Ann Surg Oncol (2014) 21:1975–1982
DOI 10.1245/s10434-013-3469-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy: An Emerging Treatment Option for Advanced Goblet Cell Tumors of the Appendix

Yarrow J. McConnell, M.D[1], Lloyd A. Mack, M.D[1], Xianyong Gui, M.D[2], Norman J. Carr, M.B[3], Lucas Sideris, M.D[4], Walley J. Temple, M.D[1], Pierre Dubé, M.D[4], Kandiah Chandrakumaran, Ph.D[5], Brendan J. Moran, M.B[5], and Tom D. Cecil, D.M[5]

[1]Division of Surgical Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [2]Department of Pathology and Laboratory Medicine, University of Calgary and Calgary Laboratory Services, Calgary, AB, Canada; [3]Department of Cellular Pathology, University Hospital Southampton, Southampton, UK; [4]Department of Surgery, Hôpital Maisonneuve-Rosemont, Université de Montréal, Montreal, QC, Canada; [5]Pseudomyxoma Peritonei Centre, Basingstoke and North Hampshire Hospital Foundation Trust, Hampshire, UK

ABSTRACT

Background. The debate remains whether appendiceal goblet cell cancers behave as classical carcinoid or adenocarcinoma. Treatment options are unclear and reports of outcomes are scarce. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) is considered optimal treatment for peritoneal involvement of other epithelial appendiceal tumors.

Methods. Prospective cohorts of patients treated for advanced appendiceal tumors from three peritoneal malignancy centres were collected (1994–2011). All patients underwent complete CRS+HIPEC, when possible, or tumor debulking. Demographic and outcome data for patients with goblet cell cancers were compared to patients with low- or high-grade epithelial appendiceal tumors treated during the same time period.

Results. Details on 45 goblet cell cancer patients were compared to 708 patients with epithelial appendix lesions. In the goblet cell group, 57.8 % were female, median age was 53 years, median peritoneal cancer index (PCI) was 24, and CRS+HIPEC was achieved in 71.1 %. These details were similar in patients with low- or high-grade epithelial tumors. Lymph nodes were involved in 52 % of goblet cell patients, similar to rates in high-grade cancers, but significantly higher than in low-grade lesions (6.4 %; $p < 0.001$). At 3 years, overall survival (OS) was 63.4 % for goblet cell patients, intermediate between that for high-grade (40.4–52.2 %) and low-grade (80.6 %) tumors. On multivariate analysis, tumor histology, PCI, and achievement of CRS+HIPEC were independently associated with OS.

Conclusions. This data supports the concept that appendiceal goblet cell cancers behave more as high-grade adenocarcinomas than as low-grade lesions. These patients have reasonable long-term survival when treated using CRS+HIPEC, and this strategy should be considered.

INTRODUCTION

Goblet cell cancers of the appendix are a rare entity and have a wide variety of names: "goblet cell carcinoid," "adenocarcinoid," "mucinous carcinoids," "crypt cell carcinoma," and "mixed adeno/neuroendocrine carcinoma," among others. These tumors account for 14–19 % of primary appendiceal tumors[1,2] and are histologically distinct, with a carcinoid-like growth pattern, clusters of cells within the stroma expressing some endocrine markers, and minimal atypia. They are distinguished from classical carcinoid tumors by their intestinal-type goblet cell morphology and common expression of epithelial markers.[3–6] The clinical behaviour of these tumors is now widely recognized to be much more akin to that of mucinous adenocarcinoma than to classical carcinoid, and for brevity and clarity will subsequently be referred to as goblet-cell adenocarcinoma (GCA).[1,4,6]

First Received: 22 September 2013;
Published Online: 8 January 2014

Y. J. McConnell, M.D
e-mail: yarrow.mcconnell@gmail.com

Treatment options for patients with GCA have not been widely studied. In patients with primary GCA without peritoneal involvement, 20–40 % have lymph node involvement and are thus generally recommended to undergo right hemicolectomy.[1,3] Adjuvant chemotherapy based on colonic adenocarcinoma regimens are recommended, based on consensus opinion.[7] In GCA patients with peritoneal involvement, various combinations of debulking surgery, systemic chemotherapy, and cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) have been used.[1,2] Debulking and/or systemic chemotherapy has achieved 2- to 3-year survival of 34–71 %, with very few 5-year survivors, in small series.[3,8] Although CRS+HIPEC is a widely accepted treatment approach for epithelial tumors of the appendix, reports of its use in GCA are limited. In patients with low-grade mucinous appendix tumors with peritoneal involvement (pseudomyxoma peritonei), CRS+HIPEC results in 5-year overall survival (OS) of 75–81 %.[9–11] Higher-grade mucinous and non-mucinous appendiceal tumors with peritoneal metastases have a 5-year OS of 45–65 % when treated with CRS+HIPEC.[12] Only two dedicated series have reported outcomes with CRS+HIPEC for GCA. In the first, which reported on only ten patients, 3-year OS of 20 % was reported, although complete cytoreduction was achieved in only 6.[13] In a slightly larger series of 22 patients, within which complete cytoreduction achieved in 6 patients and hyperthermic intraperitoneal chemotherapy applied in 20 patients, 2- and 5-year OS was 39and 25 %, respectively.[14] Several large cohort studies of CRS + HIPEC have included small numbers of GCA patients, but have grouped them with other high-grade adenocarcinomas of the appendix. Bruin et al.[15] reported 2- and 5-year OS of 40 and 20 %, respectively, for this mixed group of high-grade adenocarcinomas including some GCA, whereas Stewart et al.[16] reported a 3-year OS of 15 %.

Outcome data in larger cohorts of GCA patients are required to guide management decisions. Therefore, the goal of the current study was to compare clinical characteristics and survival outcomes for patients treated with CRS+HIPEC for advanced GCA compared to advanced low- and high-grade epithelial tumors of the appendix. A multicentre cohort study was designed to collect a sufficient sample size for meaningful analysis. We hypothesized that overall survival for GCA patients would be more similar to that of high-grade than low-grade mucinous tumors, and that the inability to achieve complete cytoreduction would be associated with worse overall survival.

METHODS

Patients with peritoneal malignancy due to advanced appendiceal malignancy who underwent surgery with the intent of CRS+HIPEC between 1994 and 2011 were abstracted from prospectively maintained databases. Demographic and clinical factors were compared between patients with GCA, and those with low- or high-grade mucinous or non-mucinous adenocarcinoma.

The histopathology of all patients included in the GCA group were reviewed by expert pathologists, with immunohistochemistry (IHC) used as necessary to confirm the diagnosis.[4,17] IHC included staining for CEA, CK7, CK20, CDX2, chromogranin, and synaptophysin.

For patients with mucinous epithelial tumors, all were classified into low-grade mucinous neoplasms (LGMN) and high-grade mucinous neoplasms (HGMN) groups, according to the World Health Organization classification of appendiceal tumors.[17] The tumors that had been classified according to Ronnett's system,[18] those diagnosed as diffuse peritoneal adenomucinosis or intermediate-type peritoneal mucinous cancer were included with the low-grade group, whereas those classified as peritoneal mucinous cancer were included in the high-grade cohort. Non-mucinous adenocarcinomas (NMAs) were classified separately.

For all patients, the extent of disease was quantified intraoperatively using the peritoneal cancer index (PCI) and the amount of residual disease at the end of the operation was classified using the completeness of cytoreduction (CCR) score.[19] The type and number of resections was recorded at the time of operation, including peritonectomy procedures. In all patients with complete cytoreduction, hyperthermic intraperitoneal chemotherapy with mitomycin C (MMC) or oxaliplatin was administered according to institutional protocols. Over the course of time of the study, one institution used MMC for all patients, one institution used oxaliplatin for all patients, and the third institution changed from MMC to oxaliplatin halfway through the study period. If complete cytoreducton could not be achieved, debulking and other palliative interventions were undertaken, and HIPEC was not routinely administered. Complications, re-operations, mortality, and re-admissions within 60 days of the index operation were recorded. Complications were graded according to the Dindo–Clavien classification.[20] Institutional ethics review board approval was obtained at each participating institution.

Overall survival (OS) and progression-free survival (PFS) data were compared between histological subgroups using Kaplan–Meier techniques and log rank testing. Multivariate analysis for survival outcomes was conducted using Cox proportional hazards modeling.

RESULTS

From a total cohort of 753 patients, 45 with GCA were identified and had histopathology confirmed on review. In patients with complete IHC results available, 100 % had positive staining for CEA and CK20, whereas only 41 %

TABLE 1 Immunohistochemical (IHC) profile of goblet cell adenocarcinoma (GCA) patients compared to non-mucinous, mucinous, and carcinoid tumors of the appendix

	van Eeden et al.[4]				Study patients
	Non-mucinous adenocarcinoma (%)	Mucinous adenocarcinoma (%)	Goblet cell carcinoid/ adenocarcinoid (%)	Carcinoid (%)	GCA ($n = 27$)
CEA	100	100	100	0	100
CK7	0	20	56	0	41
CK20	85	90	81	0	100
CDX2	100	100	100	100[a]	94
Chromogranin	0	0	44	100	50
Synaptophysin	0	0	75	100	93

[a] All cells stained, but only weakly

TABLE 2 Demographic and clinical factors compared across appendiceal lesion types

	Number	LGMN	HGMN	GCA	NMA	p[a]
Number		567	89	45	52	
Age, years, median	753	55	52	53	54	0.59
Gender						
Females	437	58.7 %	58.4 %	57.8 %	51.9 %	0.83
Males	315	41.3 %	41.6 %	42.2 %	48.1 %	
PCI, median	277	21	23	24	14	0.09
Completeness of cytoreduction						
CCR 0/1	539	75.3 %	53.9 %	71.1 %	61.5 %	<0.001
CCR 2/3	214	24.7 %	46.1 %	28.9 %	38.5 %	
HIPEC administered						
Yes	581	80.4 %	68.6 %	80.0 %	76.5 %	0.09
No	157	19.6 %	31.4 %	20.0 %	23.5 %	
Lymph nodes involved						
Yes	33	6.4 %	20.0 %	52.0 %	50.0 %	<0.001
No	101	93.6 %	80.0 %	48.0 %	50.0 %	
Grade III/IV complication						
Yes	144	19.8 %	20.4 %	18.2 %	11.5 %	0.53
No	605	80.2 %	79.6 %	81.8 %	88.5 %	
Perioperative mortality						
Yes	14	1.4 %	4.5 %	4.5 %	0 %	0.07
No	733	98.6 %	95.5 %	95.5 %	100 %	

GCA goblet cell adenocarcinoma, *HGMN* high-grade appendiceal mucinous neoplasm, *HIPEC* hyperthermic intraperitoneal chemotherapy, *LGMN* low-grade appendiceal mucinous neoplasm, *NMA* non-mucinous adenocarcinoma, *PCI* peritoneal cancer index

[a] Wilcoxon testing for difference between medians ($p < 0.05$), Chi squared test for difference in proportions ($p < 0.05$)

stained for CK7. Fifty percent stained for chromogranin and 93 % were positive for synaptophysin. Table 1 compares these values to the best available data on typical staining patterns in other mucinous, non-mucinous, and carcinoid appendiceal tumors.

Results for the 45 GCA patients were compared to 567 patients with LGMN, 89 patients with HGMN, and 52 patients with NMAs were treated under the same protocol as sequential cohorts from the same institutions within the same time period. Overall, the median age (52–55 years; $p = 0.59$) and proportion of females (51.9–56.7 %; $p = 0.83$) were similar between all types of appendiceal tumors. The intraoperative PCI had been documented in 277 patients and the median value (14–24; $p = 0.09$) was

similar across pathology types within this subgroup. The proportion of patients in whom complete cytoreduction (CCR0/1) was achieved was lower in the HGMN group than in other groups (LGMN 75.3 %, HGMN 53.9 %, GCA 71.1 %, NMA 61.5 %; $p < 0.001$). Similarly, the proportion who received HIPEC treatment was slightly lower in the HGMN group (LGMN 80.4 %, HGMN 68.5 %, GCA 80.0 %, NMA 76.5 %; $p = 0.09$). Lymph node involvement was lower in the LGMN group than all the other groups (LGMN 6.4 %, HGMN 20.0 %, GCA 52.0 %, NMA 50.0 %; $p < 0.001$). The grade III/IV complication rate and perioperative mortality rates were similar across all groups (see Table 2).

The median follow-up was 49.2 months. The estimated 3-year OS for GCA patients was 63.4 % (Fig. 1a), which was worse than that for the LGMN group (80.6 %; $p = 0.003$), slightly better than that of HGMN patients (40.4 %; $p = 0.07$), and similar to that of NMA patients (52.2 %; $p = 0.48$). Amongst patients in whom a complete cytoreduction (CCR0/1) was achieved and HIPEC was administered, a similar pattern was observed (Fig. 1b). Estimated 3-year OS in these CRS+HIPEC patients was 68.1 % for those with GCA histology, which was lower than that for the LGMN group (91.6 %; $p = 0.0005$), and similar to that for the HGMN group (61.5 %; $p = 0.64$) and the NMA group (66.3 %; $p = 0.79$). In patients in whom complete cytoreduction was not possible (CCR2/3) and HIPEC was not administered, survival was worse across all histology types (estimated 3-year OS, LGMN 50.0 %, HGMN 14.5 %, NMA 29.4 %). Follow-up on the 13 GCA patients with CCR2/3 resections was not sufficient to estimate 3-year OS.

On the Kaplan–Meier univariate analysis for OS, gender, tumor histology, PCI, completeness of cytoreduction, HIPEC administration, and lymph node status were significantly associated with OS (Table 3). On multivariate Cox proportional hazard modeling of all patients, controlling for age and gender, tumor histology, PCI, completeness of cytoreduction, and administration of HIPEC remained to be independent predictors of OS. In patients with CCR0/1 resection, multivariate modeling identified tumor histology and PCI as the only factors independently associated with OS.

Amongst patients who had CCR0/1 resection, the median disease-free survival (DFS) was 35.8 months. For patients with LGMN, DFS was significantly longer (38.1 months) than for patients with GCA (15.9 months; $p = 0.002$), HGMN (21.6 months; $p = 0.02$), or NMA (22.7 months; $p = 0.04$). There was no significant difference in DFS between the GCA, HGMN, and NMA groups. The estimated DFS at 3 years was 42.7 % for GCA patients, lower than that for LGMN (72.6 %; $p = 0.0003$),

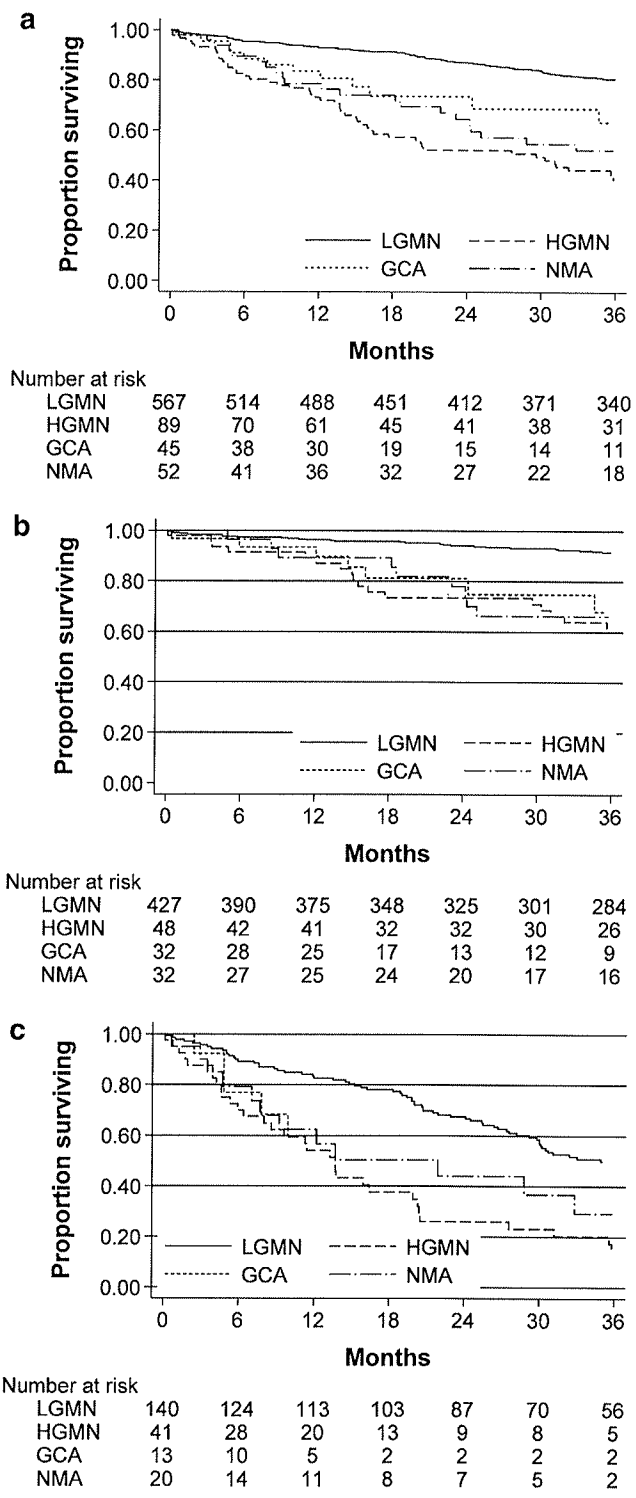

FIG. 1 Overall survival by pathologic type. Kaplan–Meier curves for overall survival amongst patients with peritoneal carcinomatosis from low-grade mucinous neoplasms (LGMN), high-grade mucinous neoplasms (HGMN), goblet cell adenocarcinoma (GCA), and non-mucinous adenocarcinoma (NMA) after cytoreduction or debulking surgery. **a** All patients. **b** Patients who had complete cytoreduction (CCR0/1) was achieved. **c** Patients in whom complete cytoreduction was not achieved (CCR2/3)

TABLE 3 Univariate and multivariate analysis of factors associated with overall survival (OS)

	Number	Univariate[a]		Multivariate[b]		Multivariate[c]	
		3-year OS	*p*	HR	*p*	HR	*p*
Age							
≤50 years	292	75.6 %	0.62	1.0	–	1.0	–
>50 years	461	71.1 %		1.43	0.14	1.49	0.20
Gender							
Female	437	75.5 %	0.02	1.0	–	1.0	–
Male	315	69.3 %		1.05	0.84	0.94	0.83
Histology							
LGMN	567	80.6 %	<0.0001	1.0	–	1.0	–
HGMN	89	40.4 %		5.94	<0.001	7.15	<0.001
GCA	45	63.4 %		4.47	<0.001	4.04	0.003
NMA	52	52.2 %		20.6	<0.001	19.3	<0.001
PCI							
<20	136	77.0 %	0.001	1.0	–	1.0	
≥20	141	61.2 %		2.48	0.001	2.37	0.007
Completeness of cytoreduction							
CCR 0/1	539	86.1 %	<0.0001	1.0	–	NA[c]	
CCR 2/3	214	41.0 %		3.42	0.009	NA[c]	
HIPEC administered							
Yes	581	81.9 %	<0.0001	1.0	–	1.0	–
No	157	43.9 %		1.83	0.18	1.85	0.18
Lymph nodes involved							
No	101	75.3 %	0.02	NA[b]		NA[c]	
Yes	33	56.7 %		NA[b]		NA[c]	
Grade III/IV complication							
No	605	73.2 %	0.70	1.0	–	1.0	–
Yes	144	71.4 %		1.43	0.17	1.45	0.23

CCR complete cytoreduction, *HGMN* high-grade appendiceal mucinous neoplasm, *GCA* goblet cell adenocarcinoma, *HR* hazards ratio, *LGMN* low-grade appendiceal mucinous neoplasm, *NMA* non-mucinous adenocarcinoma, *PCI* peritoneal cancer index

[a] Univariate testing by Kaplan–Meier survival analysis with log rank testing

[b] Multivariate testing by Cox proportional hazards modeling, which was evaluated in 275 patients with PCI data; lymph node involvement not included due to missing data

[c] Multivariate testing by Cox proportional hazards modeling, which was evaluated in 241 patients with PCI data and in whom complete cytoreduction (CCR0/1) was achieved; lymph node involvement was not included due to missing data

and similar to that for HGMN (44.2 %; $p = 0.85$) and NMA patients (43.5 %; $p = 0.82$). On univariate Kaplan–Meier survival analysis, PCI and lymph node involvement were also significantly associated with DFS (Table 4). On multivariate Cox proportional hazard modeling, histology and PCI remained as the only independent predictors.

DISCUSSION

The immunohistochemical profile of the GCA tumors in this study is more similar to that of the epithelial, rather than neuroendocrine (carcinoid) tumors of the appendix. This finding is in agreement with others who have undertaken more thorough reviews of this topic.[4,17] A discussion of IHC diagnostic criteria for GCA is beyond the scope of this paper, however, an appendiceal tumor with goblet cell morphology that stains for epithelial markers (CEA/CK20/CDX2) and neuroendocrine markers (chromogranin/synaptophysin) should be considered a goblet cell cancer.

The prognosis for patients with peritoneal involvement from GCA, treated with cytoreductive surgery, is intermediate between that of low- and high-grade epithelial neoplasms of the appendix. The 3-year OS and DFS amongst GCA patients was significantly lower than amongst LGMN patients (63.4 vs 80.6 % and 42.7 vs 72.6 %; $p < 0.0001$ and <0.0001, respectively), and this finding remained significant on multivariate analyses when controlled for PCI and completeness of cytoreduction. Both

TABLE 4 Univariate and multivariate analysis of factors associated with disease-free survival (DFS) in patients in whom complete cytoreduction (CCR0/1) was achieved

	Number	Univariate[a]		Multivariate[b]	
		3-year DFS	*p*	HR	*p*
Age					
≤50 years	209	66.1 %	0.13	1.0	–
>50 years	330	67.1 %		1.05	0.83
Gender					
Female	334	67.8 %	0.94	1.0	–
Male	204	64.8 %		1.03	0.89
Histology					
LGMN	427	72.6 %	<0.0001	1.0	–
HGMN	48	44.2 %		3.17	<0.001
GCA	32	42.7 %		2.34	0.007
NMA	32	43.5 %		8.66	<0.001
PCI					
≤20	126	64.9 %	0.0004	1.0	–
>20	116	44.4 %		2.47	<0.0001
HIPEC administered					
Yes	504	66.8 %	0.88	1.0	
No	32	65.7 %		0.88	0.72
Lymph node involvement					
No	89	62.4 %	0.002	–	
Yes	20	26.9 %		–	
Grade III/IV complication					
No	410	69.2 %	0.08	1.0	–
Yes	126	57.7 %		1.09	0.70

GCA goblet cell adenocarcinoma, *HGMN* high-grade appendiceal mucinous neoplasm, *HIPEC* hyperthermic intraperitoneal chemotherapy, *HR* hazards ratio, *LGMN* low-grade appendiceal mucinous neoplasm, *NMA* non-mucinous adenocarcinoma, *PCI* peritoneal cancer index

[a] Univariate testing by Kaplan–Meier survival analysis with log rank testing

[b] Multivariate testing by Cox proportional hazards modeling, which was evaluated in 241 patients with PCI data and in whom complete cytoreduction (CCR0/1) was achieved; lymph node involvement was not included due to missing data

OS and DFS were similar for patients with GCA, HGMN, and NMA lesions, suggesting a similar tendency to systemic metastases despite maximal surgical resection. This hypothesis is supported by the finding of similarly high lymph node involvement rates in the GCA (52.0 %), HGMN (20.0 %), and NMA (50.0 %) groups. This is in contrast to the 6.4 % of LGMN patients with lymph node involvement. These findings suggest that GCA is at least an intermediate-grade adenocarcinoma, with substantial metastatic potential, and should be treated as such with neoadjuvant and/or adjuvant systemic chemotherapy in addition to surgical resection.

The reported 3-year OS rate of 63.4 % in the GCA group is higher than that reported by the two previously published case series that have specifically examined outcomes of cytoreductive surgery in GCA patients. The Sugarbaker group reported on 22 patients, with a 2-year OS of 39 %.[14] Mahteme and Sugarbaker[14] reported on ten patients, with a 3-year OS of 20 %.[13] The disparity in these findings is likely to be related to the completeness of cytoreduction achieved. In the current study, a complete cytoreduction could not be achieved in 28.9 % of GCA patients compared to 40–72 % in the earlier studies.[13,14] As seen in the multivariate analysis, the ability to undergo complete cytoreduction is one of the strongest predictors of survival in all appendiceal tumor types, including GCA. The OS seen in the current study is therefore more representative of the survival that may be expected after CRS+HIPEC for peritoneal metastases of GCA than that reported in prior studies.

High-quality data regarding the natural history of GCA are not readily available. In their study of 5,655 patients with appendix cancer from the SEER database, Turaga et al.[1] found that GCA was associated with a better 5-year disease-specific survival (81 %) compared to all forms of adenocarcinoma (27–55 %). This disparity may be explained by the fact that only 12 % of GCA patients had M1 disease and 19 % had N1 disease, compared with 22–56 % of adenocarcinomas with M1 disease and 20–61 % with N1 disease. Data in the current study suggests that the rate of lymph node involvement in GCA is equivalent to that of high-grade adenocarcinomas. It also suggests, in the setting of advanced disease, that survival is similarly poor for GCA, high-grade mucinous, and non-mucinous adenocarcinomas.

On the other end of the spectrum, Tang et al.[3] undertook a detailed histological examination and reported survival in 63 patients with GCA from which 40 patients had stage IV disease at presentation. Within those 40 metastatic cases, 30 had primary tumors that were subclassified as high-grade adenocarcinomas with only remnants of GCA. All were reportedly treated with surgical debulking and systemic chemotherapy, without intraperitoneal chemotherapy. The reported 5-year 42 % disease-specific survival is the only available data that approximates a natural history for GCA with peritoneal metastases. However, survival data was only available for 19 of 40 patients and may be biased by follow-up losses to disease progression and death.

The CCR2/3 patients in the current study provide some additional insight into the natural history of appendix cancers with peritoneal metastases, and provide a better comparator group for survival analyses than previous cohorts. In particular, these patients had been selected for

potential cytoreduction and hence had no evidence of extra-abdominal metastases. It is unknown how many of the stage IV patients in the Turaga et al.[1] or Tang et al.[3] studies had extra-abdominal disease. In addition, on multivariate analysis, the only factor associated with CCR2/3 status in the current study was higher PCI ($p = 0.008$, data not shown). This suggests that the poorer survival seen in these patients may reflect disease burden rather than underlying biology alone, and that their outcome after failed cytoreduction likely represents the eventual fate of all such patients if not treated with full curative intent.

A complete cytoreduction (CCR0/1), along with low-grade tumor histology and a lower PCI, were all independently associated with better OS on multivariate analysis. This finding is in agreement with that of Chua et al.[9] who found completeness of cytoreduction and histopathologic subtype to be amongst the strongest predictors of OS in their analysis of 2,298 appendix tumor patients with peritoneal involvement. They also found age, major postoperative complication, and prior chemotherapy to be independently associated with OS (i.e., findings that were not replicated in the current study). Their results did not identify a subset of patients with GCA histology, although some such patients may have been included in their high-grade group. Our finding that GCA histology is independently associated with a worse OS is therefore a novel finding.

DFS was analysed in the subset of patients in which CCR0/1 was achieved. Amongst these 539 patients, there were 32 GCA patients whose 3-year DFS was 42.7 %, which was significantly less than that for the LGMN group (72.6 %; $p < 0.0001$), and similar to that for the HGMN group (44.2 %; $p = 0.85$) and the NMA group (43.5 %; $p = 0.82$). Again, this suggests a substantial risk of recurrence, even after CRS+HIPEC, which warrant post-operative treatment with systemic chemotherapy. Limitations of this study included the lack of data regarding systemic therapies received by the patients included and the sites of first recurrence. Although recent consensus guidelines recommended treatment with colonic adenocarcinoma regimens,[7] given the historic classification of GCA tumors as carcinoid-type tumors, it is likely that very few of the included patients received full adjuvant-intent, multi-agent, chemotherapy. It would be informative to evaluate prospective results from a cohort of GCA patients treated with a protocol of systemic chemotherapy and complete cytoreduction with HIPEC. Given the rarity of this disease, it is unlikely that any randomized studies will ever be feasible.

Several other limitations of this study are worthy of mention. Although the multicentre combination of cohorts was necessary to collect sufficient numbers of GCA patients for meaningful analysis, it does introduce the possibility that differences in patient selection and operative technique may have influenced the results. The current series has also been compiled from three subspecialty centres, with consequent referral biases likely to be present within the data. The included GCA cases underwent pathologic review for confirmation of the diagnosis, but it was not considered practical to undertake pathologic review of the other histological subgroups for the exploratory purposes of this study. Miss-classification is thus possible in those groups (LGMN, HGMN, and NMA) and may have biased the results. Despite the focused practice of the three centres, complete data points were not available for all patients. Data on PCI and lymph node involvement were particularly sparse, despite extensive chart reviews. Finally, although larger than previously published series, the current study remains retrospective and prospective data on patients treated under standardized protocols are needed to validate the findings.

In summary, GCA tumors of the appendix appear to behave as adenocarcinomas with a prognosis intermediate between that of LGMN and HGMN/NMA. They may involve the peritoneum with carcinomatosis, and CRS+HIPEC is associated with a 3-year PFS of 42.7 % and OS of 68.1 %. The ability to achieve complete surgical cytoreduction is the strongest prognostic factor after controlling for histology and tumor burden (PCI). Future studies should focus on validating these findings and prospectively measuring outcomes with a protocol-driven approach that involves systemic chemotherapy combined with maximal surgical resection and hyperthermic intraperitoneal chemotherapy.

ACKNOWLEDGMENT No conflicts of interest and no research grants were received for this study.

REFERENCES

1. Turaga KK, Pappas SG, Gamblin TC. Importance of histologic subtype in the staging of appendiceal tumors. *Ann Surg Oncol.* 2012;19:1379–85.
2. McCusker ME, Coté TR, Clegg LX, Sobin LH. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. *Cancer.* 2002;94:3307–12.
3. 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.
4. van Eeden S, Offerhaus GJA, Hart AAM, et al. Goblet cell carcinoid of the appendix: a specific type of carcinoma. *Histopathology.* 2007;51:763–73.
5. Alsaad KO, Serra S, Schmitt A, Perren A, Chetty R. Cytokeratins 7 and 20 immunoexpression profile in goblet cell and classical carcinoids of appendix. *Endocr Pathol.* 2007;18:16–22.
6. Jiang Y, Long H, Wang W, et al. Clinicopathological features and immunoexpression profiles of goblet cell carcinoid and typical carcinoid of the appendix. *Pathol Oncol Res.* 2011;17:127–32.
7. Plöckinger U, Couvelard A, Falconi M, et al. Consensus guidelines for the management of patients with digestive neuroendocrine

tumours: well-differentiated tumour/carcinoma of the appendix and goblet cell carcinoma. *Neuroendocrinology.* 2008;87:20–30.
8. Hristov AC, Young RH, Vang R, et al. Ovarian metastases of appendiceal tumors with goblet cell carcinoidlike and signet ring cell patterns: a report of 30 cases. *Am J Surg Pathol.* 2007;31: 1502–11.
9. Chua TC, Moran BJ, Sugarbaker PH, et al. Early- and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *J Clin Oncol.* 2012;30:2449–56.
10. Chua TC, Yan TD, Smigielski ME, et al. Long-term survival in patients with pseudomyxoma peritonei treated with cytoreductive surgery and perioperative intraperitoneal chemotherapy: 10 years of experience from a single institution. *J Clin Oncol.* 2009;16: 1903–11.
11. Baratti D, Kusamura S, Nonaka D, et al. Pseudomyxoma peritonei: clinical pathological and biological prognostic factors in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). *Ann Surg Oncol.* 2008; 15:526–34.
12. El Halabi H, Gushchin V, Francis J, et al. The role of cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/ HIPEC) in patients with high-grade appendiceal carcinoma and extensive peritoneal carcinomatosis. *Ann Surg Oncol.* 2012;19: 1–5.
13. Cashin P, Nygren P, Hellman P, et al. 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.
14. Mahteme H, Sugarbaker PH. Treatment of peritoneal carcinomatosis from adenocarcinoid of appendiceal origin. *Br J Surg.* 2004;91:1168–73.
15. Bruin SC, Verwaal VJ, Vincent A, van't Veer LJ, van Velthuysen MLF. A clinicopathologic analysis of peritoneal metastases of colorectal and appendiceal origin. *Ann Surg Oncol.* 2010;17: 2330–40.
16. Stewart JH, Shen P, Russell GB, et al. Appendiceal neoplasms with peritoneal dissemination: outcomes after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy. *Ann Surg Oncol.* 2006;13:624–34.
17. Carr N, Sobin LH. Tumors of the appendix. In: Bosman F, Carneiro F, Hruban RH, et al, editors. *Vol WHO classification of tumors of the digestive system.* 4th ed. Lyon, France: IARC Press; 2010. pp 122–125.
18. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei." *Am J Surg Pathol.* 1995;19:1390–408.
19. Gilly FN, Cotte E, Brigand C, et al. Quantitative prognostic indices in peritoneal carcinomatosis. *Eur J Surg Oncol.* 2006;32: 597–601.
20. Dindo D, Demartines N, Clavien P-A. 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.