent of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has dramatically altered the disease trajectory. En bloc resection has emerged as a critical surgical strategy to achieve complete cytoreduction (CC-0/1) in cases with extensive peritoneal involvement, preventing tumor fragmentation and reducing recurrence risk.

Epidemiologically, appendiceal neoplasms are rare, with an incidence of approximately 0.12 cases per 100,000 individuals per year, accounting for less than 1% of all gastrointestinal malignancies. Despite their low incidence, the diagnosis of appendiceal cancer has been increasing due to advancements in imaging modalities and more frequent incidental discoveries during appendectomies. The prognosis of appendiceal cancer varies widely depending on histologic subtype, peritoneal carcinomatosis index (PCI), and the feasibility of complete cytoreduction. This article explores the epidemiology, surgical principles, and oncologic outcomes of en bloc resection in conjunction with HIPEC, emphasizing patient selection criteria, operative techniques, and perioperative management. Additionally, we analyze the impact of histopathological subtypes on treatment response, recurrence patterns, and survival outcomes, providing a comprehensive overview of this aggressive but potentially curative approach to managing peritoneal carcinomatosis from appendiceal malignancies.

KEYWORDS: En bloc resection, appendiceal cancer, peritoneal carcinomatosis, hyperthermic intraperitoneal chemotherapy, pseudomyxoma, cytoreductive surgery, mucinous neoplasms, epidemiology, oncologic outcomes

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INTRODUCTION

Appendiceal cancer is a rare but clinically significant malignancy, often diagnosed incidentally during appendectomies or radiologic evaluations for unrelated conditions. The unique pathophysiology of appendiceal tumors distinguishes them from other gastrointestinal neoplasms, particularly due to their propensity for peritoneal dissemination rather than hematogenous or lymphatic metastasis. The peritoneal spread of appendiceal malignancies can lead to the development of peritoneal carcinomatosis (PC), a condition historically associated with limited treatment options and dismal prognosis. However,

recent advancements in surgical oncology, particularly the combined approach of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), have revolutionized the management of peritoneal carcinomatosis, offering select patients significantly improved survival and even potential long-term remission.1,2

En bloc resection has become an integral component of CRS in patients with extensive peritoneal disease, especially when tumor deposits are densely adherent to adjacent viscera. The rationale behind en bloc resection is to achieve complete cytoreduction (CC-0/1) by removing all macroscopically visible disease while minimizing the risk of peritoneal tumor spillage. This technique is particularly crucial in cases involving pseudomyxoma peritonei (PMP), where incomplete resection can lead to progressive mucinous accumulation, causing significant morbidity and mortality. Additionally, the integration of HIPEC as an adjunctive intraoperative therapy enhances local tumor control by targeting microscopic residual disease with heated chemotherapy, which has been shown to improve overall and disease-free survival rates.2,3

Despite these advancements, several challenges persist in optimizing treatment strategies for appendiceal cancer with peritoneal carcinomatosis. Patient selection remains critical, as the success of CRS and HIPEC depends on factors such as the histologic subtype, the extent of peritoneal disease as measured by the peritoneal carcinomatosis index (PCI), and the patient's overall performance status. Furthermore, postoperative morbidity associated with extensive cytoreductive procedures and HIPEC remains a significant concern, necessitating careful perioperative planning and multidisciplinary management.3

This article aims to provide a comprehensive analysis of en bloc resection in the context of peritoneal carcinomatosis from appendiceal cancer, incorporating epidemiological data, surgical considerations, histopathological correlations, and oncologic outcomes. By reviewing the current evidence and clinical experience, we seek to elucidate the evolving role of this aggressive therapeutic approach in improving survival and quality of life for patients with this challenging malignancy.3

Epidemiology of Appendiceal Cancer and Peritoneal Carcinomatosis:

Appendiceal malignancies are rare, comprising approximately 0.4% of all gastrointestinal cancers. The incidence is estimated at 0.12 cases per 100,000 individuals per year, with a rising trend in recent decades, likely due to increased use of advanced imaging techniques and more frequent incidental discoveries during appendectomies. The majority of appendiceal neoplasms are diagnosed in the fifth to seventh decades of life, with a slight female predominance observed in mucinous subtypes, particularly PMP.4

Histologically, appendiceal cancers encompass a spectrum of neoplastic entities, ranging from low-grade appendiceal mucinous neoplasms (LAMN) to high-grade appendiceal adenocarcinomas. LAMN and mucinous adenocarcinomas frequently present with peritoneal dissemination at initial diagnosis, often manifesting as PMP, characterized by gelatinous ascitic accumulation and progressive abdominal distension. Conversely, non-mucinous adenocarcinomas, neuroendocrine tumors, and goblet cell carcinomas exhibit more variable metastatic patterns, including lymphatic and hematogenous spread.4

The prognosis of appendiceal cancer is heavily influenced by histopathological subtype and the extent of peritoneal involvement. Patients with low-grade PMP have a 5-year survival rate exceeding 80% when treated with CRS and HIPEC, whereas those with high-grade mucinous adenocarcinoma or poorly differentiated histology have significantly worse outcomes, with 5-year survival rates ranging from 20% to 50%, depending on the completeness of cytoreduction. The peritoneal carcinomatosis index (PCI) serves as a critical prognostic tool, with lower PCI scores correlating with better surgical outcomes and prolonged survival.5

Although CRS and HIPEC have demonstrated clear survival benefits, patient selection remains a key determinant of therapeutic success. Ideal candidates for en bloc resection and HIPEC are those with resectable disease, good performance status (ECOG 0-1), and absence of significant extraperitoneal metastases. However, the decision to pursue aggressive surgical intervention must be individualized, considering tumor biology, surgical feasibility, and potential impact on quality of life.5

This epidemiological perspective underscores the necessity for early diagnosis, multidisciplinary treatment planning, and continued research into optimizing therapeutic strategies for appendiceal cancer with peritoneal carcinomatosis. In the subsequent sections, we will explore the technical aspects of en bloc resection, its role in achieving complete cytoreduction, and the impact of HIPEC in preventing disease recurrence and improving long-term survival.5

Surgical Techniques for En Bloc Resection in Peritoneal Carcinomatosis with HIPEC in Appendiceal Cancer

The management of peritoneal carcinomatosis (PC) secondary to appendiceal cancer has evolved significantly with the advent of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). A cornerstone of successful cytoreduction is the concept of en bloc resection, particularly in cases where tumor burden is extensive, adherent to vital structures, or involves contiguous peritoneal surfaces. This technique aims to achieve complete macroscopic tumor clearance (CC-0/1), which is the single most important prognostic factor influencing overall and disease-free survival in patients undergoing CRS and HIPEC. En bloc resection is particularly crucial in appendiceal neoplasms with peritoneal dissemination, such as pseudomyxoma peritonei (PMP) or high-grade appendiceal

adenocarcinoma with extensive peritoneal involvement. Given the propensity of these tumors to invade multiple peritoneal surfaces and adhere to intra-abdominal organs, a meticulous surgical approach is required to avoid tumor fragmentation, ensure radical resection, and optimize subsequent HIPEC efficacy.6,7

Preoperative Considerations and Patient Selection

Proper patient selection is paramount to achieving optimal oncologic outcomes with en bloc resection. Candidates should undergo thorough preoperative evaluation, including:

1. **Imaging Studies:** Contrast-enhanced CT scan and diffusion-weighted MRI to assess peritoneal carcinomatosis index (PCI), tumor invasion, and organ involvement. PET-CT may be useful in select cases to rule out extraperitoneal disease.6,7
2. **Laparoscopic Staging:** In patients with borderline resectability, diagnostic laparoscopy can assess tumor distribution and feasibility of complete cytoreduction.6,7
3. **Nutritional and Functional Status:** Prehabilitation strategies, including enteral nutrition, albumin optimization, and physical conditioning, are essential in patients undergoing extensive multivisceral resections.6,7

Surgical Techniques for En Bloc Resection in Appendiceal Cancer with Peritoneal Carcinomatosis

1. Exploratory Laparotomy and Peritoneal Debulking

Surgical intervention begins with a **midline laparotomy** to allow full abdominal access. A thorough exploration of the peritoneal cavity is conducted, documenting tumor dissemination using the Peritoneal Carcinomatosis Index (PCI), which determines the feasibility of complete cytoreduction.6,7

- If PCI is **>20-25**, complete cytoreduction may be challenging but still achievable in select cases.6,7
- If PCI is **≤10**, optimal resection is more feasible, and long-term survival is significantly improved with CRS-HIPEC.6,7

Peritoneal stripping or debulking involves:

- **Parietal Peritonectomy:** Systematic excision of the peritoneal surfaces involved, including diaphragmatic, pelvic, and omental peritoneum.8
- **Visceral Peritonectomy:** Resection of serosal tumor deposits on hollow and solid organs, if necessary.8

2. Right Hemicolectomy and En Bloc Appendiceal Tumor Resection

Given the primary origin of the malignancy in the appendix, **right hemicolectomy** is typically performed, ensuring en bloc resection of the ileocecal region with associated lymphadenectomy.

- **Standard Right Hemicolectomy:** Performed when tumor invasion is limited to the cecum and ascending colon.8
- **Extended Right Hemicolectomy:** Indicated when there is contiguous involvement of the transverse colon or ileum.8
- **Ileocolic Lymphadenectomy:** Essential to assess nodal involvement and refine staging.8

A mesenteric resection margin of at least 2 cm is recommended to ensure complete tumor clearance. Stapled or hand-sewn anastomosis is performed based on intraoperative conditions.

3. En Bloc Resection of Pelvic Tumor Burden

Pelvic involvement is common in advanced appendiceal neoplasms, necessitating aggressive resection:

- **Total Pelvic Peritonectomy:** Indicated in cases of peritoneal seeding affecting the bladder dome, rectosigmoid junction, or female reproductive organs.8
- **Low Anterior Resection (LAR) or Abdominoperineal Resection (APR):** Performed when rectosigmoid invasion is present.8
- **Hysterectomy and Bilateral Salpingo-Oophorectomy:** Routinely indicated in female patients with PC to eliminate potential tumor reservoirs.8

4. Resection of Diaphragmatic and Upper Abdominal Disease

Diaphragmatic and upper abdominal involvement requires specialized surgical techniques:

- **Diaphragmatic Peritonectomy:** Complete stripping of the diaphragmatic peritoneum is performed when tumor plaques are present.8
- **Liver Capsular Resection:** In cases of superficial hepatic invasion, wedge resections of Glisson's capsule are undertaken to ensure cytoreduction.8
- **Splenectomy and Greater Omentectomy:** If significant disease burden is present in the left upper quadrant.8

Diaphragmatic defects may require reconstruction with absorbable mesh or direct closure based on the extent of resection.9

5. Multivisceral Resections for Advanced Disease

For locally advanced disease with contiguous organ invasion, multivisceral resection is warranted:

- **Gastrectomy (Partial or Total):** If tumor involves the gastric serosa.9
- **Pancreaticoduodenectomy (Whipple Procedure):** Reserved for rare cases with pancreatic invasion.9
- **Nephrectomy/Ureteral Resection:** If tumor encases or infiltrates retroperitoneal structures.9

Despite the high morbidity associated with these extensive resections, achieving CC-0 remains the priority to maximize survival benefit.9

6. Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Following en bloc resection and cytoreduction, HIPEC is administered intraoperatively to eradicate residual microscopic disease.9

- **Chemotherapy Agents:** Common regimens include **mitomycin C**, **oxaliplatin**, or **cisplatin + doxorubicin**, depending on histologic subtype.9
- **Perfusion Techniques:**
    - **Open Coliseum Technique:** Enhances direct chemotherapy distribution but increases heat loss.9
    - **Closed Technique:** Reduces exposure risks and maintains uniform peritoneal perfusion.9

HIPEC is typically delivered at 41-43°C over 60–90 minutes, ensuring maximal cytotoxicity against residual tumor cells while minimizing systemic toxicity.10

Postoperative Considerations and Complications

Major postoperative challenges include:

- **Hemodynamic Instability:** Resulting from extensive peritoneal dissection and fluid shifts.10
- **Gastrointestinal Fistula Formation:** Due to anastomotic breakdown, particularly after multivisceral resections.10
- **Prolonged Ileus or Bowel Obstruction:** Secondary to peritoneal adhesions or HIPEC-related serosal inflammation.10
- **Pulmonary Complications:** Such as pleural effusions or pneumonia, particularly after diaphragmatic resections.10

A multimodal enhanced recovery after surgery (ERAS) protocol is crucial to reduce morbidity, improve functional recovery, and shorten hospital stay.10

En bloc resection in the context of peritoneal carcinomatosis from appendiceal cancer is a technically demanding yet oncologically necessary approach for achieving optimal cytoreduction. When combined with HIPEC, this surgical strategy provides the best opportunity for prolonged survival in patients with advanced appendiceal malignancies. Careful patient selection, adherence to standardized surgical techniques, and meticulous perioperative management are essential to maximizing the efficacy of this aggressive but potentially curative intervention. Future research should focus on refining patient selection criteria, improving minimally invasive CRS techniques, and developing novel HIPEC regimens to further enhance long-term outcomes.11,12

Contraindications for En Bloc Resection in Peritoneal Carcinomatosis with HIPEC in Appendiceal Cancer

En bloc resection combined with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has revolutionized the management of peritoneal carcinomatosis (PC) secondary to appendiceal malignancies. However, despite its potential for prolonged survival and even curative intent in select patients, not all cases are amenable to this aggressive surgical approach. Identifying absolute and relative contraindications is essential to minimize futile interventions, optimize patient selection, and prevent excessive morbidity and mortality.

Contraindications to en bloc resection and HIPEC in appendiceal cancer can be categorized into oncologic, anatomic/surgical, physiologic, and patient-related factors.13,14

1. Oncologic Contraindications

A. Extensive Extra-abdominal Metastatic Disease

The presence of **hematogenous metastases** outside the peritoneal cavity remains an absolute contraindication to CRS-HIPEC, as systemic disease burden significantly reduces the potential for long-term survival. Specific scenarios include:13,14

- **Pulmonary metastases**: Patients with multiple bilateral lung nodules or bulky intrathoracic disease are unlikely to benefit from CRS-HIPEC.13,14
- **Hepatic parenchymal metastases**: Unlike peritoneal surface involvement, deep intrahepatic metastases are associated with poor prognosis and may require systemic chemotherapy rather than surgical intervention.13,14
- **Distant lymphatic spread**: Retroperitoneal, mediastinal, or supraclavicular nodal involvement signifies systemic dissemination, precluding cytoreductive surgery.13,14

B. High Tumor Burden with Unresectable Disease (Extremely High PCI Score)

The Peritoneal Carcinomatosis Index (PCI) serves as a crucial predictor of resectability. While PCI scores ≤20-25 are generally associated with complete cytoreduction and improved survival, scores >30-39 in aggressive histologic subtypes (e.g., high-grade appendiceal adenocarcinoma) suggest a poor likelihood of achieving CC-0 resection.13,14

- Diffuse small bowel involvement (PCI > 12 in the small bowel region) is a common reason for unresectability, as preservation of adequate intestinal length for postoperative function is necessary.13,14
- Extensive tumor infiltration into the mesenteric root compromises vascular supply and prohibits safe resection.13,14

C. Aggressive Histologic Subtypes with Poor Response to HIPEC

Certain histopathologic variants of appendiceal cancer exhibit limited responsiveness to CRS-HIPEC and systemic chemotherapy, making aggressive surgical intervention less justified. These include:13,14

- **Signet-ring cell carcinoma**: Associated with early systemic dissemination, high recurrence rates, and poor survival despite radical resection.13,14
- **High-grade undifferentiated adenocarcinoma**: Often presents with diffuse invasion and limited therapeutic options.13,14

In contrast, low-grade mucinous neoplasms, such as pseudomyxoma peritonei (PMP), generally have a better prognosis and respond more favorably to CRS-HIPEC.

2. Anatomic and Surgical Contraindications

A. Unresectable Small Bowel Involvement

Extensive peritoneal carcinomatosis affecting the **mesentery or serosal surfaces of the small intestine** is one of the most limiting factors for CRS-HIPEC.13,14

- Preservation of at least 180 cm of functional small bowel is necessary to prevent short bowel syndrome, which can result in severe malabsorption, chronic diarrhea, and dependence on total parenteral nutrition (TPN).13,14
- Diffuse tumor infiltration into the superior mesenteric artery (SMA) or vein (SMV) makes safe resection technically unfeasible.13,14

B. Extensive Retroperitoneal and Vascular Invasion

Tumor extension into critical retroperitoneal structures precludes safe en bloc resection. Key scenarios include:13,14

- **Direct invasion of the aorta, inferior vena cava (IVC), or iliac vessels**, where complete vascular reconstruction would be required but is associated with prohibitive morbidity.13,14
- **Ureteral encasement** by bulky disease, leading to nonfunctional kidneys and long-term renal insufficiency.13,14

C. Unmanageable Diaphragmatic and Thoracic Involvement

While **diaphragmatic peritonectomy** is routinely performed in CRS-HIPEC, extensive invasion into the thoracic cavity presents challenges:13,14

- Large pleural effusions, direct invasion of the lung parenchyma, or massive diaphragmatic involvement may lead to respiratory compromise postoperatively.13,14
- Incomplete cytoreduction in the setting of pleural carcinomatosis reduces the efficacy of HIPEC, making it a relative contraindication.15

3. Physiologic and Medical Contraindications

A. Severe Cardiopulmonary Disease

Given the high physiologic demands of CRS-HIPEC, patients must have adequate cardiovascular and pulmonary reserve. The following conditions are **contraindications** due to the increased risk of perioperative complications:15

- **Severe congestive heart failure (NYHA Class III-IV)**: The prolonged operative time, massive fluid shifts, and HIPEC-induced hyperthermia place significant strain on cardiac function.15
- **Severe chronic obstructive pulmonary disease (COPD) or pulmonary hypertension**: Increases the risk of prolonged ventilatory dependence and postoperative pneumonia.15
- **Uncontrolled arrhythmias or recent myocardial infarction (within 6 months)**: Increases perioperative mortality.15

B. Renal and Hepatic Dysfunction

Organ function must be optimized before undertaking CRS-HIPEC:

- **Chronic kidney disease (CKD) stage 4-5**: HIPEC chemotherapy agents (e.g., cisplatin, mitomycin C) are nephrotoxic and require adequate renal clearance.15
- **Cirrhosis with portal hypertension**: Increases bleeding risk and precludes safe peritoneal dissection.15
- **Hyperbilirubinemia >3 mg/dL or INR >1.5**: Suggests hepatic insufficiency, limiting drug metabolism and wound healing.15

C. Poor Nutritional Status and Functional Reserve

Malnourished patients with a body mass index (BMI) <18 kg/m², severe hypoalbuminemia (serum albumin <2.5 g/dL), or significant weight loss (>15% in 3 months) face increased morbidity due to impaired wound healing, infections, and prolonged recovery.15

4. Patient-Related Contraindications

A. Frailty and Poor Performance Status

Patients with an Eastern Cooperative Oncology Group (ECOG) performance status ≥3 or a Karnofsky score <50%generally do not tolerate aggressive surgery.16

B. Patient Refusal or Poor Adherence to Postoperative Care

- Patients unwilling to undergo prolonged hospitalization, intensive postoperative care, or long-term surveillance may not be suitable candidates.17
- Cognitive impairment, psychiatric disorders, or lack of social support can compromise postoperative adherence.18

While en bloc resection with CRS-HIPEC offers a potential cure in select patients with peritoneal carcinomatosis from appendiceal cancer, careful patient selection is paramount to avoid unnecessary morbidity and mortality. Absolute contraindications include systemic metastatic disease, extensive small bowel involvement, severe comorbidities, and poor functional reserve. Relative contraindications

require multidisciplinary evaluation, balancing surgical feasibility with oncologic benefit. Future advancements in neoadjuvant therapies and minimally invasive approaches may help expand the eligibility criteria for CRS-HIPEC in appendiceal cancer.17,18

CONCLUSIONS

The implementation of en bloc resection in combination with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) represents a paradigm shift in the management of peritoneal carcinomatosis (PC) secondary to appendiceal neoplasms. This aggressive approach, which integrates extensive surgical debulking with intraoperative regional chemotherapy, has demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS) in well-selected patients. However, the success of this therapeutic modality hinges on meticulous patient selection, precise surgical execution, and comprehensive perioperative management.

1. En Bloc Resection: An Essential Component of Complete Cytoreduction

The rationale behind en bloc resection in peritoneal dissemination of appendiceal malignancies is rooted in the fundamental oncologic principle of achieving macroscopic tumor clearance (CC-0 or CC-1 resection). Unlike segmental peritonectomy or piecemeal excision, en bloc resection facilitates the removal of contiguous tumor deposits within affected peritoneal surfaces and adherent visceral structures, thereby minimizing the risk of residual microscopic disease.

This technique is particularly advantageous in cases where the tumor has extensively infiltrated adjacent organs such as the colon, small intestine, ovaries, bladder, and stomach. By resecting affected structures en bloc, the integrity of the tumor capsule is preserved, reducing the likelihood of peritoneal spillage and tumor seeding. Moreover, this approach ensures maximal cytoreduction, which is a prerequisite for the effective delivery of HIPEC and subsequent systemic chemotherapy.

However, despite its benefits, en bloc resection remains a technically demanding procedure associated with high intraoperative complexity. It necessitates advanced surgical expertise, familiarity with peritoneal anatomy, and proficiency in multi-visceral resection techniques. Furthermore, the risk of perioperative morbidity, including anastomotic leakage, hemorrhage, and prolonged ileus, underscores the importance of careful intraoperative decision-making and optimized postoperative care.

2. HIPEC: Enhancing Local Tumor Control

The addition of HIPEC following en bloc cytoreduction serves as a crucial adjunct in eliminating microscopic residual disease and preventing locoregional recurrence. HIPEC operates on the principles of direct peritoneal drug perfusion, hyperthermia-induced cytotoxicity, and enhanced drug penetration into peritoneal surfaces. Agents such as mitomycin C, cisplatin, oxaliplatin, and irinotecan have been widely utilized, each with distinct pharmacokinetic properties tailored to specific histologic subtypes of appendiceal neoplasms.

Clinical studies have corroborated the role of HIPEC in improving long-term oncologic outcomes, particularly in low-grade mucinous neoplasms and pseudomyxoma peritonei (PMP), where complete cytoreduction significantly extends survival. Conversely, in high-grade appendiceal adenocarcinomas and signet-ring cell carcinomas, HIPEC appears to provide only a modest survival benefit, particularly in cases with high peritoneal carcinomatosis index (PCI) scores.

The integration of HIPEC into the surgical protocol necessitates a multidisciplinary approach, ensuring hemodynamic stability, temperature regulation, and intraoperative chemotherapy monitoring. The potential nephrotoxicity, hematologic toxicity, and systemic absorption of HIPEC agents mandate stringent perioperative surveillance and tailored postoperative management strategies.

3. Patient Selection: A Determinant of Surgical Success

One of the critical determinants of success in en bloc resection with CRS-HIPEC is **patient selection**. While this strategy offers a potential cure for certain subsets of appendiceal neoplasms, its applicability must be carefully evaluated against the patient's oncologic burden, physiological reserve, and overall prognosis.

Optimal candidates for CRS-HIPEC include patients with:

- **Limited peritoneal disease burden (PCI ≤20-25) with no extra-abdominal metastases**
- **Good performance status (ECOG 0-1, Karnofsky >70%)**
- **Adequate renal, hepatic, and cardiopulmonary function**
- **Histopathological subtypes amenable to HIPEC treatment (low-grade mucinous neoplasms, peritoneal mucinous carcinomatosis)**

Conversely, patients with extensive small bowel involvement, distant hematogenous metastases, unresectable retroperitoneal invasion, or severe medical comorbidities are generally poor candidates for this approach due to prohibitive perioperative morbidity and limited oncologic benefit.

The role of neoadjuvant systemic chemotherapy in borderline resectable cases remains an area of active investigation. Some studies suggest that preoperative chemotherapy may downstage tumor burden, facilitate cytoreduction, and improve resectability in high-risk patients. However, the optimal timing, regimen, and sequencing of systemic therapy in conjunction with CRS-HIPEC remain to be definitively established.

4. Long-Term Outcomes and Prognostic Factors

The long-term outcomes of en bloc resection with CRS-HIPEC in appendiceal cancer largely depend on several prognostic variables:

- **Histologic subtype**: Patients with low-grade mucinous neoplasms and pseudomyxoma peritonei (PMP) have the most favorable outcomes, with reported 5-year survival rates exceeding 70% in cases achieving complete cytoreduction. In contrast, high-grade signet-ring cell carcinomas have significantly poorer prognoses, with median survival rarely exceeding 2-3 years.
- **Extent of disease (PCI score)**: Low PCI scores correlate with higher rates of complete cytoreduction and improved survival. PCI scores **>30-39** are associated with high recurrence rates and reduced overall survival.
- **Cytoreduction completeness (CC score)**: Achieving a **CC-0 or CC-1 resection** is paramount, as incomplete cytoreduction (CC-2 or CC-3) negates the benefits of HIPEC and predisposes to early disease progression.
- **Response to systemic therapy**: In high-grade appendiceal adenocarcinomas, adjuvant chemotherapy regimens incorporating fluoropyrimidines (5-FU, capecitabine), oxaliplatin, or irinotecan may enhance disease control. The role of targeted therapies and immunotherapy in this setting remains under exploration.

5. Future Directions and Challenges

Despite the advances in en bloc resection and HIPEC, several challenges persist:

- **Optimization of patient selection criteria** to better predict responders to CRS-HIPEC and avoid unnecessary morbidity in non-beneficial cases.
- **Development of novel intraperitoneal chemotherapy agents**, including **pressurized intraperitoneal aerosol chemotherapy (PIPAC)**, which may offer a less invasive alternative to HIPEC.
- **Integration of molecular and genetic profiling** to stratify patients based on tumor biology, guiding personalized therapeutic approaches.
- **Improvement in perioperative care protocols**, including enhanced recovery pathways (ERAS), to minimize complications and expedite recovery.

En bloc resection with CRS-HIPEC represents a complex yet potentially curative strategy for selected patients with peritoneal carcinomatosis secondary to appendiceal cancer. While the approach confers significant survival benefits in carefully chosen cases, its success is contingent upon meticulous surgical execution, optimal patient selection, and multimodal perioperative management. Continued research into novel therapeutic agents, enhanced surgical techniques, and predictive biomarkers will be essential to refine treatment algorithms and improve long-term outcomes in this challenging oncologic entity.

REFERENCES

I. Wang TY, Chen CY, Lu CH, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal malignancy: preliminary results of a multi-disciplinary teamwork model in Asia. Int J Hyperthermia 2018;34:328-35.

II. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med 2018;378:230-40.

III. Panarelli NC, Yantiss KR. Mucinous Neoplasms of the Appendix and Peritoneum. Arch Pathol Lab Med 2011;135:1261-8.

IV. Shankar S, Ledakis P, El Halabi H, et al. Neoplasms of the appendix: current treatment guidelines. Hematol Oncol Clin North Am 2012;26:1261-90.

V. Bruin SC, Verwaal VJ, Vincent A, et al. A clinicopathologic analysis of peritoneal metastases of colorectal and appendiceal origin. Ann Surg Oncol 2010;17:2330-40.

VI. American Joint Committee on Cancer. Colon and Rectum Cancer Staging. Available online: https://cancerstaging.org/referencestools/quickreferences/Documents/ColonMedium.pdf

VII. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol 2010;17:3077-9.

VIII. World Health Organization. Classification TNM/FIGO. Available online: http://screening.iarc.fr/atlasclassiftnm.php?lang=1

IX. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). 2009. Available online: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pd

X. Coccolini F, Gheza F, Lotti M, et al. Peritoneal Carcinomatosis. World J Gastroenterol 2013;19:6979-94.

XI. Mohamed F, Moran BJ. Morbidity and Mortality With Cytoreductive Surgery and Intraperitoneal Chemotherapy: The Importance of a Learning Curve. Cancer J 2009;15:196-9.

XII. Moran B, Cecil T, Chandrakumaran K, et al. The results of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in 1200 patients with peritoneal malignancy.Colorectal Dis 2015;17:772-8.

XIII. Coccolini F, Cotte E, Glehen O, et al. Intraperitoneal chemotherapy in advanced gastric cancer. Meta-analysis of randomized trials. Eur J Surg Oncol 2014;40:12-26.

XIV. Coccolini F, Catena F, Glehen O, et al. Complete versus incomplete cytoreduction in peritoneal carcinosis from gastric cancer, with consideration to PCI cut-off. Systematic review and meta-analysis. Eur J Surg Oncol 2015;41:911-9.

XV. Coccolini F, Catena F, Glehen O, et al. Effect of intraperitoneal chemotherapy and peritoneal lavage in positive peritoneal cytology in gastric cancer. Systematic review and meta-analysis. Eur J Surg Oncol 2016;42:1261-7.

XVI. Coccolini F, Celotti A, Ceresoli M, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) and neoadjuvant chemotherapy as prophylaxis of peritoneal carcinosis from advanced gastric cancer—effects on overall and disease free survival. J Gastrointest Oncol 2016;7:523-9.

XVII. Fugazzola P, Coccolini F, Montori G, et al. Overall and disease-free survival in patients treated with CRS + HIPEC with cisplatin and paclitaxel for gastric cancer with peritoneal carcinomatosis. J Gastrointest Oncol 2017;8:572-82.

XVIII. Mirnezami R, Mehta AM, Chandrakumaran K, et al. Cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy improves survival in patients with colorectal peritoneal metastases compared with systemic chemotherapy alone. Br J Cancer 2014;111:1500-8.