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Journal

Annals of Surgical Oncology, 27(13)

ISSN

1068-9265

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Publication Date

2020-12-01

DOI

10.1245/s10434-020-08843-6

Peer reviewed

HHS Public Access

Author manuscript

Ann Surg Oncol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Ann Surg Oncol. 2020 December ; 27(13): 4980–4995. doi:10.1245/s10434-020-08843-6.

Implications of Postoperative Complications for Survival After Cytoreductive Surgery and HIPEC: A Multi-Institutional Analysis of the US HIPEC Collaborative

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Abstract

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Meeting Presentation: 2020 SSO Advanced Cancer Therapies

DISCLOSURE There are no conflicts of interest.

Background.—Postoperative complications (POCs) are associated with worse oncologic outcomes in various cancer histologies. The impact of POCs on the survival of patients with appendiceal or colorectal cancer after cytoreductive surgery (CRS) and heated intraperitoneal chemotherapy (HIPEC) is unknown.

Methods.—The US HIPEC Collaborative (2000–2017) was reviewed for patients who underwent CCR0/1 CRS/HIPEC for appendiceal/colorectal cancer. The analysis was stratified by noninvasive appendiceal neoplasm versus invasive appendiceal/colorectal adenocarcinoma. The POCs were grouped into infectious, cardiopulmonary, thromboembolic, and intestinal dysmotility. The primary outcomes were overall survival (OS) and recurrence-free survival (RFS).

Results.—Of the 1304 patients, 33% had noninvasive appendiceal neoplasm ($n = 426$), and 67% had invasive appendiceal/colorectal adenocarcinoma ($n = 878$). In the noninvasive appendiceal cohort, POCs were identified in 55% of the patients ($n = 233$). The 3-year OS and RFS did not differ between the patients who experienced a complication and those who did not (OS, 94% vs 94%, $p = 0.26$; RFS, 68% vs 60%, $p = 0.15$). In the invasive appendiceal/colorectal adenocarcinoma cohort, however, POCs (63%; $n = 555$) were associated with decreased 3-year OS (59% vs 74%; $p < 0.001$) and RFS (32% vs 42%; $p < 0.001$). Infectious POCs were the most common (35%; $n = 196$). In Multivariable analysis accounting for gender, peritoneal cancer index (PCI), and incomplete resection (CCR1), infectious POCs in particular were associated with decreased OS compared with no complication (hazard ratio [HR] 2.08; $p < 0.01$) or other types of complications (HR, 1.6; $p < 0.01$). Similarly, infectious POCs were independently associated with worse RFS (HR 1.61; $p < 0.01$).

Conclusion.—Postoperative complications are associated with decreased OS and RFS after CRS/HIPEC for invasive histology, but not for an indolent disease such as noninvasive appendiceal neoplasm, and this association is largely driven by infectious complications. The exact mechanism is unknown, but may be immunologic. Efforts must target best practices and standardized prevention strategies to minimize infectious postoperative complications.

The literature demonstrates the existence of multiple surgery-induced, synergistic processes during the postoperative period that facilitate recurrence or distant metastases after oncologic resection. These processes include (1) perioperative factors such as tissue damage, blood transfusion, and hypothermia, (2) endocrine and paracrine factors such as secretion of catecholamines, (3) inhibition of cell-mediated immunity, (4) systemic release of growth and angiogenic factors, and (5) potential shedding of tumor cells during surgery.[1–3] In patients with peritoneal metastases who are candidates for cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), these processes are counteracted by tumor debulking, which allows the remaining cells to become more sensitive to anti-neoplastic agents and facilitates diffusion of intraperitoneal chemotherapy into remaining peritoneal nodules.[4–6] This procedure, however, is technically challenging, with potential for high morbidity secondary to postoperative complications (POCs), which can further induce inflammatory responses that prolong the aforementioned pro-metastatic processes.

Early POCs have been implicated as a mediating factor for increased recurrence and decreased survival across several cancer types including esophageal, gastric, and colorectal cancer.[7–10] A 2011 systematic review demonstrated the association of anastomotic leaks

after colorectal resection with increased recurrence and decreased cancer specific survival.[11] Similarly, a 2019 meta-analysis showed a strong relationship between POCs and diminished overall and disease-free survival after resection of colorectal liver metastases.[10] On this basis, the perioperative period should optimize interventions and implement best practices that reduce complications, thereby improving long-term outcomes.

Large series exploring the association of POCs with long-term outcomes after CRS/HIPEC are lacking. Demonstration of an association would identify a point of intervention to allow systematic improvements in processes that would subsequently have an impact on the outcomes for these patients. This study aimed to assess the association of POCs and the specific type of complication with overall survival (OS) and recurrence-free survival (RFS) after CRS/HIPEC for appendiceal neoplasms and colorectal adenocarcinoma.

METHODS

Data Source

Patients were enrolled from the US HIPEC Collaborative, a consortium of 12 U.S.-based institutions. At each study site, institutional review board approval was obtained before data collection.

Patients who underwent curative CRS/HIPEC with a completeness of cytoreduction (CCR) score of 0 (no visible peritoneal disease) or 1 (remaining tumor nodules < 2.5 mm) for appendiceal neoplasms or colorectal adenocarcinoma from 2000 to 2017 were included in the study. Patients for whom palliative CRS/HIPEC had been determined preoperatively were excluded. The survival analyses excluded 30-day mortalities.

Demographic, perioperative, histopathologic, and outcome data were collected by retrospective review of the medical records. Staging was based on the American Committee on Cancer (AJCC) seventh edition guidelines. The histologic tumors were classified into two groups for analysis: (1) noninvasive tumors including low-grade appendiceal mucinous neoplasms (LAMN) and high-grade appendiceal mucinous neoplasms, and (2) invasive tumors including appendiceal adenocarcinoma and colorectal adenocarcinoma.

The 90-day POCs were grouped into four groups: (1) infectious POCs including superficial surgical-site infection, deep surgical-site infection, intraabdominal infection, pneumonia, urinary tract infection, postoperative drainage procedure, anastomotic leak, and postoperative systemic sepsis, (2) cardiopulmonary POCs including cardiac arrest, myocardial infarction, unplanned intubation, and tracheostomy, (3) thromboembolic POCs including cerebrovascular accident, deep venous thrombosis, and pulmonary embolus, and (4) intestinal dysmotility including the need for postoperative tube feeds or total parenteral nutrition. Minor complications were defined as Clavien-Dindo 1 or 2, and major complications were defined as Clavien-Dindo 3 to 5.[12] The primary outcomes of the study were OS and RFS, both calculated as the time from surgery to the date of death or the date of the last available follow-up assessment.

Statistical Analysis

All statistical analyses were performed using SPSS statistical package 25.0 (IBM Inc., Armonk, NY, USA). Statistical significance was predefined as a two-tailed p value lower than 0.05. Chi square or Fisher's exact test was used for categorical variables. Continuous variables were analyzed using t tests or the Wilcoxon signed-rank test. Comparative analyses stratified by histologic subtype were performed to compare the patients who experienced no complications with the patients who experienced any complication. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used for comparison of survival between patients with no complication and those with any complication. Univariate Cox regression was performed to determine the association of any POC or type of POC with OS and RFS. Factors significantly associated with OS or RFS in the univariate analysis were included in a multivariable model.

RESULTS

Demographic and Clinicopathologic Characteristics

Among 2372 patients, 1303 met the inclusion criteria. Of these 1303 patients, 426 (33%) had noninvasive appendiceal neoplasm and 877 (67%) had invasive appendiceal neoplasm or colorectal adenocarcinoma. The demographic and clinicopathologic characteristics are listed in Table 1.

In the noninvasive cohort, the median age was 56 years (interquartile range [IQR] 47–63 years), 38% were male (n = 161), and the median body mass index (BMI) was 27 kg/m^2 (IQR 24–32 kg/m^2). For 70% of this cohort (n = 296), a CCR0 was performed. The median follow-up period was 24 months (IQR 9–42 months). In 55% of the cohort (n = 233), POCs were identified. The analysis showed that 36% (n = 83) of these POCs were infectious, 11% (n = 47) were cardiopulmonary, 6% (n = 24) were thromboembolic, and 19% (n = 23) were intestinal dysmotility (n = 80). Only 7% of the patients underwent adjuvant chemotherapy.

For the patients with invasive neoplasms, the median age was 54 years (IQR 47–64 years). The median BMI of this cohort was 27 kg/m^2 (IQR 23–31 kg/m^2), and 43% (n = 376) were male. For 77% (n = 672) of these patients, a CCR0 was performed. The median follow-up period was 20 months (IQR 9–39 months). The analysis identified POCs in 63% (n = 556) and found that 22% (n = 196) of these POCs were infectious, 13% (n = 117) were cardiopulmonary, 5% (n = 45) were thromboembolic, and 23% (n = 201) were intestinal dysmotility. Only 20% of the patients underwent adjuvant chemotherapy.

Comparison of Any POC Versus No POC

Among the patients with noninvasive neoplasms, those who experienced any complication and those who had no POCs were well matched in terms of demographics including age, BMI, and number of comorbidities (Table 1). With respect to treatment, the rate of neoadjuvant or adjuvant therapy did not differ between the patients who experienced complications and those who did not (neoadjuvant, 6% vs 8%; p = 0.55 vs adjuvant, 5% vs 9%; p = 0.18). Intraoperatively, the patients with complications were more likely to have a higher median PCI (15 vs 12; p < 0.01), for which they required additional procedures and

were more likely to have a greater median intraoperative blood loss (300 vs 200 ml; $p < 0.01$) but not a higher rate of intraoperative transfusion (28% vs 21%; $p = 0.71$, Table 1).

Among the patients with invasive neoplasms, those with any POCs were slightly older (55 vs 53; $p = 0.02$) and more likely to have had a previous CRS (27% vs 19%; $p = 0.02$), but were otherwise similar to those who did not experience complications in terms of demographics including BMI and number of comorbidities (Table 1). With respect to treatment, the rate of neoadjuvant or adjuvant therapy did not differ between the patients who experienced complications and those who did not (neoadjuvant, 46% vs 45%; $p = 0.85$ vs adjuvant, 28% vs 29%; $p = 0.68$). Intraoperatively, the patients with complications were more likely to have a higher median PCI (19 vs 13; $p < 0.01$), for which they required additional procedures, and were more likely to have higher median intraoperative blood loss (400 vs 200 ml; $p < 0.01$), requiring a higher rate of intraoperative transfusion (24% vs 10%; $p < 0.01$, Table 1).

Noninvasive Appendiceal Cohort: Recurrence and Survival Analysis

In the noninvasive cohort, the 3-year OS and RFS did not differ between the patients who experienced a complication and those who did not (OS, 94% vs 94%, $p = 0.26$, Fig. 1a; RFS, 68 vs 60%, $p = 0.15$, Fig. 1b). These results persisted in the univariate regression for OS and RFS, demonstrating that neither any complication (minor or major) nor the type of complication (infectious, cardiopulmonary, thromboembolic, or intestinal dysmotility) were prognostic for OS (Table 2) or RFS (Table 3).

Invasive Appendiceal/Colorectal Adenocarcinoma Cohort: Recurrence and Survival Analysis

In the invasive cohort, POCs were associated with decreased 3-year OS (59% vs 74%; $p < 0.001$; Fig. 2a) and RFS (32% vs 42%; $p < 0.001$; Fig. 2b). In the univariate regression for OS, male sex, higher PCI, and CCR1 score were associated with worse survival. The patients with any POC also had a significantly worse OS than the patients without complications (hazard ratio [HR] 1.74; 95% confidence interval [CI] 1.32–2.29; $p < 0.01$).

These results remained when the complications were stratified into minor (HR, 1.43; 95% CI, 1.06–1.93; $p = 0.02$) or major (HR, 2.01; 95% CI, 1.46–2.76; $p < 0.01$) complications and compared with no complications. This relationship persisted for type of complication including infectious (HR, 2.22; 95% CI, 1.59–3.08; $p < 0.01$), cardiopulmonary (HR, 1.74; 95% CI, 1.18–2.56; $p < 0.01$), and intestinal dysmotility (HR, 2.37; 95% CI, 1.70–3.29; $p < 0.01$).

In the multivariable analysis, with male sex, PCI, and CCR score taken into account, any complication remained associated with worse OS (HR, 1.64; 95% CI, 1.23–2.18; $p < 0.01$). Infectious complications also remained associated with worse OS (HR, 2.08; 95% CI, 1.48–2.93; $p < 0.01$; Table 2).

In the univariate regression for RFS, higher PCI, CCR1 score, previous CRS, and receipt of neoadjuvant or adjuvant chemotherapy were associated with decreased RFS. The patients with any POC also had a significantly worse RFS than those without complications (HR, 1.50; 95% CI, 1.23–1.84; $p < 0.01$). These results again persisted when complications were

stratified into minor (HR, 1.51; 95% CI, 1.21–1.88; $p < 0.01$) or major (HR, 1.52; 95% CI, 1.17–1.97; $p < 0.01$) complications and compared with no complications. This relationship persisted for type of complication including infectious (HR, 1.78; 95% CI, 1.38–2.29; $p < 0.01$), cardiopulmonary (HR, 1.27; 95% CI, 1.00–1.84; $p = 0.05$), and intestinal dysmotility (HR, 1.86; 95% CI, 1.44–2.40; $p < 0.01$).

In the multivariable analysis, with PCI, CCR score, and previous CRS taken into account, any complication remained associated with worse RFS (HR, 1.37; 95% CI, 1.11–1.70; $p < 0.01$). Infectious complications also remained associated with decreased RFS (HR, 1.61; 95% CI, 1.23–2.10; $p < 0.01$; Table 3).

DISCUSSION

To our knowledge, this is the largest study in the literature to evaluate the influence of POCs on oncologic outcomes for patients with appendiceal neoplasms or colorectal adenocarcinoma who undergo CRS/HIPEC. Similar to other studies that have assessed surgical outcomes after CRS/HIPEC, we demonstrated that POCs occur for 55% of patients with noninvasive appendiceal neoplasms and 63% of patients with invasive appendiceal neoplasms or colorectal cancer (Table 1). Although these rates are slightly higher than in other series, which have shown morbidity rates of 33% to 43%, the complication rate after this procedure remains substantial across the literature.[13–15] The discrepancy in these numbers likely is related to the exclusion of certain minor complications from the morbidity score in some series.

Regarding the relationship between POCs and long-term oncologic outcomes, this study demonstrated that the presence of any POC is associated with a decreased 3-year OS (59% vs 74%; $p < 0.001$; Fig. 2a) and RFS (32% vs 42%; $p < 0.001$, Fig. 2b) for invasive appendiceal neoplasms and colorectal adenocarcinoma but not for noninvasive appendiceal neoplasms, and that infectious complications are the primary driver of these worse long-term outcomes for the invasive histologies (Tables 2 and 3). Notably, the patients who experienced a POC for either noninvasive or invasive histologies had a higher PCI than those who had no complications (noninvasive neoplasms, 15 vs 12, $p < 0.01$; invasive neoplasms, 13 vs 10; $p < 0.01$), which is intuitively indicative of a higher tumor burden and subsequent need for more organ resections, as shown in Table 1. However, survival analysis accounted for PCI and CCR, which are known determinants of long-term outcomes, and further excluded 30-day mortalities, which are more likely to be immediate consequences of POCs. Additionally, the receipt of adjuvant chemotherapy did not differ between the patients who experienced a complication and those who did not, so the increased recurrence rate and decreased survival for the invasive histologies cannot be attributed to an inability to return to intended oncologic therapy (RIOT).[16]

Notably, the POCs in this study had an association only with recurrence and survival for the patients with invasive histologies. Although the exact driving mechanism for this is difficult to elucidate retrospectively, it perhaps is related to the synergism between the immunosuppressive and pro-inflammatory effects of POCs, which may allow minimal residual disease to proliferate.[17]] In the case of noninvasive tumors, this proliferation may be

sufficiently slow to allow the host's immune system to recover after the complication and prevent accelerated growth of residual tumor. In more invasive histologies, however, it is possible that this period of immunosuppression is long enough to result in a "tumor escape" mechanism that may allow cells to proliferate rapidly.[18] More aggressive tumors also may require more extensive resections, further leading to excessive tumor-shedding intraoperatively. These concepts are intriguing, and ongoing translational research is currently devoted to implementing anti-metastatic therapies during the perioperative period.[19]

The association between infectious complications and long-term outcomes has been demonstrated previously for other malignancies including primary, resectable colorectal and gastric cancer. In a systematic review of the impact that anastomotic leakage has on long-term outcomes after colorectal surgery, Mirnezami et al.[11] showed a twofold greater risk of local recurrence and 75% greater odds of death than for those who did not experience leaks. Similarly, Tokunaga et al.[20] demonstrated more than a twofold increase in the risk of recurrence and death for patients with intraabdominal infectious complications after curative-intent gastrectomy for gastric cancer.

For patients who undergo CRS/HIPEC, infectious complications, particularly those secondary to anastomotic leakage, are the main source of morbidity. In fact, a recent study from this same collaborative showed an anastomotic leakage rate of 8% and confirmed its association with worse OS (HR, 2.1; 95% CI, 1.3–3.4; $p < 0.01$).[21] In this study, infectious complications accounted for 36% of all the POCs in the noninvasive cohort and 22% of all those in the invasive cohort. Furthermore, in the invasive cohort, infectious complications were associated with worse RFS and OS. The importance of elucidating the relationship between POCs and long-term outcomes cannot be overstated given that some complications such as infectious complications are potentially preventable with the implementation of best-practice protocols. The most important initial criterion for reducing morbidity is appropriate patient selection, both in terms of frailty and inherent tumor biology, to ensure that only those who may derive a survival benefit are subjected to the potential morbidity of such an operation. The population used for this study, however, was already highly select, as evidenced by their low median age of 56 years, predominantly independent functional status, and low number of comorbidities, with 42% having only one comorbidity (Table 1). Additionally, this study included only patients who underwent a curative operation with no clearly visible residual tumor (CCR0/CCR1). As such, POCs represented the only modifiable risk factor that could affect long-term outcomes. Consequently, all peri- and intraoperative best practices known to prevent complications, particularly infectious complications, should be implemented including avoiding hypothermia, minimizing blood loss, and optimizing nutritional status.[22] Furthermore, early POCs could serve as predictors of outcome and may identify potential points of intervention and remediation in a systematic effort to improve outcomes after CRS/HIPEC.

The results of the current study should be interpreted with several limitations arising primarily from its retrospective design. Although strict definitions for each complication type were used during data extraction, the diagnosis of each complication type was not standardized across institutions. Additionally, although the patients with and without POCs

underwent adjuvant therapy at similar rates, the data set lacked granularity regarding the timing of adjuvant therapy initiation and the need for dose reductions. The patients who experienced POCs may have had delayed initiation of treatment, which could have resulted in earlier recurrence and decreased survival. Finally, the perioperative management of these patients was not standardized, and compliance with perioperative bundles was not captured.

CONCLUSION

This study showed that POCs are associated with decreased OS and RFS after CRS/HIPEC for invasive histology, but not for an indolent disease such as noninvasive appendiceal neoplasm. Of all the complication types, infectious complications were found to be the main driver for this association. The exact mechanism is not known, but may be immunologic. Efforts must target best practices and standardized prevention strategies to minimize infectious postoperative complications.

ACKNOWLEDGMENT

This study was supported in part by the Katz Foundation.

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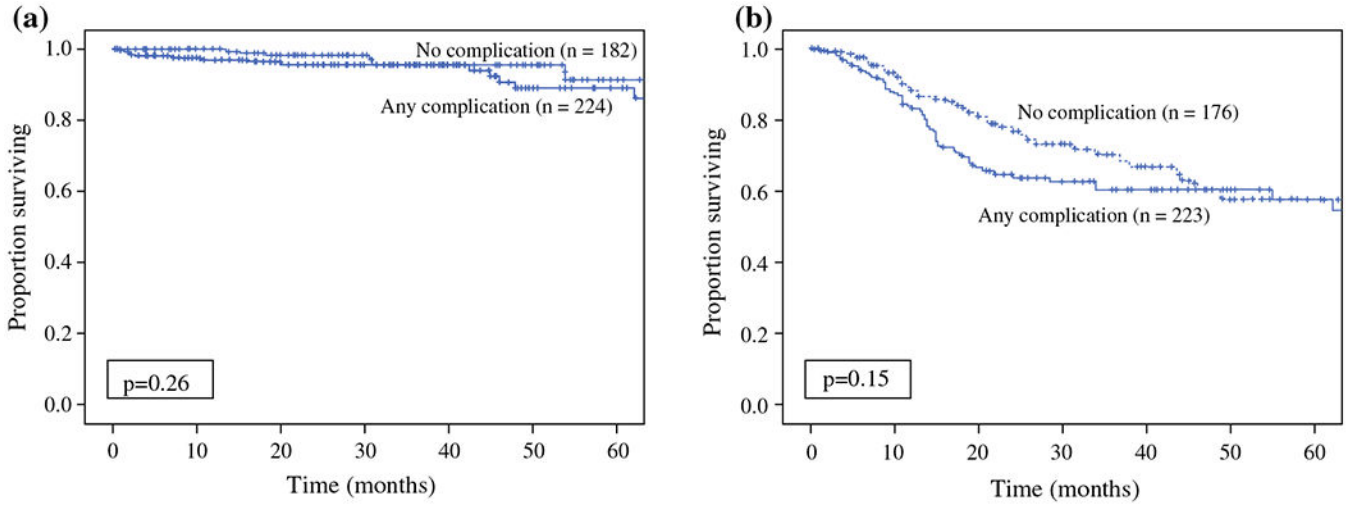

FIG. 1.

Kaplan-Meier curves for **a** overall survival and **b** recurrence-free survival comparing no complication and any complication in the noninvasive appendiceal neoplasm cohort

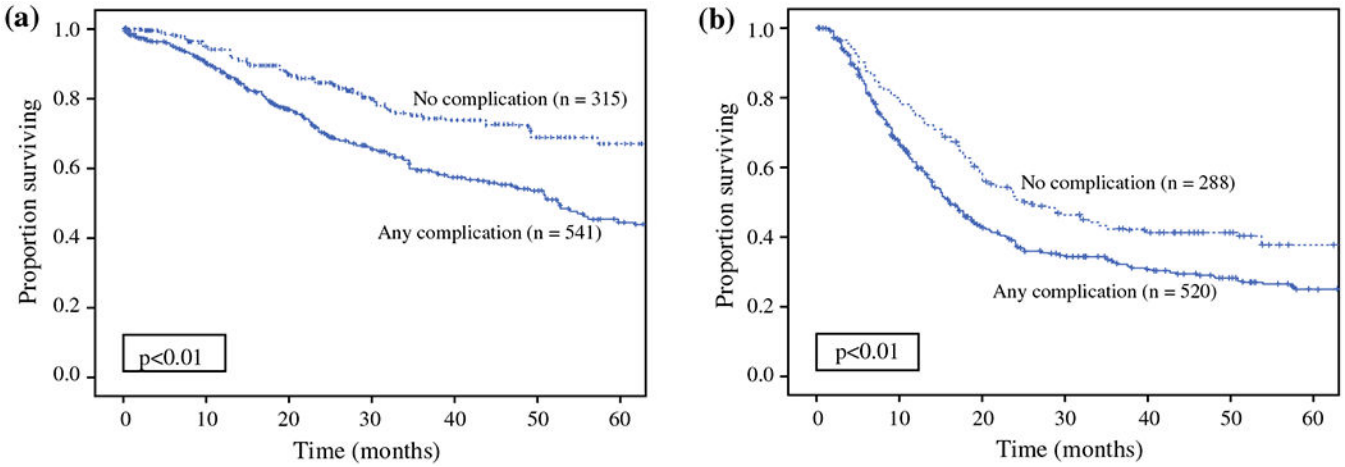

FIG. 2.

Kaplan-Meier curves for **a** overall survival and **b** recurrence-free survival comparing no complication and any complication in the invasive appendiceal neoplasm and colorectal adenocarcinoma cohort

Ann Surg Oncol. Author manuscript; available in PMC 2021 December 01.

TABLE 1

Demographic and clinicopathologic factors of the entire cohort and univariate comparison of factors by presence of any postoperative complication

	All patients	**Postoperative complications**		***P* value**[a]
		None	**≥1**	
Noninvasive appendiceal cancer	***n* = 426** ***n* (%)**	***n* = 190** ***n* (%)**	***n* = 233** ***n* (%)**	
Demographic variables				
Median age at diagnosis: years (IQR)	56 (47–65)	55 (47–63)	57 (47–66)	0.21
Sex				
Female	265 (62)	109 (57)	153 (66)	0.09
Male	161 (38)	81 (43)	80 (34)	
Race				
White	349 (82)	160 (85)	187 (81)	0.69
Black	16 (4)	8 (4)	8 (4)	
Asian	25 (6)	10 (5)	15 (7)	
Latino	19 (5)	(4)	12 (5)	
Other	14 (3)	4 (2)	9 (4)	
ASA class				
1	1 (0.2)	1 (0.6)	0 (0)	0.35
2	2 (18)	35 (21)	42 (20)	
3	284 (67)	125 (75)	157 (74)	
4	17 (4)	5 (3)	12 (6)	
Median BMI: kg/m^2 (IQR)	27 (24–32)	27 (24–30)	27 (24–32)	0.33
Functional status				
Independent	331 (78)	147 (99)	181 (96)	0.08
Partially dependent	9 (2)	1 (0.7)	8 (4)	
No. of comorbidities				
0	77 (18)	30 (18)	47 (22)	0.73
1	177 (42)	84 (51)	92 (44)	
2	85 (20)	36 (22)	49 (23)	
3	34 (8)	14 (8)	20 (10)	
4	5 (1)	2 (1)	3 (1)	

	All patients	Postoperative complications		*P* value[a]
		None	≥1	
Noninvasive appendiceal cancer	***n* = 426 *n* (%)**	***n* = 190 *n* (%)**	***n* = 233 *n* (%)**	
Missing	48 (11)	–	–	
Previous CRS	67 (16)	27 (1423)	40 (17)	0.80
Previous CRS + HIPEC	32 (8)	16 (8)	16 (7)	0.69
Intraoperative variables				
Operative intent				
Curative	421 (99)	187 (98)	231 (99)	0.66
Prophylactic	5 (1)	3 (2)	2 (1)	
Intraoperative procedures				
Right diaphragm peritonectomy	238 (56)	91 (54)	147 (69)	< **0.01**
Left diaphragm peritonectomy	135 (32)	36 (21)	98 (46)	< **0.01**
Major right peritonectomy	207 (49)	82 (53)	125 (61)	0.17
Major left peritonectomy	106 (25)	26 (17)	80 (39)	< **0.01**
Gastrectomy	10 (2)	1 (0.6)	9 (4)	0.05
Splenectomy	157 (37)	55 (33)	101 (48)	**0.01**
Distal pancreatectomy	11 (3)	2 (1)	9 (4)	0.12
Hysterectomy without oophorectomy	32 (8)	13 (8)	19 (9)	0.74
Partial colectomy	158 (37)	55 (34)	103 (48)	< **0.01**
Small bowel resection	53 (12)	10 (6)	43 (20)	< **0.01**
Nephrectomy	0 (0)	–	–	–
Median PCI (IQR)	13 (7–20)	12 (5–17)	15 (9–21)	< **0.01**
CCR				
CCR0	296 (70)	146 (77)	148 (64)	< **0.01**
CCR1	130 (30)	44 (23)	85 (37)	
Median EBL: ml (IQR)	250 (150–500)	200 (100–300)	300 (150–500)	< 0.01
Intraoperative transfusion	49 (12)	21 (12)	28 (14)	0.71
Multimodal treatment				
Neoadjuvant chemotherapy	31 (7)	16 (8)	15 (6)	0.55
Adjuvant chemotherapy	23 (7)	14 (9)	9 (5)	0.18

	All patients	Postoperative complications		*P* value[a]
		None	≥1	
Noninvasive appendiceal cancer	***n* = 426** ***n* (%)**	***n* = 190** ***n* (%)**	***n* = 233** ***n* (%)**	
Postoperative variables				
Median follow-up: months (IQR)	24 (9–42)			
ICU admission	362 (86)	155 (82)	205 (89)	0.05
Median ICU LOS: days (IQR)	2 (1–3)	2 (1–3)	2 (1–3)11 (9–16)	0.94
Any complication	233 (55)		233 (55)	
Infectious	83 (36)	–	83 (36)	–
Cardiopulmonary	47 (11)	–	47 (11)	–
Thromboembolic	24 (6)	–	24 (6)	–
Intestinal dysmotility	80 (19)	–	80 (19)	–
Median LOS: days (IQR)	9 (7–13)	8 (6–10)	11 (9–16)	< **0.01**
Discharge destination				
Home	246 (58)	114 (98)	130 (90)	**0.01**
Non-home	16 (4)	2 (2)	14 (10)	
Missing	164 (39)	–	–	
Readmission	80 (19)	5 (3)	75 (32)	< **0.01**
Reason for readmission				
Cardiovascular	1 (1)	0 (0)	1 (1)	0.87
Failure to thrive	25 (31)	1 (33)	24 (34)	
Ileus/small bowel obstruction	15 (19)	0 (0)	15 (21)	
Infection	13 (16)	1 (33)	12 (17)	
Venous thromboembolism	7 (9)	0 (0)	7 (10)	
Other	13 (16)	1 (33)	12 (17)	
30-Day mortality	0 (0)	0 (0)	0 (0)	–
Recurrence	105 (26)	41 (23)	64 (29)	0.27
Invasive appendiceal and colorectal cancer	***n* = 877**	***n* = 322**	***n* = 555**	
Demographic variables				
Median age at diagnosis: days (IQR)	54 (47–64)	53 (46–62)	55 (47–64)	**0.02**
Sex				

Noninvasive appendiceal cancer	All patients *n* = 426 *n* (%)	Postoperative complications None *n* = 190 *n* (%)	Postoperative complications ≥1 *n* = 233 *n* (%)	*P* value[a]
Female	501 (57)	178 (55)	323 (58)	0.44
Male	376 (43)	144 (45)	232 (42)	
Race				
White	701 (80)	255 (80)	446 (81)	0.29
Black	52 (6)	16 (5)	36 (7)	
Asian	43 (5)	14 (4)	29 (5)	
Latino	41 (5)	20 (6)	21 (4)	
Other	30 (3)	14 (4)	16 (3)	
ASA class				
1	3 (0.3)	1 (0.3)	2 (0.4)	0.20
2	94 (11)	44 (15)	50 (10)	
3	642 (73)	227 (79)	415 (84)	
4	47 (5)	17 (6)	30 (6)	
Missing	91 (10)	–	–	
Median BMI: kg/m^2 (IQR)	27 (23–31)	27 (24–31)	27 (23–31)	0.27
Functional status				
Independent	701 (80)	256 (98)	445 (98)	0.99
Partially dependent	15 (2)	6 (2)	9 (2)	
No. of comorbidities				
0	172 (20)	72 (26)	100 (20)	0.15
1	324 (37)	115 (41)	209 (41)	
2	206 (24)	70 (25)	136 (27)	
3	68 (8)	17 (6)	51 (10)	
4	17 (2)	5 (2)	12 (2)	
Missing	90 (10)	–	–	
Previous CRS	142 (33)	3962 (21)	103 (44)	**0.02**
Previous CRS + HIPEC	68 (8)	23 (7)	45 (8)	0.68
Intraoperative variables				

Noninvasive appendiceal cancer	All patients *n* = 426 *n* (%)	Postoperative complications None *n* = 190 *n* (%)	Postoperative complications ≥1 *n* = 233 *n* (%)	*P* value[a]
Operative intent				
Curative	873 (99)	319 (99)	554 (99)	0.14
Prophylactic	4 (1)	3 (1)	1 (1)	
Intraoperative procedures				
Right diaphragm peritonectomy	382 (44)	97 (35)	285 (56)	< **0.01**
Left diaphragm peritonectomy	198 (23)	42 (15)	156 (31)	< **0.01**
Major right peritonectomy	262 (30)	60 (23)	202 (41)	< **0.01**
Major left peritonectomy	110 (13)	24 (10)	86 (18)	< **0.01**
Gastrectomy	45 (5)	10 (4)	35 (7)	0.08
Splenectomy	205 (23)	58 (21)	147 (26)	**0.02**
Distal pancreatectomy	30 (3)	7 (3)	23 (5)	0.23
Hysterectomy without oophorectomy	106 (12)	23 (8)	83 (17)	< **0.01**
Partial colectomy	400 (46)	104 (38)	296 (59)	< **0.01**
Small bowel resection	233 (27)	64 (23)	168 (33)	< **0.01**
Nephrectomy	10 (1)	5 (3)	5 (2)	0.55
Ureteral resection	27 (3)	6 (2)	21 (4)	0.20
Median PCI (IQR)	12 (7–18)	10 (5–16)	13 (8–19)	< **0.01**
CCR				
CCR0	672 (77)	257 (80)	415 (75)	0.11
CCR1	205 (23)	65 (20)	140 (25)	
Median EBL: ml (IQR)	300 (150–600)	200 (100–450)	400 (200–700)	< **0.01**
Intraoperative transfusion	147 (17)	29 (10)	118 (24)	< **0.01**
Multimodal treatment				
Neoadjuvant chemotherapy	399 (45)	145 (45)	254 (46)	0.85
Adjuvant chemotherapy	177 (20)	68 (29)	109 (28)	0.68
Postoperative variables				
Median follow-up: (IQR)	20 (9–39)	24 (10–42)	19 (9–37)	
ICU admission	709 (81)	245 (76)	464 (84)	**0.01**

	All patients	Postoperative complications		*P* value[a]
		None	≥1	
Noninvasive appendiceal cancer	***n* = 426** ***n* (%)**	***n* = 190** ***n* (%)**	***n* = 233** ***n* (%)**	
Median ICU LOS: days (IQR)	2 (1–3)	2 (1–3)	2 (1–3)	**0.01**
Any complication	555 (63)		555 (63)	
Infectious	196 (22)	–	196 (22)	–
Cardiopulmonary	117 (13)	–	117 (13)	–
Thromboembolic	45 (5)	–	45 (5)	–
Intestinal dysmotility	201 (23)	–	201 (23)	–
Median LOS: days (IQR)	10 (8–14)	8 (7–10)	12 (9–17)	< **0.01**
Discharge destination				
Home	562 (64)	222 (97)	340 (90)	< **0.01**
Non-home	42 (5)	6 (3)	36 (10)	
Missing	274 (31)	–	–	
Readmission	210 (24)	19 (6)	191 (35)	< 0.01
Reason for readmission				
Cardiovascular	52 (6)	6 (35)	46 (26)	0.58
Failure to thrive	30 (3)	4 (24)	26 (15)	
Ileus/small bowel obstruction	55 (6)	3 (18)	52 (30)	
Infection	9 (1)	0 (0)	9 (5)	
Venous thromboembolism	45 (5)	4 (24)	41 (24)	
30-Day mortality	11 (1)	2 (4)	9 (6)	0.73
Recurrence	437 (50)	141 (49)	296 (57)	0.04

IQR, interquartile range; ASA, American Society of Anesthesiology; BMI, body mass index; CRS, cytoreductive surgery; HIPEC, heated intraperitoneal chemotherapy; PCI, peritoneal cancer index; CCR, completeness of cytoreduction; EBL, estimated blood loss; ICU, intensive care unit; LOS, hospital length of stay

[a]Bold indicates statistical significance ($p < 0.05$)

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TABLE 2

Cox regression for overall survival

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* value**[a]	**HR (95% CI)**	***P* value**[a]
Noninvasive appendiceal cancer				
Age at diagnosis	1.00 (0.97–1.04)	0.97		
Sex				
Female	Reference			
Male	0.99 (0.43–2.28)	0.97		
Race				
White	Reference			
Black	3.31 (0.77–14.37)	0.11		
Asian	1.29 (0.27–5.22)	0.75		
Latino	2.73 (0.35–20.99)	0.34		
Other	–	–		
BMI	1.04 (0.98–1.11)	0.19		
Functional status				
Independent	Reference			
Partially dependent	6.88 (1.96–24.21)	< **0.01**		
No. of comorbidities				
0	Reference			
1	0.44 (0.14–1.40)	0.16		
2	0.19 (0.04–1.08)	0.06		
3	2.04 (0.48–8.67)	0.34		
4	0.76 (0.08–6.95)	0.81		
PCI score	1.02 (0.97–1.07)	0.40		
CCR				
CCR0	Reference			
CCR1	3.60 (1.58–8.19)	< **0.01**		
Tumor grade				
Well-differentiated	Reference			

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value[a]
Moderately differentiated	2.73 (0.59–12.61)	0.19		
Poorly/undifferentiated	6.35 (1.33–30.29)	**0.02**		
Previous CRS	2.27 (0.98–5.25)	0.06		
Previous HIPEC	1.85 (0.55–6.25)	0.32		
ICU admission	25.26 (0.8–8057.18)	0.27		
Readmission	0.97 (0.38–2.51)	0.95		
Any complication	1.66 (0.68–4.03)	0.26		
Complication grade	2.82 (0.96–8.26)	0.06		
No complication	Reference			
Minor complication	1.08 (0.42–2.79)	0.86		
Major complication	2.82 (0.96–8.26)	0.06		
Infectious complication				
None	Reference			
Non-infectious complication	1.35 (0.49–3.68)	0.55		
Infectious complication	2.17 (.78–6.01)	0.14		
Cardiopulmonary complication				
None	Reference			
Non-cardiopulmonary complication	1.38 (0.54–3.55)	0.50		
Cardiopulmonary complication	3.01 (0.95–9.56)	0.06		
Thromboembolic complication				
None	Reference			
Non-thromboembolic complication	1.65 (0.67–4.09)	0.28		
Thromboembolic complication	1.69 (0.34–8.41)	0.52		
Intestinal dysmotility complication				
None	Reference			
Non-malnutrition complication	1.31 (0.49–3.51)	0.59		
Malnutrition	1.96 (0.68–5.66)	0.21		
Discharge destination				
Home	Reference			
Non-home (acute rehab, SNF)	8.66 (2.93–25.58)	< **0.01**		

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	*P* value[a]	HR (95% CI)	*P* value[a]
Invasive appendiceal and colorectal cancer				
Age at diagnosis	0.99 (0.99–1.01)	0.88		
Sex				
Female	Reference			
Male	1.33 (1.04–1.70)	**0.03**	1.37 (1.07–1.76)[b]	**0.01**
			1.37 (1.07–1.76)[c]	**0.01**
Race				
White	Reference			
Black	1.032 (0.61–1.74)	0.91		
Asian	1.33 (0.79–2.25)	0.28		
Latino	0.522 (0.22–1.27)	0.15		
Other	0.44 (0.16–1.18)	0.10		
BMI	0.98 (0.96–1.00)	**0.05**		
Functional status				
Independent	Reference			
Partially dependent	0.23 (0.06–0.91)	**0.04**		
No. of comorbidities				
0	Reference			
1	1.05 (0.74–1.49)	0.80		
2	0.99 (0.68–1.46)	0.98		
3	1.25 (0.77–2.05)	0.26		
4	2.09 (0.89–4.89)	0.09		
PCI	1.02 (1.00–1.04)	**0.01**	1.01 (0.99–1.03)[b]	0.38
			1.01 (0.99–1.03)[c]	0.49
CCR score				
CCR0	Reference			
CCR1	1.54 (1.18–2.02)	< **0.01**	1.37 (1.02–1.84)[b]	**0.04**
			1.37 (1.02–1.85)[c]	**0.04**

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* value**[a]	**HR (95% CI)**	***P* value**[a]
Previous CRS	1.23 (0.93–1.61)	0.14		
Previous HIPEC	0.81 (0.52–1.27)	0.36		
EBL (ml)	1 (1.00–1.00)	< **0.01**		
Multimodal therapy				
Neoadjuvant chemotherapy	1.99 (1.55–2.55)	< **0.01**		
Adjuvant chemotherapy	1.65 (1.21–2.25)	< **0.01**		
ICU admission	1.88 (1.24–2.84)	< **0.01**		
Readmission	1.62 (1.24–2.11)	< **0.01**		
Any complication	1.74 (1.32–2.29)	< **0.01**	1.64 (1.23–2.18)[b]	< **0.01**
Complication grade				
No complication	Reference			
Minor complication	1.43 (1.06–1.93)	**0.02**		
Major complication	2.01 (1.46–2.76)	< **0.01**		
Infectious complication				
None	Reference		Reference	
Non-infectious complication	1.57 (1.16–2.12)	< **0.01**	1.59 (1.10–2.04)[c]	**0.01**
Infectious complication	2.22 (1.59–3.08)	< **0.01**	2.08 (1.48–2.93)[c]	< **0.01**
Cardiopulmonary complication				
None	Reference			
Non-cardiopulmonary complication	1.73 (1.30–2.30)	< **0.01**		
Cardiopulmonary complication	1.74 (1.18–2.56)	< **0.01**		
Thromboembolic complication				
None	Reference			
Non-thromboembolic complication	1.76 (1.33–2.33)	< **0.01**		
Thromboembolic complication	1.46 (0.81–2.63)	0.21		
Intestinal dysmotility complication				
None	Reference			
Non-intestinal dysmotility complication	1.49 (1.09–2.03)	0.01		
Intestinal dysmotility complication	2.37 (1.70–3.29)	< **0.01**		

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* value**[a]	**HR (95% CI)**	***P* value**[a]
Discharge destination				
Home	Reference			
Non-home	1.73 (1.05–2.84)	**0.03**		

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PCI, peritoneal cancer index; CCR, completeness of cytoreduction; CRS, cytoreductive surgery; HIPEC, heated intraperitoneal chemotherapy; ICU, intensive care unit; SNF, skilled nursing facility; EBL, estimated blood loss

[a] Bold indicates statistical significance ($p < 0.05$)

[b] Multivariable model 1 evaluating any complication

[c] Multivariable model 2 evaluating infectious complications

TABLE 3

Cox regression for recurrence-free survival

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* Value**[a]	**HR (95% CI)**	***P* Value**[a]
Noninvasive appendiceal cancer				
Age at diagnosis	1.00 (0.99–1.02)	0.88		
Sex				
Female	Reference			
Male	1.36 (0.92–2.00)	0.12		
Race				
White	Reference			
Black	0.26 (0.04–1.89)	0.18		
Asian	1.40 (0.68–2.89)	0.36		
Latino	0.34 (0.05–2.44)	0.28		
Other	0.77 (0.19–3.15)	0.72		
BMI	1.01 (0.98–1.04)	0.39		
Functional status				
Independent	Reference			
Partially dependent	2.76 (1.11–6.85)	**0.03**		
No. of comorbidities				
0	Reference			
1	0.99 (0.56–1.76)	0.96		
2	1.20 (0.65–2.23)	0.56		
3	1.91 (0.87–4.20)	0.11		
4	1.11 (0.26–4.84)	0.89		
PCI score	1.06 (1.04–1.08)	< **0.01**		
CCR				
CCR0	Reference			
CCR1	2.94 (1.99–4.34)	< **0.01**		
Tumor grade				
Well-differentiated	Reference			

Ann Surg Oncol. Author manuscript; available in PMC 2021 December 01.

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	*P* Value[a]	HR (95% CI)	*P* Value[a]
Moderately differentiated	2.12 (0.97–4.64)	0.06		
Poorly/undifferentiated	1.77 (0.71–4.41)	0.22		
Previous CRS	1.77 (1.16–2.68)	**0.01**		
Previous HIPEC	1.62 (0.91–2.90)	0.10		
ICU admission	0.93 (0.54–1.56)	0.79		
Readmission	1.41 (0.89–2.22)	0.14		
Any complication	1.36 (0.92–2.03)	0.13		
Complication				
No complication	Reference			
Minor complication	1.09 (0.72–1.69)	0.67		
Major complication	1.68 (0.99–2.86)	0.06		
Infectious complication				
None	Reference			
Non-infectious complication	1.44 (0.94–2.22)	0.09		
Infectious complication	1.15 (0.67–1.97)	0.61		
Cardiopulmonary complication				
None	Reference			
Non-cardiopulmonary complication	1.25 (0.82–1.90)	0.29		
Cardiopulmonary complication	1.72 (0.95–3.11)	0.07		
Thromboembolic complication				
None	Reference			
Non-thromboembolic complication	1.33 (0.89–1.99)	0.16		
Thromboembolic complication	1.39 (0.62–3.09)	0.43		
Intestinal dysmotility complication				
None	Reference			
Non-malnutrition complication	1.16 (0.74–1.82)	0.52		
Malnutrition	2.24 (1.37–3.66)	< **0.01**		
Discharge destination				
Home	Reference			
Non-home	1.82 (0.70–4.72)	0.22		

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* Value**[a]	**HR (95% CI)**	***P* Value**[a]
Invasive appendiceal and colorectal cancer				
Age at diagnosis	0.99 (0.98–1.00)	0.28		
Sex				
Female	Reference			
Male	1.01 (8.84–1.22)	0.92		
Race				
White	Reference			
Black	1.19 (0.80–1.76)	0.39		
Asian	1.56 (1.06–2.29)	**0.03**		
Latino	1.32 (0.85–2.06)	0.21		
Other	1.09 (0.65–1.82)	0.76		
BMI	0.98 (0.96–0.99)	**0.01**		
Functional status				
Independent	Reference			
Partially dependent	0.60 (0.29–1.28)	0.19		
No. of comorbidities				
0	Reference			
1	1.07 (0.83–1.39)	0.59		
2	0.95 (0.71–1.26)	0.72		
3	1.08 (0.73–1.60)	0.69		
4	1.89 (0.98–3.65)	0.06		
PCI score	1.03 (1.02–1.04)	< **0.01**	1.02 (1.01–1.03)[b]	< **0.01**[b]
			1.02 (1.01–1.03)[c]	< **0.01**[c]
CCR				
CCR0	Reference		Reference	
CCR1	1.34 (1.08–1.67)	**0.01**	1.12 (0.88–1.43)[b]	0.34[b]
			1.13 (0.88–1.43)[c]	0.34[c]
Previous CRS	1.44 (1.16–1.78)	< **0.01**	1.36 (1.09–1.69)[b]	< **0.01**[b]

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	*P* Value[a]	HR (95% CI)	*P* Value[a]
			1.37 (1.11–1.71)[c]	< **0.01**[c]
Previous HIPEC	1.17 (0.85–1.63)	0.34		
EBL	1.00 (1.00–1.00)	**0.02**		
Multimodal therapy				
Neoadjuvant chemotherapy	1.83 (1.51–2.21)	< **0.01**		
Adjuvant chemotherapy	1.61 (1.29–2.01)	< **0.01**		
ICU admission	1.24 (0.96–1.61)	0.09		
Readmission	1.44 (1.17–1.78)	< **0.01**		
Any complication	1.50 (1.23–1.84)	< **0.01**	1.37 (1.11–1.70)[b]	< **0.01**[b]
Complication				
No complication	Reference			
Minor complication	1.51 (1.21–1.88)	< **0.01**		
Major complication	1.52 (1.17–1.97)	< **0.01**		
Infectious complication				
None	Reference		Reference	
Non-infectious complication	1.38 (1.11–1.73)	**0.01**	1.27 (1.01–1.60)[b]	**0.04**[c]
Infectious complication	1.78 (1.38–2.29)	< **0.01**	1.61 (1.23–2.10)[c]	< **0.01**[c]
Cardiopulmonary complication				
None	Reference			
Non-cardiopulmonary complication	1.52 (1.23–1.88)	< **0.01**		
Cardiopulmonary complication	1.27 (1.00–1.84)	**0.05**		
Thromboembolic complication				
None	Reference			
Non-thromboembolic complication	1.51 (1.23–1.86)	< **0.01**		
Thromboembolic complication	1.32 (0.84–2.09)	0.23		
Intestinal dysmotility complication				
None	Reference			
Non-intestinal dysmotility complication	1.35 (1.08–1.69)	**0.01**		
Intestinal dysmotility complication	1.86 (1.44–2.40)	< **0.01**		

	Univariable Cox regression		Multivariable Cox regression	
	HR (95% CI)	***P* Value**[a]	**HR (95% CI)**	***P* Value**[a]
Discharge destination				
Home	Reference			
Non-home	0.75 (0.46–1.25)	0.27		

HR, hazard ratio; CI, confidence interval; BMI, body mass index; PCI, peritoneal cancer index; CCR, completeness of cytoreduction; CRS, cytoreductive surgery; HIPEC, heated intraperitoneal chemotherapy; ICU, intensive care unit; EBL, estimated blood loss

[a] Bold indicates statistical significance ($p < 0.05$)

[b] Multivariable model 1 evaluating any complication

[c] Multivariable model 2 evaluating infectious complications