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Cytoreduction and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Versus Surgery Without HIPEC for Goblet-Cell Carcinoids and Mixed Adenoneuroendocrine Carcinomas: Propensity Score–Matched Analysis of Centers in the Netherlands and Belgium

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Abstract

The value of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with peritoneally metastasized goblet-cell carcinoids (GCCs) and mixed adenoneuroendocrine carcinomas (MANECs) is unclear. In a large propensity-matched cohort of patients with peritoneally metastasized GCCs and MANECs, CRS-HIPEC was significantly associated with improved survival compared to surgery alone. Such treatment is supported in expert centers offering this multimodal treatment.

Background: The value of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for patients with peritoneally metastasized goblet-cell carcinoids (GCCs) and mixed adenoneuroendocrine carcinomas (MANECs) is currently unclear. We compared outcomes of CRS-HIPEC to surgery alone for peritoneally metastasized GCCs and MANECs. **Patients and Methods:** Two cohorts were obtained from the Netherlands Cancer Registry (n = 569): patients with peritoneally metastasized GCCs and MANECs treated with CRS-HIPEC in Dutch and Belgian centers (n = 45), and patients treated with surgery alone. Primary outcome was overall survival (OS). Secondary outcomes were morbidity and hospital mortality. After propensity score matching, OS was compared in univariate and multivariate analyses. A systematic literature review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines from database inception to June 25, 2018. **Results:** After matching for sex, tumor stage, lymph node stage, and liver metastases, CRS-HIPEC was associated with improved median OS in the combined GCC and MANEC group and the separate GCC subgroup in univariate (GCC + MANEC: 39 vs. 12 months, $P < .001$; GCC: 39 vs. 12 months, $P = .017$) and multivariate analysis (GCC + MANEC: hazard ratio 4.27, 95% confidence interval 1.88-9.66, $P = .001$; GCC: hazard ratio 2.77, 95% confidence interval 1.06-7.26,

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$P = .038$). Acceptable grade III-IV morbidity (17.5%) and mortality (0) were seen after CRS-HIPEC. The literature review supported these findings. **Conclusion:** CRS-HIPEC is associated with substantial survival benefit in patients with peritoneally metastasized GCCs and MANECs compared to surgery alone and is a safe treatment option. These data support centralized care of GCC and MANEC patients with peritoneal spread in expert centers offering CRS-HIPEC.

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Introduction

Goblet-cell carcinoids (GCCs) and mixed adenoneuroendocrine carcinoma (MANECs) are rare types of gastrointestinal neoplasms, displaying pathologic and biologic features of both adenocarcinomas and neuroendocrine neoplasms.[1-3] Both entities are characterized by a more aggressive biologic behavior compared to classic neuroendocrine neoplasms and patients frequently present with lymph node and distant metastases at time of diagnosis.[2-4]

Peritoneal metastases (PM) are a common feature of GCCs and MANECs. In patients with GCCs, the peritoneum is the main site of dissemination, with 40% of these patients presenting with PM at time of diagnosis and 77% in case of recurrence.[2] The tendency of these tumors for locoregional spread without hematogenous dissemination[2] justifies aggressive local treatment strategies such as cytoreductive surgery (CRS) and subsequent hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). The recently presented results of the PRODIGE-7 randomized controlled trial failed to demonstrate an OS benefit of CRS-HIPEC with oxaliplatin compared to CRS alone.[5] However, CRS-HIPEC increases the median overall survival (OS) of patients with colorectal PM to 35 months compared to 12 to 16 months after systemic chemotherapy and is still the preferred option for these patients.[6-8] Patients with PM of GCCs and MANECs may benefit from CRS-HIPEC as well, which is supported by in vitro measurements of drug sensitivity showing comparable sensitivity profiles for GCCs and colorectal adenocarcinomas.[9] However, at present, the evidence for CRS-HIPEC as treatment for PM of GCCs and MANECs is unclear and the current literature on this subject consists of relatively small, noncomparative, retrospective cohort studies presenting heterogeneous outcomes.[2,3,10,11]

The lack of evidence to support this multimodality approach stresses the importance of evaluating its value in a well-defined cohort of GCC and MANEC patients. Therefore, the aims of the present study were: (1) to present available evidence in a systematic review of the literature and (2) to compare clinical outcomes of GCC and MANEC patients with PM treated with CRS-HIPEC to patients that underwent surgery without HIPEC using an international multicenter cohort together with a nationwide cancer database.

Patients and Methods

Patients and Data Collection

Patients with a minimum age of 18 years and histologically confirmed PM of GCCs and MANECs of colorectal or appendiceal origin were included. The neuroendocrine component was defined according to the World Health Organization 2010 guidelines (neuroendocrine tumor in case of a Ki-67 $\leq$ 20% and neuroendocrine carcinoma in case of Ki-67 $>$ 20%).[12,13] A GCC was diagnosed in case both adenocarcinoma and well-differentiated neuroendocrine tumor components were present[2,13] and a MANEC in case 30% to 70% of the tumor was made up of neuroendocrine carcinoma.[3,13] Patients treated with palliative intent were excluded. Data from 2 cohorts were collected: (1) a study cohort treated with CRS-HIPEC and (2) a control cohort treated with surgery without HIPEC. The study cohort was obtained from prospectively collected databases of 13 HIPEC centers in the Netherlands and Belgium and contained patients treated between 2003 and 2016. Patients were qualified for CRS-HIPEC following follow-up according to standard guidelines[8,14] and were preoperatively disqualified if the estimated extent of PM was deemed to be irresectable by subsequent positron emission tomography with or without computed tomography or diagnostic laparoscopy or systemic metastases were detected (excluding resectable liver metastases). The control cohort was provided by the Netherlands Cancer Registry (NCR). This cohort contained data of all patients diagnosed with PM of gastrointestinal neuro-endocrine neoplasms between 2003 and 2015.[15]

Demographic data, primary tumor information, presence of ovarian and liver metastases, treatment information, and follow-up data were extracted from the HIPEC centers and the NCR. The HIPEC centers provided the following additional information for 40 out of the 45 identified CRS-HIPEC patients: American Society of Anesthesiology Classification of Physical Health (ASA) score, prior surgical score,[16] peritoneal cancer index (PCI),[16] completeness of cytoreduction (CC) scores,[17] and information on hospital stay. Complications occurring during hospital admission were scored according to the Clavien and Dindo classification.[18] Data on immunohistochemistry was not obtained since these data were not available and are not considered to be mandatory.[19] The exact Ki-67 index was often missing and was instead provided as $\leq$ 20 (neuroendocrine tumor) or $>$ 20 (neuroendocrine carcinoma).

The study was approved by the local investigational review board of Amsterdam UMC, location VUmc (METC VUmc 2018.232).

Operative Management

All patients in the study cohort underwent CRS-HIPEC. CRS consisted of an attempt to completely debulk the primary tumor, stripping of the affected parietal peritoneum, removal of omentum and -if applicable- removal of adnexa and multi-organ resections.[20] Subsequently, the HIPEC procedure was carried out with intraperitoneal administration of oxaliplatin combined with intravenous administration of 5-fluorouracil or mitomycin C with a target temperature of 41°C for 30 or 90 minutes. The surgical procedures in the control group were performed with curative intent and

consisted of removal of visible tumor tissue with metastasectomy, and, if required, multiorgan resections. No further detailed information of the operative procedures of the control group could be obtained from the NCR.

Statistical Analysis

Propensity Score Matching. Patients were matched based on propensity scores, blinded to outcome data. Propensity scores were calculated using forward stepwise logistic regression with treatment as dependent variable and age, sex, morphology, N stage, T stage, and liver or ovarian metastases as independent variables. Sex, T stage, N stage, and liver metastases were selected in the final model. All HIPEC patients were matched to control patients using nearest neighbor matching with a 1:1 ratio without replacement by R 3.4.2 software (Rstudio, Boston, MA). Matching was separately performed in the combined GCC and MANEC subgroup, and the separate GCC and MANEC cohorts.

Comparison of Baseline Characteristics and OS. Baseline differences were tested by the chi-square test or Fisher exact test (2 categorical/dichotomous variables) or the independent *t* test (continuous normally distributed variable with a dichotomous variable). Variables were dichotomized if necessary to provide a minimum of 10 events per category in the survival analysis. Continuous variables were dichotomized on the basis of their mean values (normally distributed variables) or median values (not normally distributed variables). OS was defined as time in months from date of diagnosis to the date of death from any cause or date of last follow-up. In univariate analysis, differences in OS between potentially prognostic variables were tested for significance using the log-rank test. Variables of $P \leq .1$ were included in a multivariate Cox regression analysis. Variable selection in the Cox model was done using backward selection with a threshold *P* value of .1 for exclusion from the model. Statistical analyses were performed using the package for the social sciences version 23 for Windows (IBM, Armonk, NY, USA).

Systematic Review

A systematic literature search was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines (www.prisma-statement.org) in the bibliographic databases PubMed and Embase from inception to June 25, 2018. Search terms included indexed terms from MeSH in PubMed, EMtree in Embase as well as free text terms. Search terms expressing 'HIPEC' OR 'chemotherapy' were used combined with terms comprising 'neuroendocrine tumors,' 'goblet cell carcinoids,' AND 'peritoneum.' The references of the identified articles were searched for relevant publications. Duplicate articles were excluded. All languages were accepted. The full search strategies can be found in Supplemental Table 1 in the online version.

All available cohort studies were initially considered. After title and abstract screening, full-text papers describing CRS-HIPEC for patients with GCCs or MANECs were individually reviewed. Studies providing data on OS or disease-free survival (DFS) were included. When studies overlapped, those papers with the most complete data on our outcomes of interest were included. Two authors (NRS and DMRC) performed all inclusion independently. If necessary, articles were reread and discussed to achieve consensus. Relevant data were extracted from all selected full-text papers. Data on primary outcomes (OS and DFS) and secondary outcomes (morbidity and mortality) were retrieved. Other extracted data included: inclusion period, study design, study population characteristics, details on the CRS-HIPEC procedure, and hospital stay.

Results

Baseline Characteristics

Supplemental Figure 1 in the online version provides a flowchart of the patient inclusion and selection process. The study cohort consisted of 45 GCC (n = 29) and MANEC (n = 16) patients treated with CRS-HIPEC. For the control cohort, 30 of the 569 patients identified in the NCR were included after exclusion of patients with esophageal (n = 2), gastric (n = 14), gallbladder (n = 6), pancreatic (n = 35), or unknown (n = 145) primary tumor location, and patients receiving only systemic treatment (n = 57), no treatment (n = 48), or unknown therapy (n = 4). Also patients with PM of typical neuroendocrine tumors (n = 206) and neuroendocrine carcinomas (n = 22) were excluded. Table 1 describes the baseline characteristics of all patients. Of these patients, 45 patients underwent CRS-HIPEC and 30 patients surgical treatment without HIPEC. Supplemental Table 2 in the online version represents the baseline differences in the unmatched and propensity-matched cohorts, and Supplemental Figure 2 provides Kaplan-Meier curves of unmatched cohorts. Matching of the 30 GCC and MANEC

Table 1 Baseline Characteristics of 75 Patients

Characteristic	Variable	Value
Follow-up (months), mean (SD)		21.2 (18.5)
Age (years), mean (SD)		58.5 (13.0)
Male sex		29 (38.7%)
Location of primary lesion	Colorectal	9 (12.0%)
	Appendix	66 (88.0%)
Morphology	MANEC	24 (32.0%)
	GCC	51 (68.0%)
T stage	T1	2 (4.2%)
	T2	3 (6.2%)
	T3	12 (25.0%)
	T4	31 (64.6%)
N stage	N0	20 (35.7%)
	N1	17 (30.4%)
	N2	19 (33.9%)
Ovarian metastases		36 (48.0%)
Liver metastases		13 (17.3%)
Therapy	CRS-HIPEC	45 (60.0%)
	Surgery alone	16 (21.3%)
	Surgery + chemotherapy	12 (16.0%)
	Surgery + chemotherapy + targeted therapy	2 (2.7%)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: CRS = cytoreductive surgery; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; MANEC = mixed adenoneuroendocrine carcinoma; SD = standard deviation.

Table 2 Univariate Overall Survival Analysis by Treatment

Characteristic	Variable	GCC + MANEC			GCC		
		No. of Patients	OS (Months), Median (95% CI)	P[a]	No. of Patients	OS (Months), Median (95% CI)	P[a]
All		60	20.0 (13.5-26.5)		44	19.0 (11.1-26.9)	
Sex	Male	23	39.0 (21.4-56.7)	.009	14	35.0 (20.1-49.9)	.086
	Female	37	15.0 (10.6-19.4)		30	15.0 (9.9-20.1)	
Age	≤58 y	34	27.0 (9.7-44.3)	.006	29	23.0 (12.7-33.3)	.062
	>58 y	26	12.0 (7.1-16.9)		15	11.0 (7.2-14.8)	
Location	Colorectal	8	9.0 (0-22.9)	.022	3	2.0 (-)	.010
	Appendix	52	23.0 (15.4-30.6)		41	20.0 (12.0-28.0)	
Morphology	MANEC	22	20.0 (12.8-27.2)	.926	NA	NA	
	GCC	38	20.0 (12.4-27.6)		NA	NA	
T stage	T1-3	16	20.0 (5.4-34.6)	.297	9	15.0 (0-34.0)	.208
	T4	27	27.0 (11.3-42.7)		14	39.0 (9.6-68.4)	
N stage	N0-1	29	27.0 (6.4-47.6)	.034	20	27.0 (8.4-45.6)	.075
	N2	17	15.0 (0-30.1)		10	7.0 (0-27.1)	
Ovarian metastases	No	37	35.0 (17.4-52.6)	.019	20	39.0 (27.0-51.0)	.013
	Yes	23	15.0 (9.6-20.4)		24	11.0 (5.4-16.6)	
Liver metastases	No	56	20.0 (12.7-27.3)	.968	36	20.0 (12.4-27.6)	.705
	Yes	4	20.0 (0-46.1)		8	9.0 (3.5-14.5)	
Systemic chemotherapy	No	31	20.0 (0-47.8)	.342	19	36.0 (10.2-61-8)	.121
	Yes	29	20.0 (15.5-24.5)		25	16.0 (11.4-20.6)	
Treatment	Surgery	30	12.0 (7.0-17.0)	<.001	22	12.0 (4.6-19.4)	.017
	CRS-HIPEC	30	39.0 (20.8-57.2)		22	39.0 (14.4-63.6)	

Abbreviations: CI = confidence interval; CRS = cytoreductive surgery; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; MANEC = mixed adenoneuroendocrine carcinoma; NA = not available; OS = overall survival; SD = standard deviation.
[a]Log-rank test (test statistic and degree of freedom not applicable).

patients treated with CRS-HIPEC to the patients treated without HIPEC (1:1 ratio) led to a total number of 60 patients in the propensity-matched cohort. The separate MANEC subgroup was considered too small for further analysis. Although some differences in baseline characteristics remained, matching reduced these differences and the propensity scores in the treatment groups were comparable.

Additional data were available for 40 out of 45 HIPEC patients. Seven patients were classified as ASA-1, 23 as ASA-2, and 10 as ASA-3 and most patients had a prior surgical score of 1 or 2 score (n = 31). Intraoperatively, the mean PCI was 10 (standard deviation 7) and a CC-0 resection was achieved in 27 patients. Eighteen patients received intraperitoneal mitomycin C for 90 minutes, 21 patients oxaliplatin combined with intravenous administration of 5-fluorouracil for 30 (n = 8) or 90 minutes (n = 13), and 1 patient cisplatin for 90 minutes.

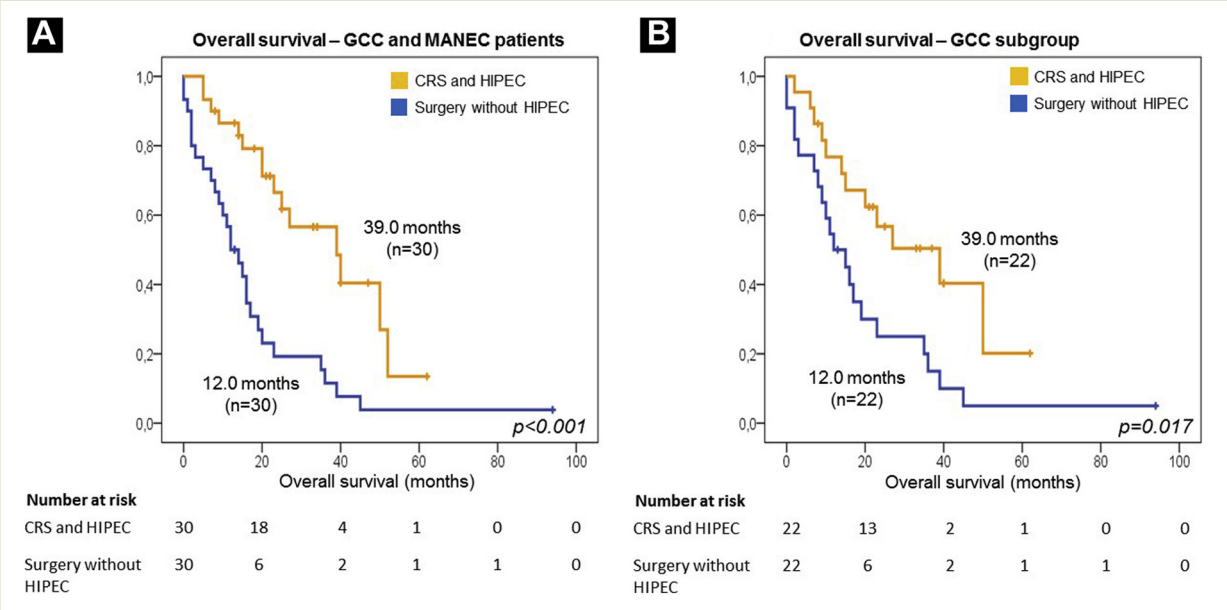
Primary Outcomes

Table 2 displays the results of univariate survival analysis in the matched cohorts. Figure 1 presents the Kaplan-Meier curves of the matched treatment groups. Supplemental Table 2 in the online version shows the analysis of the unmatched groups.

GCCs and MANECs

In the propensity-matched GCC and MANEC cohort (n = 60), CRS-HIPEC was associated with better median OS compared to surgical treatment without HIPEC (39.0 vs. 12.0 months, $P < .001$). Female sex (15.0 vs. 39.0 months, $P = .009$), age > 58 years (12.0 vs. 27.0 months, $P = .006$), colorectal vs. appendiceal primary tumor location (9.0 vs. 23.0 months, $P = .022$), N2 lymph node stage (15.0 vs. 27.0 months, $P = .034$), and the presence of ovarian metastases (15.0 vs. 35.0 months, $P = .019$) were significantly associated with poor survival. In the multivariate model, surgery without HIPEC was the most important risk factor for poor survival (hazard ratio [HR] 4.27, 95% confidence interval [CI] 1.88-9.66, $P = .001$, Wald 12.1, *df* 4). Furthermore, age (HR 1.05, 95% CI 1.02-1.08, $P = .001$, Wald 10.6, *df* 4), N2 lymph node stage (HR 2.66, 95% CI 1.24-5.70, $P = .012$, Wald 6.3, *df* 4), and the presence of ovarian metastases (HR 2.99, 95% CI 1.24-7.23, $P = .015$, Wald 5.9, *df* 4) were significantly associated with poor survival in multivariate analysis (Table 3). Within the control group, there were no differences in median OS between the group that received surgery (n = 16), surgery with chemotherapy (n = 12), and surgery with chemotherapy and targeted therapy (n = 2) (10.0 vs. 16.0 vs. 19.0 months, $P = .637$).

Figure 1 Kaplan-Meier Curves of Propensity-Matched Cohorts. (A) OS Curves of Combined GCC and MANEC Groups Treated With CRS-HIPEC vs. Surgery Without HIPEC. (B) OS Curves of GCC Subgroup Treated With CRS-HIPEC vs. Surgery Without HIPEC



Abbreviations: CRS = cytoreductive surgery; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; MANEC = mixed adenoneuroendocrine carcinoma; OS = overall survival.

Goblet-Cell Carcinoids

In the propensity-matched GCC cohort (n = 44), HIPEC surgery was associated with better median OS than surgery without HIPEC (39.0 vs. 12.0 months, $P = .017$). Additionally, colorectal versus appendiceal primary tumor location (2.0 vs. 20.0 months, $P = .010$) and the presence of ovarian metastases (11.0 vs. 39.0 months, $P = .013$) were correlated with poor survival. In the multivariate model, surgery without HIPEC (HR 2.77, 95% CI 1.06-7.26, $P = .038$, Wald 4.3, *df* 4), high age (HR 1.06, 95% CI 1.02-2.00, $P = .007$, Wald 7.3, *df* 4), and the presence of ovarian metastases (HR 4.50, 95% CI 1.54-13.07, $P = .006$, Wald 7.6, *df* 4) were significantly associated with poor survival (Table 3).

Table 3 Overview of Multivariate Overall Survival Analysis by Treatment Regimen

Characteristic	HR (95% CI)	*P*
GCC + MANEC		
Age	1.05 (1.02-1.08)	.001 (Wald 10.6, *df* 4)
N stage	2.66 (1.24-5.70)	.012 (Wald 6.3, *df* 4)
Ovarian metastases	2.99 (1.24-7.23)	.015 (Wald 5.9, *df* 4)
CRS-HIPEC	4.27 (1.88-9.66)	.001 (Wald 12.1, *df* 4)
GCC		
Age	1.06 (1.02-2.00)	.007 (Wald 7.3, *df* 4)
N stage	2.45 (0.95-6.31)	.063 (Wald 3.5, *df* 4)
Ovarian metastases	4.50 (1.54-13.07)	.006 (Wald 7.6, *df* 4)
CRS-HIPEC	2.77 (1.06-7.26)	.038 (Wald 4.3, *df* 4)

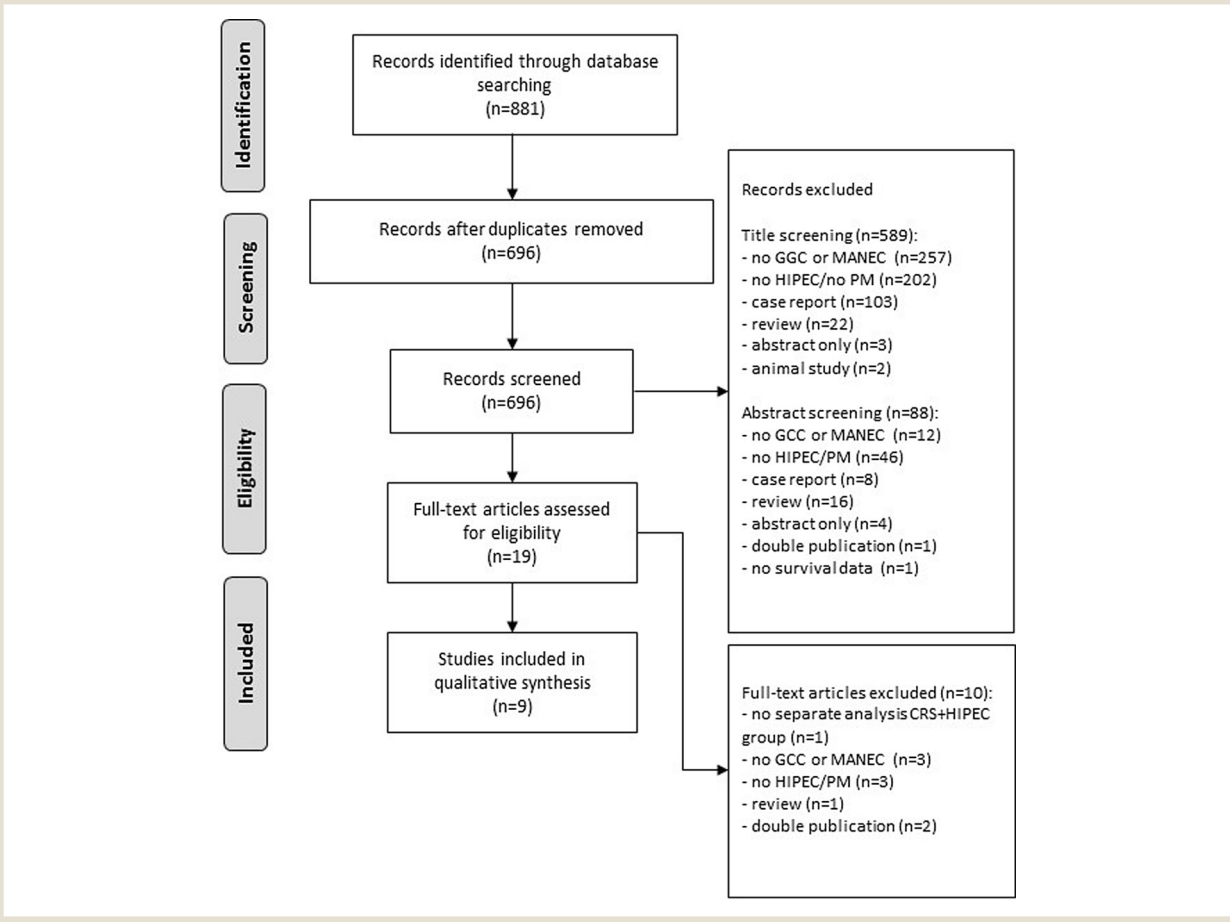
Abbreviations: CI = confidence interval; CRS = cytoreductive surgery; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; HR = hazard ratio; MANEC = mixed adenoneuroendocrine carcinoma.

Table 4 Hospital Complications and Stay

Event	Value
In-hospital complications	21 (52.5)
Grade III/IV complications	7 (17.5)
Pneumonia	1 (2.5)
Urinary tract infection	4 (10.0)
Abscess	0
Sepsis	2 (5.0)
Gastroparesis	5 (12.5)
Ileus	4 (10.0)
Leakage	3 (7.55)
High output stoma	1 (2.5)
Lung embolism	2 (5.0)
Respiratory distress	3 (7.5)
Bleeding	3 (7.5)
Other[a]	5 (2.5)
Hospital mortality	0
Readmission to hospital	3 (7.5)
Reintervention needed	4 (10.0)
Hospital stay (days), mean ± SD	17 ± 9
Intensive care unit stay (days), mean ± SD	2 ± 3

Data are presented as n (%) unless otherwise indicated.
Abbreviation: SD = standard deviation.
[a]Other complications include: pneumatosis intestinalis (n = 1), broken suprapubic catheter (n = 1), delirium (n = 1), chylous leakage (n = 1), and development of atonic bladder (n = 1).

Figure 2 PRISMA Flowchart



Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Safety Outcomes

Table 4 provides an overview of in-hospital complications and stay of the 40 of 45 identified HIPEC patients for which additional data was available. The mean hospital stay was 17 days (standard deviation 9). In-hospital complications occurred in 21 patients (62.5%) and grade III-IV complications in 7 patients (17.5%). Four patients (10.0%) received a reintervention and 3 patients (7.5%) were readmitted to the hospital. No treatment-related mortality was observed.

Systematic Review

All identified articles (n = 881) were submitted to a thorough selection process (Figure 2). Eventually, 9 publications were considered eligible for this review, 8 being retrospective cohort studies[1,9,21-26] and 1 prospective cohort study.[27] The articles were published between 2008 and 2018, and represented data on a total of 272 patients with peritoneally metastasized GCCs treated with intention of CRS-HIPEC. None of the studies described data on patients with MANECs as a separate group. Furthermore, none of these studies compared CRS-HIPEC to CRS alone. Table 5 displays the main study characteristics and outcomes, which are further described in the discussion section of this paper. Overall, for GCC patients with PM a median OS between 17 and 51 months[1,21,22,24-27] and a median DFS between 13 and 16 months[23,24] was reported after CRS-HIPEC.

Discussion

In the present propensity-matched cohort of patients with PM of GCCs and MANECs, CRS-HIPEC performed in specialized centers was associated with a substantially and statistically significant improved outcome compared to surgery alone, improving OS from a median of 12 to 39 months. The survival benefit was independent of tumor stage, lymph node involvement, and the presence of ovarian or liver metastases in both univariate and multivariate analysis. Importantly, CRS-HIPEC resulted in relatively low grade III-IV morbidity (17.5%) and hospital mortality rates (0%). The systematic literature review performed in the current study is in line with these outcomes. So far, this is the only matched analysis and the largest study comparing CRS-HIPEC in specialized centers for patients with PM of GCCs or MANECs.

Table 5 Overview of Studies in Systematic Review

Characteristic	Variable	Cashin[9]	Ihemelandu[21]	Madsen[27]	Mahteme[22]	McConnel[23]	Radomski[24]	Randle[1]	Yan[25]	Yu[26]
Methods	Design	Retrospective cohort study	Retrospective cohort study	Prospective cohort study	Retrospective cohort study	Retrospective cohort study, multicenter	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study	Retrospective cohort study
	Inclusion period	2004-2008	1989-2012	2009-2016	1981-2003	1994-2011	2005-2013	1991-2014	1990-2006	2006-2016
	Country	Sweden	USA	Denmark	USA	Canada	USA	USA	USA	Taiwan
Participants	N	10	53	27	22	45	43	31	26	15
	Inclusion	GCC with PM, CRS-HIPEC	GCC with PM, CRS-EPIC	GCC with PM, eligible for CRS-HIPEC	GCC with PM, CRS-HIPEC	GCC with PM, intention of CRS-HIPEC	GCC with PM, CRS-HIPEC	GCC with PM, CRS-HIPEC	GCC with PM, CRS-HIPEC	GCC with PM, CRS-HIPEC
	Diagnostic criteria	Goblet cells; chromogranin^{+} synaptophysin^{+} serotonin^{+}	Goblet cells; periodic acid—Schiff^{+} Alcian blue^{+} chromogranin^{+}	World Health Organization criteria (2010)	Not specified	Goblet cells; chromogranin^{+} synaptophysin^{+}; CEA^{+} CK7^{+} CK20^{+} CDX2^{+}	Goblet cells; according to Tang classification[c]	Goblet cells; neuroendocrine markers^{+}	Goblet cells; chromogranin^{+} synaptophysin^{+} neurospecific enolase^{+}	Not specified
	Age (y)	Mean (range): 53 (23-73)	Mean (SD): 48 (8)	Median (range): 54 (37-72)	Mean (range): 45 (22-62)	Median: 53	Mean (SD): 56 (2)	Mean (range): 53 (36-72)	Mean (SD): 45 (8)	Mean (range): 52 (36-74)
	PCI	Mean (range): 20.4 (4-39)	Mean (SD): 18.3 (13.5)	Median (range): 3 (0-5), Dutch Region Count Score	NA	Median: 24	Median (range): 20 (0-39)	Mean (range): 15.3 (0-32)	Mean (SD): 23 (10)	Mean (SD): 23 (13)
	Equivalence of baseline characteristics (treatment groups)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Procedure	CRS-HIPEC (oxaliplatin n = 7; mitomycin n = 3)$^{+}$ EPIC (5-FU)	CRS-EPIC (mitomycin^{+} 5-FU^{+} doxorubicin)	CRS-HIPEC (mitomycin)	(1) CRS-HIPEC^{+} EPIC (n = 10); (2) CRS-HIPEC (n = 3); (3) CRS-EPIC (n = 7); (4) Only CRS (n = 2)	CRS-HIPEC (oxaliplatin, mitomycin)	CRS-HIPEC	CRS-HIPEC (oxaliplatin n = 5; mitomycin n = 26)	CRS-HIPEC (mitomycin)	CRS-HIPEC/EPIC (mitomycin/ oxaliplatin) (n = 11), no HIPEC/EPIC (N = 4)
Outcomes	Median OS/DFS (months)	30 months[a] (mean)/ NA	27 months/NA	3.2 years/NA (CRS-HIPEC and open-close)	19 months[b]/NA	NA/16 months	22 months ~/13 months	18 months ~/unknown	51 months[d]/NA	17 months[#]/NA
	1-year OS/DFS	80%/NA	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA	100%/NA	86%/NA
	2-year OS/DFS	75%/NA	NA/NA	76%/NA (CRS-HIPEC)	39%/NA	NA/NA	NA/NA	NA/NA	NA/NA	69%/NA
	3-year OS/DFS	20%/NA	26%/NA	NA/NA	NA/NA	68%/43%	39%/17%	NA/NA	54%/unknown	57%/NA
	5-year OS/DFS	NA/NA	15%/NA	57%/NA (CRS-HIPEC)	25%/NA	NA/NA	9%/4%	NA/NA	43%/unknown	0/NA

Table 5 Continued

Characteristic	Variable	Cashin[9]	Ihemelandu[21]	Madsen[27]	Mahteme[22]	McConnel[23]	Radomski[24]	Randle[1]	Yan[25]	Yu[26]
Safety	Mortality	90 days: 0	NA	30 days: 0	Postoperative: 0	NA	60 days: 0	30 days: 6.5%; 90 days: 9.7%	NA	Postoperative: 1%
	Morbidity	Diaphragm perforation (n = 1), enterocutaneous fistula (n = 2)	NA	Postoperative: 40%	Septicemia (n = 1)	NA	60 days: 30%	90 days: 39%	NA	Postoperative: 47%
	Hospital stay in days (mean, range)	NA	NA	Median (range): 14 (11-40)	23 (7-57)	NA	NA	21 (4-76) of which ICU 4	NA	Median (SD): 28 (53)

HIPEC 39 vs. no HIPEC 7 months ($P = .001$). Age, < 50 vs. 39 vs. ≥ 50 years 16 months ($P = .044$). PCI indicates PCI < 27 39 PCI ≥ 27 16 months ($P = .026$). Adjuvant chemotherapy. no 16 vs. yes 39 months ($P = .037$). Lymph nodes: negative 29 vs. positive 10 months ($P = .002$).

Abbreviations: CC = completeness of cytoreduction score; CEA = carcinoembryonic antigen; CRS = cytoreductive surgery; DFS = disease-free survival; EPIC = early postoperative intraperitoneal chemotherapy; 5-FU = 5-fluorouracil; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; ICU = intensive care unit; NA = not available; OS = overall survival; PCI = peritoneal cancer index; PM = peritoneal metastases; SD = standard deviation.

[a]CC-0, 37 vs. CC-1-2, 16 months, $P = .04$.

[b]PCI 0-10, 62 vs. PCI 11-20, 21, vs. PCI 21-39, 6 months. $P = .008$. Resection score: CC-0/1, 29 vs. CC-2, 18 vs. CC-3, 6 months, $P = .007$. HIPEC/EPIC 20 vs. no HIPEC/EPIC 5 months ($P = .006$).

[c]Tang classification: Tang A, 59 vs. Tang B, 22 vs. Tang C, 13 months ($P = .005$); CC-0, 49 vs. CC-1/2/3, 17 months ($P = .004$).

[d]Discordant pathology associated with better survival ($P = .026$).

The role of both HIPEC and systemic chemotherapy for patients with GCCs and MANECs is debated.[28-30] Although patients are often treated with systemic 5-fluorouracil–based chemotherapy,[28,31,32] surgery is considered the keystone for the treatment of resectable metastases[31,33] whether or not combined with systemic chemotherapy.[2,34] Current standard care for patients with PM of GCCs and MANECs does not include CRS-HIPEC. This is reflected by the data obtained from the NCR demonstrating that the majority of these patients has been offered surgery without HIPEC. This might be caused by patient selection, but the majority of these patients was probably not being offered CRS-HIPEC due to unfamiliarity with this multimodal treatment and an uncertain benefit for these tumors.[35] Currently, no randomized data are available on the value of CRS-HIPEC for GCCs and MANECs. Although up to 40% of GCC patients present with PM,[2] a randomized study is not feasible due to the relatively low overall incidence. OS rates after CRS-HIPEC seem to exceed survival rates from historical cohorts with PM, but this is partly based on confounding by treatment indication.[31]

The systematic search performed in addition to the cohort study identified 9 studies, predominantly retrospective case series on GCC patients. Most studies reported a median OS from 17 to 27 months after CRS-HIPEC in these patients,[1,21,22,24,26] which is lower than the OS in the present GCC cohort (39.0 months). One retrospective study reported a higher median OS of 51 months in 26 GCC patients that underwent CRS-HIPEC.[25] The 1- and 3-year OS rates ranged from 80% to 100%[9,25] and 20% to 68%,[9,23-25] respectively. In a recently published study, 13 of 27 GCC patients scheduled for CRS-HIPEC underwent a complete procedure, resulting in 3- and 5-year OS rates of 76% and 57%, respectively.[27] DFS has less frequently been reported and ranges from 13 to 16 months, with a 3-year DFS of 17% to 43%.[23,24] Several authors identified variables with possible prognostic impact, of which incomplete resection[9,22,24] and high PCI scores[22] were the best validated.[16] One study described Tang classification[4] to be a poor prognosticator compared to Tang A and B subtypes.[1] Unfortunately, cohorts were too small to perform a multivariate analysis.

The survival rates published in the abovementioned studies were accompanied by relatively low morbidity and mortality rates. The percentage of 30-day grade III-IV morbidity ranged from 39% to 56% and mortality from 0% to 7%,[1,24,36] which is in line with the percentages observed in the present cohort and those in patients with colorectal PM after CRS-HIPEC.[37-39] Although the morbidity of surgery without HIPEC is probably associated with less morbidity than surgery with HIPEC,[40] the present results of both the cohort analysis and the systematic review suggest an acceptable morbidity for the procedure.

GCCs and MANECs differ from classic adenocarcinomas by their neuroendocrine characteristics[3,32] and were previously regarded as a subtype of neuroendocrine neoplasms, a group comprising typical neuroendocrine tumors and neuroendocrine carcinomas.[19] However, the biologic relationship between these tumor types is debated and has led to the exclusion of GCCs from current neuroendocrine neoplasm guidelines.[41] Patients with neuroendocrine neoplasms also frequently present with PM (10%-30% of patients)[42-45] and when present, PM are the direct cause of death in 40%[43] and an important predictor of survival.[15] The peritoneum

has been reported to be the sole site of metastases in at least 40% of patients with neuroendocrine neoplasms,[15] indicating that CRS-HIPEC might be a feasible option in these patients as well. However, there is no evidence for this treatment in patients with neuroendocrine neoplasms.[42] One study investigated the additional effect of HIPEC in patients with PM of neuroendocrine neoplasms. One and 2-year OS rates (89% and 81% vs. 88% and 73%, respectively) did not improve after CRS-HIPEC compared to CRS alone.[36] These results are in line with the current view to consider GCCs and MANECs as separate entities and not as a subgroup of neuroendocrine neoplasms.[32,46]

Some other notes should be taken into consideration as well. Despite explicitly addressing the issue of selection bias by both propensity score matching and the use of a multivariate model, confounding by treatment indication cannot be ruled out. The most important reason is that information on some potentially important variables could not be obtained from the NCR: ASA classification, PCI, tumor markers (synaptophysin, chromogranin A),[47] Ki-67 indexes,[47] and Tang classification.[1,4] Furthermore, primary tumors from different sites of origin, and potentially different biologic behavior, were included. Nevertheless, morphology and primary tumor origin were not significantly associated with survival in our final model. Another limitation is the lack of details on the surgical treatment in the control group. It should, however, be noted that most patients in the control group did not receive further treatment regimens apart from surgery and no survival differences were observed between patients that did and did not receive additional systemic therapies. Whether the group treated with surgery alone received meticulous cytoreduction is unclear, but it seems unlikely that gross R2 resections are present in this group as all these patients received surgery with curative intent. A thorough evaluation of the attributive value of HIPEC cannot be made since the quality of cytoreduction is potentially better in the HIPEC centers compared to those in the national database. Fact remains that the dedicated treatment offered by HIPEC centers is associated with substantial survival benefit.

The added value of HIPEC is also debated for patients with PM of colorectal adenocarcinoma. The recent PRODIGE-7 study randomized 265 patients with colorectal PM between CRS and CRS-HIPEC with oxaliplatin.[5] No statistically significant difference in OS was observed between both treatment arms (CRS-HIPEC 41.7 vs. CRS 41.2 months), while HIPEC was associated with significantly more long-term complications. A subgroup analysis did show a significantly better OS after HIPEC in patients with a PCI between 11 and 15 (41.6 vs. 32.7 months). Some important notes should be made when interpreting these results. First, the power calculation was based on an estimated improvement in OS of 18 months, which is likely to be an overestimation of the additional effect of HIPEC alone. Second, the samples size was powered on OS, but this outcome is heavily influenced by additional systemic treatments in case of disease recurrence. DFS would therefore be a more accurate primary endpoint. Third, the results obtained with HIPEC with oxaliplatin cannot be automatically extrapolated to HIPEC with other chemotherapeutic compounds. Overall, up until now there is no reason to conclude that HIPEC is of no benefit for colorectal PM.

The results of our systematic review underline the necessity of good qualitative studies on CRS-HIPEC for GCCs and MANECs, meanwhile demonstrating the difficulty of providing high-quality evidence for a condition with a low incidence. The current body of literature mainly consists of noncomparative, retrospective cohorts that are too small to correctly identify variables for patient selection. Moreover, the cohorts are heterogeneous in terms of patient- and operative parameters such as PCI, chemotherapeutic treatment, and completeness of cytoreduction. To provide robust evidence, a randomized controlled trial in a homogeneous cohort of patients with a single tumor entity, all treated in an expert center, would be required. However, this not feasible due to the low incidence of peritoneally metastasized GCCs and MANECs. Patients with metastasized GCCs and MANECs should be prospectively registered in a single large database, with accurate collection of possibly important variables such as performance status and PCI indexes.

Conclusion

In conclusion, treatment with CRS-HIPEC for patients with PM of GCCs and MANECs in specialized HIPEC centers seems associated with substantially better outcome compared to surgery without HIPEC at the expense of acceptable morbidity and mortality. These data support that care of patients with PM of GCCs and MANECs should be offered in expert centers that have the option for CRS-HIPEC.

Clinical Practice Points

- Multimodal CRS and HIPEC treatment in specialized centers improves survival of patients with PM of colorectal adenocarcinoma. However, its value in patients with PM of GCCs and MANECs is unclear.
- Our multicenter propensity-matched cohort demonstrated CRS and HIPEC in expert centers to be associated with better survival compared to surgery without HIPEC and to have acceptable morbidity.
- The systematic review accompanying these data shows that the current literature on CRS and HIPEC for GCCs and MANECs consists of retrospective noncomparative cohorts, making the present study the best evidence so far.
- On the basis of these data, patients with PM of CRS and HIPEC should be referred to expert centers offering multimodal treatment. A randomized study is not feasible because of the low incidence of this disease, so further studies will depend on large prospective registries on patients with PM of GCCs and MANECs.

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Disclosure

The authors have stated that they have no conflict of interest.

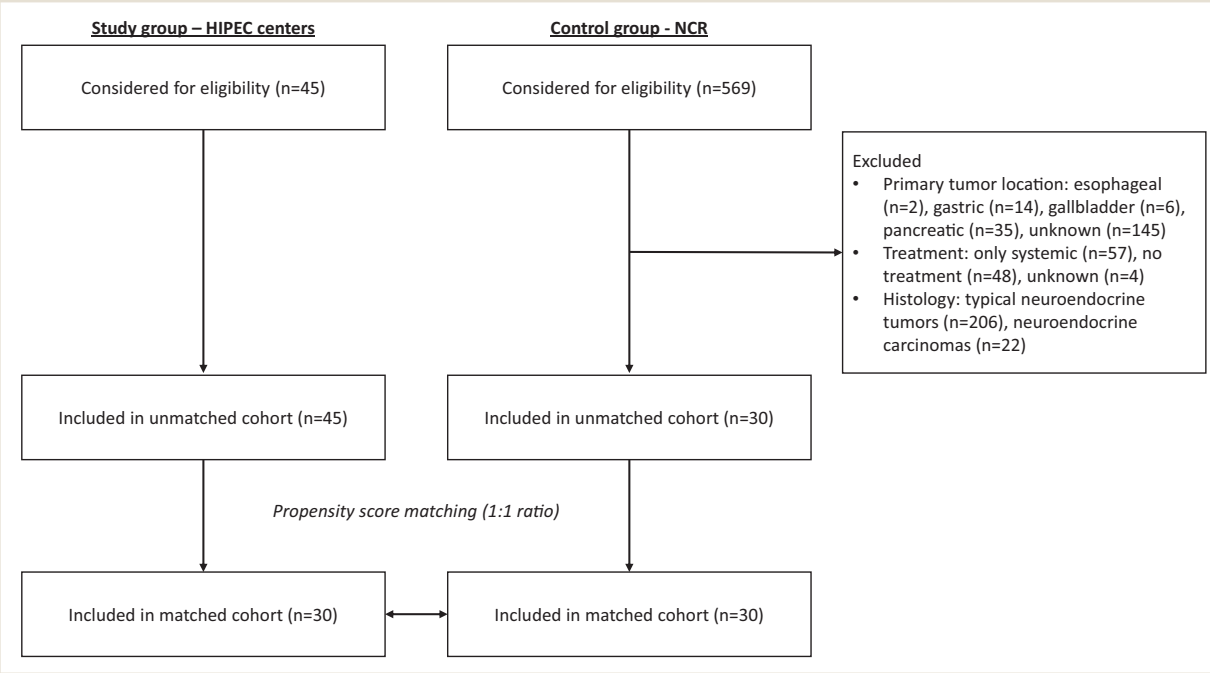
Supplemental Data

Supplemental tables and figures accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2020.01.002.

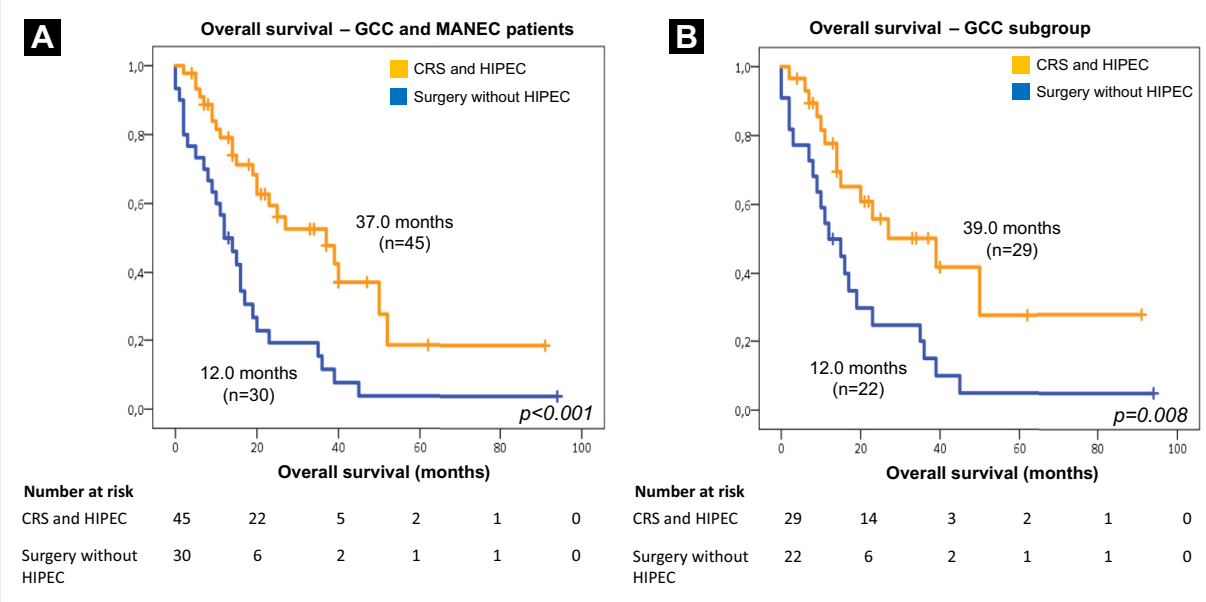
References

1. Randle RW, Griffith KF, Fino NF, et al. Appendiceal goblet cell carcinomatosis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Surg Res* 2015; 196:229-34.
2. Lamarca A, Nonaka D, Lopez Escola C, et al. Appendiceal goblet cell carcinoids: management considerations from a reference peritoneal tumour service centre and ENETS centre of excellence. *Neuroendocrinology* 2016; 103:500-17.
3. Brathwaite S, Rock J, Yearsley MM, et al. Mixed adeno-neuroendocrine carcinoma: an aggressive clinical entity. *Ann Surg Oncol* 2016; 23:2281-6.
4. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. *Am J Surg Pathol* 2008; 32:1429-43.
5. Quenet F, Elias D, Roca L, et al. A UNICANCER phase III trial of hyperthermic intra-peritoneal chemotherapy (HIPEC) for colorectal peritoneal carcinomatosis (PC): PRODIGE 7. *J Clin Oncol* 2018; 36:LBA3503.
6. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. *Ann Surg Oncol* 2008; 15:2426-32.
7. 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.
8. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21:3737-43.
9. Cashin P, Nygren P, Hellman P, Granberg D, Andreasson H, Mahteme H. Appendiceal adenocarcinoids with peritoneal carcinomatosis treated with cytoreductive surgery and intraperitoneal chemotherapy: a retrospective study of in vitro drug sensitivity and survival. *Clin Colorectal Cancer* 2011; 10:108-12.
10. Tsang ES, McConnell YJ, Schaeffer DF, et al. Outcomes of surgical and chemotherapeutic treatments of goblet cell carcinoid tumors of the appendix. *Ann Surg Oncol* 2018; 25:2391-9.
11. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut* 2012; 61:6-32.
12. Rindi G, Petrone G, Inzani F. The 2010 WHO classification of digestive neuroendocrine neoplasms: a critical appraisal four years after its introduction. *Endocr Pathol* 2014; 25:186-92.
13. de Mestier L, Cros J, Neuzillet C, et al. Digestive system mixed neuroendocrine-non-neuroendocrine neoplasms. *Neuroendocrinology* 2017; 105:412-25.
14. Kuijpers AM, Mirck B, Aalbers AG, et al. Cytoreduction and HIPEC in the Netherlands: nationwide long-term outcome following the Dutch protocol. *Ann Surg Oncol* 2013; 20:4224-30.
15. Madani A, Thomassen I, van Gestel YR, et al. Peritoneal metastases from gastroenteropancreatic neuroendocrine tumors: incidence, risk factors and prognosis. *Ann Surg Oncol* 2017; 24:2199-205.
16. Kwakman R, Schrama AM, van Olmen JP, et al. Clinicopathological parameters in patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal cancer metastases: a meta-analysis. *Ann Surg* 2016; 263:1102-11.
17. Verwaal VJ, van Ruth S, Witkamp A, Boot H, van Slooten G, Zoetmulder FA. Long-term survival of peritoneal carcinomatosis of colorectal origin. *Ann Surg Oncol* 2005; 12:65-71.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240:205-13.
19. Klimstra DS, Modlin IR, Adsay NV, et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. *Am J Surg Pathol* 2010; 34:300-13.
20. Sugarbaker PH. Patient selection and treatment of peritoneal carcinomatosis from colorectal and appendiceal cancer. *World J Surg* 1995; 19:235-40.
21. Ihemelandu C, Sugarbaker PH. Clinicopathologic and prognostic features in patients with peritoneal metastasis from mucinous adenocarcinoma, adenocarcinoma with signet ring cells, and adenocarcinoid of the appendix treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2016; 23:1474-80.
22. Mahteme H, Sugarbaker PH. Treatment of peritoneal carcinomatosis from adenocarcinoid of appendiceal origin. *Br J Surg* 2004; 91:1168-73.
23. McConnell YJ, Mack LA, Gui X, et al. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: an emerging treatment option for advanced goblet cell tumors of the appendix. *Ann Surg Oncol* 2014; 21:1975-82.
24. Radomski M, Pai RK, Shuai Y, et al. Curative surgical resection as a component of multimodality therapy for peritoneal metastases from goblet cell carcinoids. *Ann Surg Oncol* 2016; 23:4338-43.
25. Yan TD, Brun EA, Sugarbaker PH. Discordant histology of primary appendiceal adenocarcinoid neoplasms with peritoneal dissemination. *Ann Surg Oncol* 2008; 15:1440-6.
26. Yu HH, Yonemura Y, Hsieh MC, Mizumoto A, Wakama S, Lu CY. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for appendiceal goblet cell carcinomas with peritoneal carcinomatosis: results from a single specialized center. *Cancer Manag Res* 2017; 9:513-23.
27. Madsen AH, Ladekarl M, Villadsen GE, et al. Effects of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of goblet cell carcinoma: a prospective cohort study. *Ann Surg Oncol* 2018; 25:422-30.
28. Rossi RE, Luong TV, Caplin ME, et al. Goblet cell appendiceal tumors—management dilemmas and long-term outcomes. *Surg Oncol* 2015; 24:47-53.
29. Shaib W, Krishna K, Kim S, et al. Appendiceal neuroendocrine, goblet and signet-ring cell tumors: a spectrum of diseases with different patterns of presentation and outcome. *Cancer Res Treat* 2016; 48:596-604.
30. Pham TH, Wolff B, Abraham SC, Drelichman E. Surgical and chemotherapy treatment outcomes of goblet cell carcinoid: a tertiary cancer center experience. *Ann Surg Oncol* 2006; 13:370-6.
31. Holt N, Gronbaek H. Goblet cell carcinoids of the appendix. *ScientificWorldJournal* 2013; 2013:543696.
32. Pape UF, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. *Neuroendocrinology* 2012; 95:135-56.
33. Berardi R, Rinaldi S, Torniai M, et al. Gastrointestinal neuroendocrine tumors: searching the optimal treatment strategy—a literature review. *Crit Rev Oncol Hematol* 2016; 98:264-74.
34. Olsen IH, Holt N, Langer SW, et al. Goblet cell carcinoids: characteristics of a Danish cohort of 83 patients. *PLoS One* 2015; 10:e0117627.
35. Rovers KP, Simkens GA, Vissers PA, et al. Survival of patients with colorectal peritoneal metastases is affected by treatment disparities among hospitals of diagnosis: a nationwide population-based study. *Eur J Cancer* 2017; 75:132-40.
36. Elias D, David A, Sourrouille I, et al. Neuroendocrine carcinomas: optimal surgery of peritoneal metastases (and associated intra-abdominal metastases). *Surgery* 2014; 155:5-12.
37. Randle RW, Doud AN, Levine EA, et al. Peritoneal surface disease with synchronous hepatic involvement treated with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). *Ann Surg Oncol* 2015; 22:1634-8.
38. Saxena A, Yan TD, Morris DL. A critical evaluation of risk factors for complications after cytoreductive surgery and perioperative intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis. *World J Surg* 2010; 34:70-8.
39. Ihemelandu CU, McQuellon R, Shen P, Stewart JH, Votanopoulos K, Levine EA. Predicting postoperative morbidity following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CS + HIPEC) with preoperative FACT-C (Functional Assessment of Cancer Therapy) and patient-rated performance status. *Ann Surg Oncol* 2013; 20:3519-26.
40. Quenet F. Colorectal peritoneal carcinomatosis: what is the future of HIPEC? *Eur J Surg Oncol* 2018; 44:1847-8.
41. Pape UF, Niederle B, Costa F, et al. ENETS consensus guidelines for neuroendocrine neoplasms of the appendix (excluding goblet cell carcinomas). *Neuroendocrinology* 2016; 103:144-52.
42. de Mestier L, Lardiere-Deguelte S, Brixi H, et al. Updating the surgical management of peritoneal carcinomatosis in patients with neuroendocrine tumors. *Neuroendocrinology* 2015; 101:105-11.
43. Elias D, Sideris L, Liberale G, et al. Surgical treatment of peritoneal carcinomatosis from well-differentiated digestive endocrine carcinomas. *Surgery* 2005; 137:411-6.
44. Strosberg J, Gardner N, Kvols L. Survival and prognostic factor analysis of 146 metastatic neuroendocrine tumors of the mid-gut. *Neuroendocrinology* 2009; 89:471-6.
45. Cives M, Strosberg J. Treatment strategies for metastatic neuroendocrine tumors of the gastrointestinal tract. *Curr Treat Options Oncol* 2017; 18:14.
46. Carr NJ, Sobin LH. Neuroendocrine tumors of the appendix. *Semin Diagn Pathol* 2004; 21:108-19.
47. Oberg K, Knigge U, Kwekkeboom D, Perren A, ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; 23(suppl 7):vii124-30.

Supplemental Figure 1 Patient Flowchart of Inclusion and Selection Process



Supplemental Figure 2 Kaplan-Meier Curves of Unmatched Cohorts. (A) OS Curves of Combined GCC and MANEC Group Treated With CRS-HIPEC vs. Surgery Without HIPEC. (B) OS Curves of GCC Subgroup Treated With CRS-HIPEC vs. Surgery Without HIPEC



Abbreviations: CRS = cytoreductive surgery; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; MANEC = mixed adenoneuroendocrine carcinoma; OS = overall survival.

Supplemental Table 1 Search Terms and Boolean Combinations

Database (Date)	Set	Search Terms	No. of Results
PubMed (June 25, 2018)	#4	#1 AND #2 AND #3	338
	#3	HIPEC[tiab] OR "Antineoplastic Agents"[Mesh] OR "Antineoplastic Agents" [Pharmacological Action] OR "Antineoplastic Combined Chemotherapy Protocols"[Mesh] OR "Drug Therapy"[Mesh:NoExp] OR "Chemotherapy, Adjuvant"[Mesh] OR "Consolidation Chemotherapy"[Mesh] OR "Induction Chemotherapy"[Mesh] OR "Maintenance Chemotherapy"[Mesh] OR "Cytostatic Agents"[Mesh] OR "oxaliplatin" [Supplemental Concept] OR "Mitomycin"[Mesh] OR chemotherap*[tiab] OR ((anti neoplast*[tiab] OR antineoplast*[tiab]) AND (drugs[tiab] OR agents[tiab])) OR oxaliplatin[tiab] OR mitomycin*[tiab]	1,314,474
	#2	"Carcinoid Tumor"[Mesh] OR "Neuroendocrine Tumors"[Mesh] OR "Carcinoma, Neuroendocrine"[Mesh] OR "Adenocarcinoid tumor" [Supplemental Concept] OR carcinoid*[tiab] OR goblet[tiab] OR argentaffinoma*[tiab] OR neuroendocrine[tiab] OR adenocarcinoid[tiab]	201,827
	#1	"Peritoneum"[Mesh] OR peritone*[tiab] OR parametrium*[tiab] OR mesenter*[tiab] OR omentum*[tiab] OR mesocolon[tiab]	182,365
Embase (June 25, 2018)	#4	#1 AND #2 AND #3	543
	#3	hipec:ab,ti OR 'cancer chemotherapy'/exp OR 'antineoplastic agent'/exp OR 'drug therapy'/de OR 'chemotherapy'/exp OR 'oxaliplatin'/exp OR 'mitomycin'/exp OR chemotherap*:ab,ti OR ('anti neoplast*':ab,ti OR antineoplast*:ab,ti AND (drugs:ab,ti OR agents:ab,ti)) OR oxaliplatin:ab,ti OR mitomycin*:ab,ti	2,735,220
	#2	carcinoid'/exp OR 'neuroendocrine tumor'/exp OR carcinoid*:ab,ti OR goblet:ab,ti OR argentaffinoma*:ab,ti OR neuroendocrine:ab,ti OR adenocarcinoid:ab,ti	160,016
	#1	peritoneum'/exp OR peritone*:ab,ti OR parametrium*:ab,ti OR mesenter*:ab,ti OR omentum*:ab,ti OR mesocolon:ab,ti	238,533

Read searches from bottom up.

Supplemental Table 2 Baseline Characteristics in Unmatched Cohorts and Propensity-Matched Cohorts

		GCC + MANEC					GCC				
		Matching Group	Unmatched		Propensity Matched		Matching Group	Unmatched		Propensity Matched	
Characteristic	Variable	Surgery	HIPEC	*P*	HIPEC	*P*	Surgery	HIPEC	*P*	HIPEC	*P*
Propensity score, mean ± SD		0.607 ± 0.293	0.723 ± 0.239		0.711 ± 0.807		0.654 ± 0.310	0.708 ± 0.222		0.700 ± 0.229	
All		30	45		30		22	29		22	
Age (y), mean ± SD		63 ± 14	56 ± 12	.024[a] (*t* 2.3, *df* 73)	54 ± 12	.012[a] (*t* 2.6, *df* 58)	60 ± 14	56 ± 9	.277[a] (*t* 1.2, *df* 49)	55 ± 9	.163[a] (*t* 1.4, *df* 42)
Sex	Male	7 (23.3)	22 (48.9)	.026[b]	16 (53.3)	.017[b]	3 (13.6)	13 (44.8)	.017[b]	11 (50.0)	.10[b]
	Female	23 (76.7)	23 (51.1)	(χ^2 5.0, *df* 1)	14 (46.7)	(χ^2 5.7, *df* 1)	19 (86.4)	16 (55.2)	(χ^2 5.7, *df* 1)	11 (50.0)	(χ^2 6.7, df 1)
Location	Colorectal	5 (16.7)	4 (8.9)	.575[c]	3 (10.0)	.706[c]	2 (9.1)	1 (3.4)	.571[c]	1 (4.5)	1.000[c]
	Appendix	25 (83.3)	41 (89.1)		27 (90.0)		20 (90.9)	28 (96.6)		21 (95.5)	
Morphology	MANEC	8 (26.7)	16 (35.6)	.419[b]	14 (46.7)	.108[b]	NA				
	GCC	22 (73.3)	29 (64.4)	(χ^2 0.6, *df* 1)	16 (53.3)	(χ^2 2.6, *df* 1)					
T stage	T1-3	7 (41.2)	10 (32.3)	.537[b]	9 (34.6)	.663[b]	5 (55.6)	5 (31.2)	.397[c]	4 (28.6)	.383[c]
	T4	10 (58.8)	21 (67.7)	(χ^2 0.4, *df* 1)	17 (65.4)	(χ^2 0.2, *df* 1)	4 (44.4)	11 (68.8)		10 (71.4)	
N stage	N0-1	11 (57.9)	26 (70.3)	.354[b]	18 (66.7)	.544[b]	5 (45.5)	18 (78.3)	.114[c]	15 (78.9)	.108[c]
	N2	8 (42.1)	11 (29.7)	(χ^2 0.8, *df* 1)	9 (33.3)	(χ^2 0.4, *df* 1)	6 (54.5)	5 (21.7)		4 (21.1)	
Ovarian metastases	No	15 (50.0)	24 (53.3)	.817[b]	22 (73.3)	.063[b]	8 (36.4)	13 (44.8)	.543[b]	12 (54.5)	.226[b]
	Yes	15 (50.0)	21 (46.7)	(χ^2 0.1, *df* 1)	8 (26.7)	(χ^2 3.5, *df* 1)	14 (63.6)	16 (55.2)	(χ^2 0.4, df 1)	10 (45.5)	(χ^2 1.5, df 1)
Liver metastases	No	29 (96.7)	33 (73.3)	.009[b]	27 (90.0)	.612[c]	21 (95.5)	20 (69.0)	.030[c]	15 (68.2)	.046[c]
	Yes	1 (3.3)	12 (26.7)	(χ^2 6.8, *df* 1)	3 (10.0)		1 (4.5)	9 (31.0)		7 (31.8)	
Systemic chemotherapy	No	16 (53.3)	20 (44.4)	.450[b]	15 (50.0)	.796[b]	10 (45.5)	13 (44.8)	.964[c]	9 (40.9)	.761[b]
	Yes	14 (46.7)	25 (55.6)	(χ^2 0.6, *df* 1)	15 (50.0)	(χ^2 0.7, *df* 1)	12 (54.5)	16 (55.2)		13 (59.1)	(χ^2 0.1, df 1)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: *df* = degree of freedom; GCC = goblet-cell carcinoid; HIPEC = hyperthermic intraperitoneal chemotherapy; MANEC = mixed adenoneuroendocrine carcinoma; NA = not available; SD = standard deviation.
[a]Independent *t* test.
[b]Chi-square test.
[c]Fisher exact test (test statistic and *df* not applicable).