The impact of HIPEC vs. EPIC for the treatment of mucinous appendiceal carcinoma: a study from the US HIPEC collaborative

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ABSTRACT

Introduction: Mucinous appendiceal carcinoma is a rare malignancy that commonly spreads to the peritoneum leading to peritoneal metastases. Complete cytoreduction with perioperative intraperitoneal chemotherapy (PIC) is the mainstay of treatment, administered as either hyperthermic intraperitoneal chemotherapeutic agent, temperature, dose, duration and timing of application. Considerations, and survival outcomes were compared among patients who underwent HIPEC vs. EPIC with inverse probability weighting (IPW) used for adjustment. Results: Among 921 patients with mucinous appendiceal carcinoma, 9% underwent EPIC while 91% underwent HIPEC. There was no difference in Grade III–V complications between the two groups (18.5% for HIPEC vs. 15.0% for EPIC, p = .43) though patients who underwent HIPEC had higher rates of readmissions (21.2% vs. 8.8%, p < .01). Additionally, PIC method was not an independent predictor for overall survival (OS) or recurrence-free survival (RFS) after adjustment on multivariable analysis. Conclusions: Among patients with mucinous appendiceal carcinoma, both EPIC and HIPEC appear to be associated with similar perioperative and long-term outcomes.

Introduction

Mucinous appendiceal carcinoma is a rare malignancy that has a predilection for peritoneal dissemination leading to peritoneal metastases [1]. Given the indolent nature, typical confinement to the peritoneal cavity and superficial mucinous nature, surgical resection with perioperative intraperitoneal chemotherapy (PIC) has been the cornerstone of treatment for patients with peritoneal metastases [2–4]. There are two methods by which PIC can be administered: as hyperthermic intraperitoneal chemotherapy (HIPEC) or as early post-operative intraperitoneal chemotherapy (EPIC). While definitions and techniques have been clearly standardized for cytoreductive surgery [5], there remains no standardization of PIC treatment and the method of PIC used has generally been based on surgeon preference and training practices. Important pharmacological variables to be considered in defining the optimal PIC include: chemotherapeutic agent, temperature, dose, duration and timing of application.

The early use of PIC began with EPIC using chemotherapy and/or radioisotopes [6]. PIC has the advantages of allowing...
repeated administration and longer dwell times of chemo-
therapeutic agents including anti-metabolites. However, this
administration technique is limited by patient discomfort and
post-operative adhesions limiting peritoneal exposure. Additionally, EPIC does not permit the application of
hyperthermia.
In contrast, HIPEC has the perceived benefits of increased
patient comfort, improved cytotoxicity and local concentra-
tion, as well as the ability to achieve hyperthermia [7,8]. The
addition of hyperthermia may augment the penetration and
effectiveness of some chemotherapeutic agents [9]. However, it
implies a single application over a short duration and therefore non cell-cycle specific chemotherapeutic agent
is necessary.
Currently, HIPEC is more commonly used than EPIC, how-
ever, both are still used today without a clear superiority of
one technique over the other [10]. Additionally, techniques
and chemotherapy regimens continue to differ considerably
across the world without standardization.
While numerous studies have reported acceptable safety
and efficacy with either PIC method, there has not been a
direct comparison in regards to their impact on post-opera-
tive or long-term outcomes. Two small retrospective series
demonstrated no difference in the recurrence-free or overall
survival (OS) between patients with peritoneal carcinomatosis
from appendical malignancies [11,12], and there are con-
flicting results regarding HIPEC and/or EPIC in peritoneal
carcinomatosis from colon cancer [10,13]. In order to advance
the field, more investigations identifying the optimal chemo-
therapeutic agent(s), dose, duration, temperature and deliv-
ery method are necessary in order to standardize approaches
for patient care throughout the world. Our goal was to
assess the perioperative and survival outcomes associated
with the two PIC methods to determine if there is a benefit
to one method over the other for patients with peritoneal
metastases from mucinous appendiceal carcinoma.

Materials and methods
Patients were identified in the US HIPEC Collaborative data-
bases as those who underwent curative intent surgery for
mucinous appendiceal carcinoma from 2000 to 2017. The US
HIPEC Collaborative includes the following 12 academic insti-
tutions: Mayo Clinic, The Ohio State University, MD Anderson
Cancer Center, Moffitt Cancer Center, University of California
San Diego, Medical College of Wisconsin, Emory University,
University of Cincinnati, University of Massachusetts,
University of Wisconsin, City of Hope National Medical
Center, and Johns Hopkins University [14,15]. This study was
approved by the Institutional Review Board at all 12 institu-
tions. Clinical, pathologic, post-operative and survival
outcomes were collected. Patients were divided into two
groups: CRS with HIPEC and CRS with EPIC.
Only one institution (Mayo Clinic) performed EPIC and this
was standardized with 5-fluorouracil (5-FU) and radioactive
phosphorus. This was the only form of PIC used at this insti-
tution. When patients were clinically stable following CRS,
they received 3 d of intraperitoneal 5-FU infusion at a dose
of 1000 mg/d. On the 4th day, patients were given 10 mCi of
intraperitoneal chromic phosphate (P32) and peritoneal drain
was then removed. HIPEC regimens were performed by the
other 11 institutions with nearly 99% using mitomycin
C (MMC).
There were no PCI values available for the EPIC group so
the number of resections for each patient was calculated
and used to estimate extent of disease. See Supplementary
Table 1 for greater detail on how number of resections was
determined. The highest number of resections was 25 with
an IQR of 3–10. This was dichotomized into extensive disease
(more than 10 resections) and less extensive disease (less
than or equal to 10) given that 10 was the 75th percentile.

Statistical analysis
Differences in patient demographics, clinical characteristics,
and early complications were assessed using Chi-square for
categorical factors and Wilcoxon rank-sum tests for continu-
fous factors. Categorical data are reported as number and
percent while continuous data are reported as median and
IQR. Univariate and multivariable Cox proportional hazards
regression was utilized to assess factors associated with
recurrence and post 90-d survival. All clinically relevant vari-
ables were included in the multivariable models. Of note, for
the multivariable analysis, 46% of patients had missing clinical
variables and were excluded to obtain an accurate analy-
was baseline characteristics were compared between the
included and excluded group and there were minimal signifi-
cant differences noted (Supplementary Table 2). Inverse
probability weighting (IPW) was utilized for adjustment with
the weight developed from a logistic regression model pre-
dicting EPIC vs. HIPEC (C-statistic = 0.87) where the sole pre-
dictor was surgery year. Analysis was performed using SAS
version 9.4 (SAS Inc., Cary, NC) and p-values <.05 were con-
sidered statistically significant.

Results
Clinical and pathological characteristics
Out of the 2372 patients in the US HIPEC Collaborative data-
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chemotherapy were used more often in the HIPEC group. The marker for extent of disease, number of resections, was not statistically different between the two groups with a median of seven resections each. Patients with moderately or poorly differentiated tumors were more likely to receive neoadjuvant chemotherapy (34% vs. 12%, \( p < .01 \)) and adjuvant chemotherapy (27% vs. 7%, \( p < .01 \)) than patients with well-differentiated tumors.

There was no difference in rates of Grade III–V complications between the two groups (18.5% for HIPEC vs. 15.0% for EPIC, \( p = .43 \)) (Table 2). HIPEC operations took longer to complete (7.9 (IQR: 6.1, 9.9) hours vs. 5.4 (IQR: 3.3, 7.2), \( p < .01 \)) but had fewer CC2/3 resections than the EPIC group (7.1% vs. 13.8%, \( p = .03 \)). Patients undergoing HIPEC had higher rates of readmissions (21.2% vs. 8.8%, \( p < .01 \)) when compared to those receiving EPIC (Table 2). There was no difference in 90-d mortality between the two groups (0.0% in EPIC and 1.4% in HIPEC, \( p = .29 \)).

**Survival**

Median follow-up in the overall cohort was 35 months (IQR: 17.6, 59.5) and was not statistically different between the two PIC cohorts. PIC method was not found to be an independent predictor for OS (HR 1.25, 95% CI 0.56–2.81, \( p = .59 \)) or RFS (HR 1.24, 95% CI 0.81–1.90, \( p = .31 \)) after adjustment on multivariable analysis (Table 3). Factors that were independent predictors of worse OS include ASA 3–4 (HR 1.93, 95% CI 1.01–3.70, \( p = .046 \)), moderate or poorly differentiated histology (HR 2.64, 95% CI 1.51–4.63, \( p < .01 \)), CC score (HR 2.12, 95% CI 1.02–4.39, \( p = .04 \)), neoadjuvant chemotherapy (HR 2.98, 95% CI 1.59–5.57, \( p = .01 \)) and adjuvant chemotherapy (HR = 2.05, 95% CI 1.10–3.84, \( p = .03 \)). Variables that were independent predictors of worse RFS included older age (HR 1.47, 95% CI 1.05–2.06, \( p = .03 \)), moderate or poorly differentiated histology (HR 1.40, 95% CI 1.01–1.94, \( p = .045 \)), higher CC score (HR 1.69, 95% CI 1.05–2.72, \( p = .03 \)), neoadjuvant chemotherapy (HR 3.08, 95% CI 2.08–4.57, \( p < .01 \)), and adjuvant chemotherapy (HR 1.75, 95% CI 1.18–2.59, \( p < .01 \)).

Given the significant role that tumor differentiation has on survival and recurrence, the patients were divided into well-differentiated and moderately- or poorly-differentiated and analyzed separately. In the well-differentiated cohort, PIC method was not an independent risk factor for survival or recurrence (Table 4). Similarly, PIC method was not significant for survival or recurrence in the moderately- and poorly-differentiated cohort (Table 5).

**Discussion**

CRS and PIC have become the standard of care for the treatment of peritoneal metastases from mucinous appendiceal neoplasms with multiple retrospective series supporting its safety and efficacy [7,16,17]. Similar to our study, two previous small single institutional studies have failed to demonstrate any difference in survival outcomes between HIPEC and EPIC for mucinous appendiceal neoplasms [11,12]. No study to our knowledge has compared postoperative morbidity, hospital length of stay and readmissions between the two techniques. The randomized phase II ICARuS (NCT01815359) trial is currently enrolling patients with peritoneal carcinomatosis from the appendix, colon or rectum to EPIC with 5-fluorouracil (5-FU) and leucovorin or HIPEC with Mitomycin-C after complete (CC-0 and CC-1) cytoreduction. The primary outcome of disease-free survival and the secondary outcomes of surgical and chemotherapy-related grade III–V toxicity is anticipated to provide further data regarding the optimal method of PIC.

The question of whether the combination of HIPEC and EPIC could potentially provide additional survival benefit for patients with peritoneal metastases from mucinous appendiceal neoplasms compared to HIPEC alone remains unanswered and is an area with a conflicting conclusion in the literature [18]. A previous study from Australia of 185 patients with high grade appendiceal peritoneal metastasis found that the combination of HIPEC and EPIC resulted in improved OS (hazard ratio [HR] = 0.42) and disease-free survival (HR = 0.66), without increasing postoperative morbidity and mortality [19].

In contrast, a Canadian study of 198 patients with peritoneal metastases from a multitude of tumor types reported a higher rate of grade III/IV complications in patients who received HIPEC and EPIC when compared to patients who received HIPEC alone (44.7% vs. 31.0%, \( p = .05 \)) [20]. A second study from the same group looked at 93 patients with peritoneal metastasis from high grade appendiceal or colorectal...
Table 1. Demographics and clinical characteristics.

|                                | EPIC (N = 80) | HIPEC (N = 841) | Total (N = 921) | p Value |
|--------------------------------|---------------|-----------------|----------------|---------|
| **Age at time of surgery**     |               |                 |                |         |
| N                              | 80            | 841             | 921            | .02a    |
| **Mean (SD)**                  | 58.3 (12.7)   | 54.8 (11.8)     | 55.1 (11.9)    |         |
| **Median**                     | 59.0          | 55.0            | 55.0           |         |
| Q1, Q3                         | 48.0, 67.5    | 48.0, 64.0      | 48.0, 64.0     |         |
| **Range**                      | (32.0–86.0)   | (19.0–86.0)     | (19.0–86.0)    |         |
| **Age group**                  |               |                 |                | .01b    |
| <65 (%)                        | 51 (63.8)     | 650 (77.3)      | 701 (76.1)     |         |
| ≥65 (%)                        | 29 (36.3)     | 191 (22.7)      | 220 (23.9)     |         |
| **Gender**                     |               |                 |                | .91b    |
| Male (%)                       | 48 (60.0)     | 510 (60.6)      | 558 (60.6)     |         |
| Female (%)                     | 32 (40.0)     | 331 (39.4)      | 363 (39.4)     |         |
| **Race**                       |               |                 |                |         |
| Missing                        | 0             | 8               | 8              |         |
| White (%)                      | 77 (96.3)     | 686 (82.4)      | 763 (83.6)     |         |
| Black (%)                      | 0 (0.0)       | 42 (5.0)        | 42 (4.6)       |         |
| Asian (%)                      | 1 (1.3)       | 44 (5.3)        | 45 (4.9)       |         |
| Latino (%)                     | 0 (0.0)       | 33 (4.0)        | 33 (3.6)       |         |
| Other (%)                      | 2 (2.5)       | 28 (3.4)        | 30 (3.3)       |         |
| **Albumin**                    |               |                 |                | .02a    |
| N                              | 45            | 657             | 702            |         |
| **Mean (SD)**                  | 4.0 (0.4)     | 4.1 (0.5)       | 4.1 (0.5)      |         |
| **Median**                     | 4.0           | 4.2             | 4.2            |         |
| Q1, Q3                         | 3.8, 4.3      | 3.9, 4.4        | 3.9, 4.4       |         |
| **Range**                      | (3.1–4.8)     | (1.4–7.5)       | (1.4–7.5)      |         |
| **ASA Score**                  |               |                 |                | .01b    |
| Missing                        | 1             | 126             | 127            |         |
| ASA 1–2 (%)                    | 50 (63.3)     | 156 (21.8)      | 206 (25.9)     |         |
| ASA 3–4 (%)                    | 29 (36.7)     | 559 (78.2)      | 588 (74.1)     |         |
| **Number of previous CRS**     |               |                 |                | .04b    |
| Missing                        | 0             | 1               | 1              |         |
| 0 (%)                          | 45 (56.3)     | 631 (75.1)      | 676 (73.5)     |         |
| 1 (%)                          | 33 (41.3)     | 182 (21.7)      | 215 (23.4)     |         |
| 2+ (%)                         | 2 (2.5)       | 27 (3.2)        | 29 (3.2)       |         |
| **Tumor differentiation**      |               |                 |                | <.01b   |
| Missing                        | 2             | 235             | 237            |         |
| Well differentiated (%)        | 45 (57.7)     | 445 (73.4)      | 490 (71.6)     |         |
| Moderate/poor differentiated (%)| 33 (42.3)   | 161 (26.6)      | 194 (28.4)     |         |
| **Signet ring cell**           |               |                 |                | .06a    |
| Missing                        | 1             | 280             | 281            |         |
| Yes (%)                        | 4 (5.1)       | 71 (12.7)       | 79 (12.3)      |         |
| No (%)                         | 75 (94.9)     | 490 (87.3)      | 561 (87.7)     |         |
| **EBL**                        |               |                 |                | .42a    |
| N                              | 19            | 825             | 844            |         |
| **Mean (SD)**                  | 431.6 (353.2) | 453.5 (573.0)   | 453.0 (568.9)  |         |
| **Median**                     | 300.0         | 300.0           | 300.0          |         |
| Q1, Q3                         | 200.0, 500.0  | 150.0, 500.0    | 150.0, 500.0   |         |
| **Range**                      | (100.0–1250.0)| (0.0–7000.0)    | (0.0–7000.0)   |         |
| **Operative time**             |               |                 |                | <.01a   |
| N                              | 80            | 757             | 837            |         |
| **Mean (SD)**                  | 5.6 (2.7)     | 8.2 (2.7)       | 7.9 (2.8)      |         |
| **Median**                     | 5.4           | 7.9             | 7.7            |         |
| Q1, Q3                         | 3.3, 7.2      | 6.1, 9.9        | 6.0, 9.6       |         |
| **Range**                      | (1.0–14.2)    | (3.0–20.0)      | (1.0–20.0)     |         |
| **Number of resections**       |               |                 |                | .38a    |
| Missing                        | 0             | 63              | 63             |         |
| N                              | 80            | 778             | 858            |         |
| **Mean (SD)**                  | 6.8 (3.7)     | 7.5 (4.6)       | 7.4 (4.6)      |         |
| **Median**                     | 7.0           | 7.0             | 7.0            |         |
| Q1, Q3                         | 3.0, 10.0     | 4.0, 10.0       | 4.0, 10.0      |         |
| **Range**                      | (1.0–15.0)    | (0.0–25.0)      | (0.0–25.0)     |         |
| **CC score**                   |               |                 |                | .03b    |
| Missing                        | 0             | 35              | 35             |         |
| CC 0 or 1 (%)                  | 69 (86.3)     | 749 (92.9)      | 818 (92.3)     |         |
| CC 2 or 3 (%)                  | 11 (13.8)     | 57 (7.7)        | 68 (7.7)       |         |
| **Chemotherapy type**          |               |                 |                | <.01b   |
| MMC (%)                        | 0 (0.0)       | 830 (98.7)      | 830 (90.1)     |         |
| 5-FU (%)                       | 80 (100.0)    | 0 (0.0)         | 80 (8.7)       |         |
| Others (%)                     | 0 (0.0)       | 11 (1.3)        | 11 (1.2)       |         |
| **Neoadjuvant chemotherapy**   |               |                 |                | <.01b   |
| Missing                        | 0             | 5               | 5              |         |
| No (%)                         | 76 (95.0)     | 658 (78.7)      | 734 (80.1)     |         |
| Yes (%)                        | 4 (5.0)       | 178 (21.3)      | 182 (19.9)     |         |
cancer and found no difference in OS and RFS between patients treated with CRS and HIPEC + EPIC vs. HIPEC alone but also found a higher incidence of grade III/IV complications [13]. A second group also found higher rates of grade III and above complications in 111 patients receiving EPIC after CRS and HIPEC compared to CRS and HIPEC alone (58% vs. 25%, \( p = .05 \)) [21]. Further investigation is warranted to determine what if any benefit EPIC may have in addition to HIPEC for patients with peritoneal metastasis from mucinous appendiceal neoplasms.

There are several limitations in this study. First, it was a retrospective study so there is significant risk for confounding and selection bias. Missing data resulted in exclusion of a large subset of patients from the multivariable analysis. Though there were some differences between the patients who remained in the analysis and those that were excluded (Supplementary Table 2), it is unlikely that this has resulted in significant changes to the data or conclusions generated from them. Chemotherapy agent, dose, and duration were not standardized for the HIPEC arm but were standardized for the EPIC arm which can introduce bias. There were significant differences in some of the baseline characteristics between patients treated with HIPEC and EPIC, which were controlled for in the multivariate model. However, other unmeasured differences could also have biased the results. Additionally, prospective PCI information was not available for the EPIC group and was therefore unable to be used in the analysis. We attempted to account for this as described with number of resections but this is of course not identical. EPIC was used at a single institution and as such had a significantly smaller sample size than the HIPEC group which can impact these results as well. Despite these limitations, our study reflects the largest multi-institutional US experience comparing two methods of PIC. We conclude that there

Table 1. Continued.

|                      | EPIC (N = 80) | HIPEC (N = 841) | Total (N = 921) | \( p \) Value |
|----------------------|--------------|-----------------|----------------|-------------|
| Adjuvant chemotherapy|              |                 |                | <.01\textsuperscript{b} |
| Missing              | 0            | 125             | 125            |             |
| No (%)               | 78 (97.5)    | 605 (84.5)      | 683 (85.6)     |             |
| Yes (%)              | 2 (2.5)      | 111 (15.5)      | 113 (14.2)     |             |

\textsuperscript{a} Wilcoxon. \textsuperscript{b} Chi-square.

EPIC: early post-operative intraperitoneal chemotherapy; HIPEC: hyperthermic intraperitoneal chemotherapy; ASA: American Society of Anesthesiologists; CRS: cytoreductive surgery; EBL: estimated blood loss; CC: completeness of cytoreduction; MMC: mitomycin-C; 5-FU: 5-fluorouracil.

Table 2. Complications.

|                      | EPIC (N = 80) | HIPEC (N = 841) | Total (N = 921) | \( p \) Value |
|----------------------|--------------|-----------------|----------------|-------------|
| Length of stay       |              |                 |                | .73\textsuperscript{a} |
| \( N \)              | 80           | 837             | 917            |             |
| Mean (SD)            | 10.6 (3.8)   | 13.1 (20.2)     | 12.8 (19.4)    |             |
| Median               | 10.0         | 10.0            | 10.0           |             |
| Q1, Q3               | 8.0, 12.0    | 8.0, 13.0       | 8.0, 13.0      |             |
| Range                | (4.0–29.0)   | (0.0–381.0)     | (0.0–381.0)    |             |
| ICU                  |              |                 |                | <.01\textsuperscript{b} |
| Missing              | 0            | 1               | 1              |             |
| No (%)               | 73 (91.3)    | 147 (17.5)      | 220 (23.9)     |             |
| Yes (%)              | 7 (8.8)      | 693 (82.5)      | 700 (76.1)     |             |
| Length of stay in ICU|              |                 |                | .08\textsuperscript{a} |
| \( N \)              | 7            | 635             | 642            |             |
| Mean (SD)            | 3.3 (1.4)    | 2.9 (4.1)       | 2.9 (4.1)      |             |
| Median               | 3.0          | 2.0             | 2.0            |             |
| Q1, Q3               | 2.0, 5.0     | 1.0, 3.0        | 1.0, 3.0       |             |
| Range                | (2.0–5.0)    | (0.0–57.0)      | (0.0–57.0)     |             |
| Grade                |              |                 |                | .43\textsuperscript{b} |
| No comp or grade I or II (%) | 68 (85.0) | 685 (81.5) | 753 (81.8) |             |
| Grade III or IV (%)  | 12 (15.0)    | 156 (18.5)      | 168 (18.2)     |             |
| Readmission          |              |                 |                | .01\textsuperscript{b} |
| Missing              | 0            | 5               | 5              |             |
| No (%)               | 73 (91.3)    | 659 (78.8)      | 732 (79.9)     |             |
| Yes (%)              | 7 (8.8)      | 177 (21.2)      | 184 (20.1)     |             |
| Reoperation          |              |                 |                | .18\textsuperscript{b} |
| Missing              | 0            | 66              | 66             |             |
| No (%)               | 75 (93.8)    | 689 (88.9)      | 764 (89.4)     |             |
| Yes (%)              | 5 (6.3)      | 86 (11.1)       | 91 (10.6)      |             |
| 90-d mortality       |              |                 |                | .29\textsuperscript{b} |
| Missing              | 0            | 47              | 47             |             |
| No (%)               | 80 (100.0)   | 783 (98.6)      | 863 (98.7)     |             |
| Yes (%)              | 0 (0.0)      | 11 (1.4)        | 11 (1.3)       |             |

\textsuperscript{a} Wilcoxon. \textsuperscript{b} Chi-Square.

EPIC: early post-operative intraperitoneal chemotherapy; HIPEC: hyperthermic intraperitoneal chemotherapy; ICU: intensive care unit.
is no difference in neither perioperative nor survival outcomes between HIPEC and EPIC for patients with peritoneal dissemination of mucinous appendiceal adenocarcinoma.

**Conclusions**

For patients with mucinous appendiceal carcinoma, both EPIC and HIPEC when combined with high-quality cytoreductive surgery are associated with excellent short- and long-term outcomes. Until prospective trials clarify the optimal regimen, either method of PIC can be used.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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