APPENDICEAL GOBLET CELL CARCINOMAS HAVE POOR SURVIVAL DESPITE COMPLETION SURGERY

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ABSTRACT

Purpose: Appendiceal goblet cell carcinomas (aGCCs) are rare but aggressive tumours associated with significant mortality. We retrospectively reviewed the outcomes of aGCC patients treated at our tertiary referral centre.

Methods: We analysed aGCC patients, diagnosed between 1990-2016, assessing the impact of completion surgery and tumour factors on survival. Survival was assessed using Kaplan-Meier analysis.

Results: We identified 41 patients (23F, 18M); median age 61 (range 27–79) years. Mean tumour size was 10.5 (range 0.5-50) mm; most tumours were located in the appendiceal tip (n=18, 45%). Appendicectomy was the index surgery in 32 patients, 24 of whom subsequently underwent completion surgery at median 3 (range 1.3–13.3) months later. Histology from completion surgery showed residual disease in 8 patients: nodal disease (n=2) or residual tumour (n=6). Index surgery for the rest was either colectomy (n=7) or cytoreductive surgery plus intraperitoneal chemotherapy (CRS-HIPEC) (n=1). Index and completion surgery had 0% mortality and 2.5% morbidity. Overall and recurrence-free survival were not significantly affected by tumour grade or completion surgery. Disease recurred in 9 patients after a median follow-up of 57.0 (4.6 to 114.9) months; 7 of these patients died during follow-up. Recurrences were treated with CRS-HIPEC (n=1), palliative chemotherapy (n=3) or supportive care (n=5). Five- and ten- year overall survival were 85.3% and 62.3% respectively; 5-year and 10-year recurrence-free survival were 73.6% and 50.6%.

Conclusion: The prognosis of aGCCs remains relatively poor. Completion surgery did not prevent recurrence or improve survival, but this needs to be verified with a larger patient cohort. The high mortality associated with tumour recurrence questions current treatment recommendations.

KEYWORDS: Appendix, Appendiceal, Goblet cell carcinomas, Goblet cell carcinoids, Completion right hemicolectomy, Completion surgery

1. INTRODUCTION

Appendiceal goblet cell carcinomas (aGCCs), previously known as goblet cell carcinoids, account for 15% of all appendiceal cancers [1]. Patients typically present with acute appendicitis as occurs with appendiceal neuroendocrine tumours (NETs), [2] but median age of presentation is about 10 years older [3]. Recent studies suggest diagnosis of aGCCs remains mostly incidental following appendicectomy or ileocaecal resection [4]. Appendiceal GCCs show biological features consistent with both adenocarcinomas and NETs, hence they behave more aggressively than most appendiceal NETs [5] and have therefore been excluded from the most recent European Neuroendocrine Tumour Society (ENETS) consensus guidelines for appendiceal NETs [6]. The North American Neuroendocrine Tumour Society (NANETS) [7] consensus guidelines, prior ENETS [5] consensus guidelines, and recent UKINETS guidance on aGCC [8] all advocate performing oncological right hemicolectomy within 3 months of appendicectomy. Female patients are also recommended to have bilateral salpingo-oophorectomy (BSO) [8]. Appendicectomy alone has been proposed for localised non-invasive aGCC < 1cm, with low proliferative index, as these tumours are deemed to have a low risk of developing metastases [8]. None of these treatment recommendations have been prospectively studied as a consequence of the rarity of aGCCs, so the clinical value of these treatment recommendations remains uncertain. Some studies have not shown a benefit of performing a right hemicolectomy, nor has the advantage of BSO been proven, suggesting that completion surgery may not be the optimal treatment strategy for aGCC patients [4, 9]. Our study attempts to address these uncertainties by analysing prospectively recorded data on aGCC patients at our ENETS Centre of Excellence.

2. MATERIALS AND METHODS

2.1 Data Collection

All patients managed with an aGCC at our ENETS Centre of Excellence between 1990 and 2016 were identified from a prospectively maintained database. Inclusion was dependent upon confirmation of original histology diagnosing aGCC in patients over 18 years of age. Tumours were classified using the 2017 WHO classification system for gastro-enteropancreatic neuroendocrine neoplasms [10]. Patients underwent surgery at our tertiary centre, but some underwent resection elsewhere prior to referral to our tertiary centre. Histology of all specimens was reviewed by our experienced NET histopathologists who confirmed the diagnosis of aGCC using appropriate immunohistochemistry (IHC) techniques. We used the TNM staging for GCC proposed by the Union for International Cancer Control/ American Joint Committee on Cancer (UICC/AJCC) [5]. As recent publications suggest Ki-67 analysis is not necessary for grading aGCCs [11] and does not predict outcome of aGCC patients [12], in contrast to previous ENETS guidelines [5], we assessed the role of Ki67 index on outcome by grading aGCCs as grade 1 (Ki67 <2%), grade 2 (Ki67 = 3–20%), or grade 3 (Ki67 >20%) as outlined in previous ENETS guidelines [5]. We obtained details of patients' demographic and clinical characteristics, details of significant post-operative complications that required treatment (Clavien-Dindo [13] Grade II-IV), and post-operative mortality. Patients were initially followed up at 3–6 months, then yearly thereafter by clinical review, measurement of serum concentrations of tumour markers (Chromogranin A [CgA], Chromogranin B [CgB], CEA, CA125, and CA19-9), and cross-sectional abdominal imaging with CT or MRI. Functional imaging was used in cases where curative resection was not certain, distant metastasis were suspected, or recurrence queried. Functional imaging involved ^{111}Indium pentetreotide scintigraphy (Octreoscan), ^{123}Iodine-metaiodobenzylguanidine (MIBG) scintigraphy, or ^{68}Ga-DOTA Tyr(3)-octreotate (^{68}Ga-DOTATATE) PET/ CT.

All cases of GCC recurrence were considered for treatment by cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) and discussed with the regional Peritoneal Malignancy Unit (The Christie Hospital, Manchester) where all cases of CRS-HIPEC in our cohort were performed.

Time to recurrence was defined as the period between diagnosis of disease recurrence and initial resection surgery: either appendicectomy or in cases where done, completion surgery. Overall survival (OS) was defined as the time between diagnosis and last recorded clinical episode or

death. Recurrence-free survival (RFS) was defined as the time between diagnosis and recurrence or last recorded clinical episode without recurrence.

All statistical analyses were performed using R version 3.6.1 (The R Foundation, Vienna, Austria) and SAS version 9.4 (SAS UK, Marlow, UK). Summary measurements were presented as a mean or median with upper and lower limit of range. OS and RFS were estimated by Kaplan-Meier method. Statistical significance was taken at the 5% level. This study was approved by the Liverpool University Hospitals NHS Foundation Trust's Clinical Audit committee (approval number 10113).

3. RESULTS

3.1 Patient details and Index surgery

41 patients (23 F, 18M) presented with aGCC at a median age of 61 (range 27 – 79) years. Surgical resection was performed in 40 patients while one patient was managed non-operatively after intra-operative biopsies of a tumour mass incidentally found at elective total abdominal hysterectomy bilateral salpingo-oophorectomy (TAHBSO) confirmed the diagnosis of aGCC with peritoneal metastases. The majority of the 40 patients who had surgery (70%, n=28) were initially diagnosed with aGCC and underwent index surgery in other hospitals before referral to our centre. Index surgery performed was appendicectomy (n=32), right hemicolectomy (n=6), subtotal colectomy (n=1), or cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) (n=1). The patient who underwent CRS-HIPEC as index surgery presented as an emergency with colonic obstruction secondary to a TNM stage IV aGCC tumour mass involving the recto-sigmoid junction and ureter, initially underwent emergency de-functioning colostomy, and subsequently had CRS-HIPEC as definitive index treatment 2 months later. Index surgery was indicated by suspected appendicitis (n=30), abdominal mass on imaging (n=8), or by incidental finding of aGCC at other surgical

operations (n=2). The other surgical operations leading to aGCC diagnosis were laparotomy to remove an infected vascular graft (n=1) and Amyand's hernia (n=1) (Table 1).

There was only one significant complication following index surgery and this was a pelvic collection (Clavien-Dindo Grade III) that required return to theatre for laparoscopic drainage following laparoscopic appendicectomy, thus a clinically significant complication rate of 2.5%. The 90-day post-operative mortality after index surgery was 0%.

3.2 GCC Histology

Mean size of resected aGCC was 10.5 (range 0.5 - 50) mm and size distribution was as follows: <10mm (n=4), 10-20mm (n=24), and >20mm (n=12). Tumour location in the appendix was mainly at the tip (n=18, 45%) and in the body (n=16, 40%), but also in the base (n=2, 5%) or multifocal (n=4, 10%). Tumour size and location were not discernible for the single patient with a metastasised aGCC mass managed non-operatively. We used the TNM staging for GCC proposed by the Union for International Cancer Control/ American Joint Committee on Cancer (UICC/AJCC) [(5)] as follows: stage 1 (n=2), stage 2 (n=22), stage 3 (n=14), and stage 4 (n=3). In order to assess whether Ki67 index and tumour grade affect outcome of aGCC patients, tumours were graded G1 (n=15), G2 (n=10) or G3 (n=16) according to previous ENETS guidelines [(5)].

3.3 Completion surgery

All patients with aGCC diagnosed following appendicectomy were considered for completion right hemicolectomy, with BSO was also recommended for female patients. Of the 32 patients who had appendicectomy as index surgery, 24 patients underwent completion surgery. 8 patients did not undergo completion surgery either because they declined (n=5) or were deemed medically unfit (n=3) for completion surgery. The 5 patients who declined completion surgery had G1 tumours sized ≤10mm (n=4) or a G2 tumour measuring 21mm (n=1). The patient with a 21mm-sized G2 tumour who declined completion surgery had tumour recurrence in the caecum 2 years later; was treated with CRS-HIPEC and

remained alive at follow-up three years later. The 3 patients deemed medically unfit to undergo completion surgery had 10mm-sized tumours of grade G1 (n=1), G2 (n=1) or G3 (n=1). Eligible patients had completion surgery (n=24) comprising right hemicolectomy +/- BSO, at a median of 3.0 (range 1.3 – 13.3) months after index resection of aGCC. The time to completion surgery was longer than 3 months for 11 patients who had their surgery at a median of 4.8 (range 3.1 - 13.3) months, but this did not significantly affect recurrence-free or overall survival (p=1.000). Histology from completion surgery showed residual GCC disease in 8 patients comprising lymph nodes alone (n=2) or residual tumour alone (n=6). Completion surgery was done by laparoscopic (n=9) or open (n=15) surgical approach combined with BSO in 1 and 3 cases respectively. Significant complications were experienced by 2 patients (5%) following completion surgery; anastomotic leak requiring re-operation with formation of ileostomy (n=1), and anastomotic bleed requiring re-operation for haemostasis (n=1). These were both Clavien-Dindo Grade III complications and the overall clinically significant complication rate after completion surgery was 5%. The 90-day post-operative mortality after completion surgery was 0%.

3.4 GCC recurrence

Recurrent disease occurred in 9 patients (**Table 2**) at a median of 4.8 (0.4 - 9.6) years at the following sites: peritoneum (n=4), small bowel (n=2), liver (n=1), caecum (n=1), and bladder (n=1). Recurrences were diagnosed via symptomatic presentation (n=6), by CT surveillance (n=2), or incidentally at cystoscopy (n=1). Two patients who developed recurrence had previously declined completion surgery (**Table 2, Pt # 7 and Pt # 9)**; one of these 2 patients had their recurrence treated with CRS-HIPEC. This patient (**Table 2, Pt # 7**) was the only one deemed suitable for CRS-HIPEC to treat disease recurrence and is one of only 2 patients with recurrence who was still alive in our cohort. The other patient with recurrence (**Table 2, Pt # 9**) who was still alive in our cohort had initially undergone CRIS-HIPEC as index surgery and was diagnosed with bladder recurrence at cystoscopy performed 5 months later to change an obstructed ureteric stent when bladder biopsy revealed poorly differentiated adenocarcinoma with signet ring cell morphology. She was treated with CAPOX chemotherapy regime. The other 7 patients received palliative

chemotherapy (n=1), palliative surgery to relieve bowel obstruction (n=3), or best supportive care (n=3). These 7 patients died due to GCC recurrence at a median of 5.0 (range 1.0 - 33.3) months following diagnosis of the recurrence. The longest survivor among these 7 patients died 33.3 months after diagnosis of small bowel and omental recurrence; his treatment comprised 2 laparotomies to treat bowel obstruction and CAPOX chemotherapy regime after being deemed unsuitable for CRS-HIPEC.

Serum CgA/B concentrations were not elevated during surveillance in any of the patients who presented with recurrent disease. One patient who later developed tumour recurrence transiently had a mildly elevated CgA that was caused by Proton pump inhibitor therapy; imaging scans were normal and CgA levels returned to normal values after stopping Proton pump inhibitor therapy. We also measured serum CEA, CA 19-9 and CA 125 during surveillance of 4 other patients who developed recurrence, but none of these tumour markers were elevated in any of these patients. Functional imaging with Octreoscan scintigraphy (n=6); MIBG scintigraphy (n=1); or ^{68}Ga-DOTATATE PET/ CT (n=1) did not identify recurrence in any of our patients.

3.5 Survival

Patients in our cohort had a median follow-up of 5.2 (0.3 – 16.2) years following diagnosis of aGCC. There were 11 deaths in our series: all deaths being GCC-related. The 5-year and 10-year overall survival of aGCC patients were 85.3% (95% CI 73.9 - 98.4) and 62.3% (95% CI 43.3 - 89.5); both significantly reduced by increasing TNM stage ($p<0.001$) (Figs 1a, 1b). The 5-year and 10-year recurrence-free survival of aGCC patients were 73.6% (95% CI 59.7 - 90.6) and 50.6% (95% CI 32.5 - 78.6) both also significantly reduced by increasing TNM stage ($p<0.001$) (Figs 1c, 1d). The presence of involved lymph nodes also significantly ($p<0.001$) reduced 5- and 10-year overall (Fig 2a, 2b) and recurrence-free survivals (Figs 2c, 2d). Kaplan-Meier analysis showed 5- and 10-year overall and recurrence-free survival were not significantly affected by tumour grade, by patients undergoing completion right hemicolectomy, or by patients undergoing completion BSO (Table 3). Kaplan-Meier analysis showed that

patients who experienced disease recurrence also had significantly (p=0.005) reduced 10-year overall survival (Fig 3), but 5-year overall survival was not significantly affected ($X^2_{\text{Log Rank} - 1df} = 0.51$, p value = 0.476).

4. DISCUSSION

This retrospective analysis shows aGCCs prognosis remains relatively poor. Population-based studies show aGCC prognosis exceeds that of appendiceal adenocarcinomas but is worse than that of appendiceal NETs [1, 3]. The 5-year and 10-year overall survival rates of 88% and 63% respectively and 5-year and 10-year recurrence-free survival as low as 73% and 50% respectively in this study; both overall and recurrence-free survival being inversely related to tumour stage. Notably, completion surgery did not reduce the risk of either tumour recurrence or death. These data draw into question the value of this surgical recommendation.

Some aGCCs are so aggressive that they are more akin to colonic adenocarcinomas and less so to typical neuroendocrine tumours [1, 3]. This phenotypic variation is reflected by the Tang classification which recognises 3 GCC types based on goblet cell morphology, atypia, and degree of desmoplasia: Group A (Typical GCC), poorer prognosis Group B (adenocarcinoma ex-GCC, signet ring cell), and poorest prognosis Group C (adenocarcinoma ex-GCC, poorly differentiated) [14]. It was not possible to assign Tang classification to all the cases in our cohort as the required histologic variables were not available for some of the cases. Tumours were staged according to the UICC/AJCC TNM system.

Our study data show Ki67-derived tumour grade is not significantly associated with survival outcome in aGCC patients, suggesting Ki67 may have limited value prognostic in aGCCs. Others have shown Ki-67 index is unnecessary for GCC grading [11] and has no prognostic significance in aGCC [4, 12].

Previous reports demonstrate worsening 5-year overall survival with higher TNM stage; 100% for stage I, 76% for stage II, 22% for stage III, and 14% for stage IV [14, 15]. Similar worsening of 5-year overall survival is seen with higher Tang stages; 100% for group A, 36% for group B, and 0% for group C [14].

Appendicectomy alone has been proposed for patients with aGCC of TNM T1 and T2 stage, or Tang group A histology. Right hemicolectomy has been recommended for TNM T3 and T4 tumours, or Tang group B and C histology [14-17].

In fact, both the North American and UK Neuroendocrine Tumour Societies recommend completion surgery for aGCC due to the high risk of metastases [8, 16]. The rarity of aGCC is such that there have been no large randomized controlled trials to provide an evidence base for these recommendations. It thus remains uncertain which patients require completion surgery after appendicectomy and whether right hemicolectomy +/- BSO is an adequate treatment strategy for those patients with more aggressive tumours. Several UK centres have published their aGCC experience and completion right hemicolectomy appears to be safe. There was minimal morbidity following completion right hemicolectomy in 41 of 48 patients from the Royal Free Hospital [18], and 9 of 21 patients from St Mark's and Imperial College Hospitals [19].

In our cohort, 24 of 32 eligible patients underwent completion surgery and although this was associated with minimal morbidity and mortality, it did not appear to affect recurrence-free or overall survival. The median time to completion surgery in our cohort was 4.8 months after index appendicectomy, and although longer than the 3-month window recommended by ENETS guidelines, did not affect recurrence-free survival.

Several studies have explored the role of completion right hemicolectomy in aGCC patients. The Christie Hospital, Manchester reported that despite 36 of 74 aGCC patients undergoing curative completion right hemicolectomy, there was no impact on recurrence-free survival [4]. A meta-analysis of 13 studies showed no benefit of completion right hemicolectomy in patients who had localized disease and low-grade histology [9] and this was also supported by subsequent cohort studies [20, 21]. A retrospective analysis of 3137 patients using the Surveillance, Epidemiology,

and End Results (SEER) database showed there was no significant survival benefit for right hemicolectomy versus appendectomy for typical GCC, but patients with signet ring cell adenocarcinoma histology did have a statistically significant survival benefit [22].

There are currently no evidenced-based guidelines determining the choice of systemic chemotherapy in metastatic aGCC as this is such a rare tumour type. Previous ENETS Guidelines recommended palliative chemotherapy with fluoropyrimidine-based regimens in the setting if non-resectable locoregional disease or distant metastasis [5]. Current UK guidance bases selection of chemotherapy regimens on the similarity of metastatic aGCC to colonic adenocarcinoma and recommends 5-fluorouracil (5-FU)-based regimens; FOLFOX (5-FU, leucovorin, oxaliplatin) or CAPOX (capecitabine and oxaliplatin) [8]. In our cohort, we used chemotherapy with palliative intent to treat recurrence in 3 patients. CAPOX regimen akin to the colorectal cancer treatment protocol was used in 2 patients as per colonic adenocarcinoma guidelines. The other patient was initiated on 1st line palliative chemotherapy elsewhere before relocating to our region and was treated with a total of 6 cycles of 1st line Cisplatin and Etoposide akin to the small cell lung cancer treatment protocol as also described in other published series [23, 24]. This patient was subsequently diagnosed with peritoneal progression on interval CT imaging and was switched over to a 2nd line IMdG (Irinotecan, 5-Fluorouracil and Folinic Acid) chemotherapy regimen.

Recent UK guidance proposes the use of chemotherapy as adjuvant treatment for TNM stage II - IV disease [8] although this is not supported by randomised clinical trial evidence. Other Centres have published their experience of adjuvant chemotherapy and it is unclear whether there is any survival benefit. A retrospective review of the Mayo Clinic database included 57 patients with aGCC treated over a 20-year period and 27 of these patients with stage II to IV disease received adjuvant 5-FU-based chemotherapy. Adjuvant chemotherapy did not confer a statistically significant survival benefit [15]. The Royal Free Hospital reported 9 out of 48 aGCC patients received adjuvant chemotherapy after right

hemicolectomy; but disease recurred in 3 of these 9 patients [18]. The Christie Hospital reported that adjuvant chemotherapy was used in 16 of 74 patients following completion surgery or CRS-HIPEC, but did not affect recurrence-free survival [4].

Using data prospectively collected from 1994–2011, three peritoneal malignancy centres in Canada and the UK reported on the outcomes of 45 aGCC patients, 32 of whom underwent CRS-HIPEC. The authors showed that it was possible to achieved reasonable long-term survival if patients were suitably selected based on likelihood of complete surgical cytoreduction, favourable histology and tumour burden [25].
More recently, two Japanese centres have reported their experience of 15 aGCC patients who had peritoneal carcinomatosis managed by CRS-HIPEC. They showed improved survival in selected patients who had low tumour burden and thus a higher likelihood of achieving complete cytoreduction [26]. Published studies on aGCC are summarised in (**Table 4)**.

Although high quality evidence is lacking, current UKINETS guidance [8] summarised from available cohort studies is to consider completion right hemicolectomy +/- BSO for aGCC staged as TNM 1 or Tang A [14] and consider Cytoreductive Surgery +/- HIPEC for all higher disease stages [4, 25]. Again, there is no evidence on which to base adjuvant chemotherapy and its use therefore has to be decided on a patient-by-patient basis [4, 18]. Robust MDT discussion is crucial, and some cases may require specialist opinion from a Peritoneal malignancy centre.

The main limitation of our cohort study is potential referral bias as some patients with small tumours may not have been referred to our tertiary referral centre, especially in the earlier years of the study. It is thus possible we have not captured some small aGCCs from our referral catchment area, but this is likely to also be the same limitation experienced by other similarly designed cohort studies. Functional imaging with ^{18}F-fluorodeoxyglucose (FDG) PET/ CT was not used during surveillance of any patients in our cohort because the evidence supporting its use in

GCC patients has only become available in recent years [8, 19]. Based on current UKINETS guidance, we are now using FDG PET/CT to assess for disseminated disease in high grade tumours.

5. Conclusion

Appendiceal GCCs in this series had relatively poor 10-year overall and recurrence-free survival of 63% and 50% respectively. The small sample in our study suggests completion surgery does not prevent recurrence in all patients but this needs to be verified with a larger patient cohort. Other treatment strategies including CRS-HIPEC and adjuvant chemotherapy may therefore need urgent prospective evaluation.

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7.0 Declarations

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Variable	Detail
Gender n (F, M)	23, 18
Median age at diagnosis (range)	61 (27 – 79) years
Mean size	10.5 (0.5 – 50.0) mm
Indication for surgery	Appendicitis (n=30), abdominal mass on imaging (n=8), or incidental finding (n=2)
Index surgery	Appendicectomy (n=32), right hemicolectomy (n=6), subtotal colectomy (n=1), and CRS-HIPEC (n=1)
Tumour location on appendix (n, %)	Tip (18, 45%), Body (16, 40%), Base (2, 5%), or Multifocal (n=4, 10%)
Grade	G1 (n=15), G2 (n=10), G3 (n=16)
TNM Stage (UICC/AJCC)	1 (n=2), 2 (n=22), 3 (n=14), and 4 (n=3)

***Table 1*: Summary of GCC patient characteristics.** *CRS-HIPEC (cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy)*

Pt #	Age (years)	Sex	Index Surgery	Completion surgery (Yes/ No)	TNM stage	Grade	Time to recurrence from index surgery	Site of recurrence	Diagnosis recurrence	Treatment of recurrence	Dead/ Alive	Time from recurrence to death or last f/up
1	73.9	f	Appendicectomy	No	2b	G1	6 years, 8 months	liver, lung	Weight loss + Pain	Palliation	Dead	3 months
2	58.5	m	Appendicectomy	Yes	2b	G1	4 years, 8 months	SB, Omentum	SBO	CAPOX, Surgery	Dead	2 years, 9 months
3	42.8	m	Appendicectomy	Yes	2b	G1	5 years	SB, Peritoneum	SBO	Surgery, Palliation	Dead	2 months
4	67.5	m	Right hemicolectomy	n/a	3b	G3	9 years, 6 months	Peritoneum	Weight loss + SBO	Palliation	Dead	7 months
5	60.0	m	Appendicectomy	Yes	3b	G2	4 years, 10 months	Peritoneum	Ascites	Palliation	Dead	1 month
6	38.5	m	Appendicectomy	Yes	2a	G3	3 years, 5 months	SB, Peritoneum	CTS	1st line Cisplatin & Etoposide, 2nd line IMdG	Dead	1 year, 5 months
7	71.9	f	Appendicectomy	No	2b	G2	2 years	Caecum	CTS	CRS-HIPEC	Alive	3 years, 3 months
8	61.3	m	Right hemicolectomy	n/a	3a	G1	9 years, 7 months	Peritoneum	SBO	Surgery, Palliation	Dead	5 months

9	75.8	f	CRS + HIPEC	n/a	4	G1	5 months	Bladder	Cystoscopy	CAPOX		Alive	6 months

***Table 2*: Details of patients with appendiceal goblet cell carcinoid relapse.** *SB (*Small Bowel), *SBO (*Small Bowel Obstruction), *CTS (*CT surveillance), *CRS-HIPEC (cytoreductive surgery with hyperthermic intraperitoneal chemotherapy), CXT (*Chemotherapy), *CAPOX (capecitabine and oxaliplatin), IMdG (Irinotecan, 5-Fluorouracil and Folinic Acid)*

Factor	BSO (n=23)	CRH (n=24)	Grade (n=41)
5YOS	$X^2_{\text{Log Rank – 1df}} = 0.89$, p value = 0.344	$X^2_{\text{Log Rank – 1df}} = 0.05$, p value = 0.831	$X^2_{\text{Log Rank – 1df}} = 0.90$, p value = 0.636
10YOS	$X^2_{\text{Log Rank – 1df}} = 0.24$, p value = 0.624	$X^2_{\text{Log Rank – 1df}} = 0.11$, p value = 0.740	$X^2_{\text{Log Rank – 1df}} = 0.18$, p value = 0.914
5YRFS	$X^2_{\text{Log Rank – 1df}} = 0.46$, p value = 0.497	$X^2_{\text{Log Rank – 1df}} = 0.01$, p value = 0.955	$X^2_{\text{Log Rank – 1df}} = 0.42$, p value = 0.809
10YRFS	$X^2_{\text{Log Rank – 1df}} = 0.10$, p value = 0.753	$X^2_{\text{Log Rank – 1df}} = 0.03$, p value = 0.867	$X^2_{\text{Log Rank – 1df}} = 0.02$, p value = 0.989

***Table 3*: Patient and tumour variables that did not significantly affect survival.** *BSO (Bilateral oophorectomy), CRH (completion right hemicolectomy), LNI (Lymph node involvement), 5YOS (5-year overall survival), 5YOS (5-year overall survival), 10YOS (10-year overall survival), 5YRFS (5-year recurrence-free survival), and 10YRFS (10-year recurrence-free survival).*

Authors, study year	N (M,F)	Type	Age (range) in years	CRH (done/ eligible)	CRS-HIPEC (n)	Chemotherapy	Overall (OS) or Disease-specific Survival (DSS) (range or *95% CI)	Follow-up (range or *95% CI)	Key message(s)
Nonaka et al, 2018[22]	105 (54M, 51F)	Retrospective	Median 54 (25–79)	12/19	34	Adjuvant (regimen n/s)	Median DSS 67 (*38.2-95.8) m	Median 56 (4-277) m	High tumour grade correlates with poorer cancer-related survival
Tsang et al, 2018[23]	86 (42M, 44F)	Retrospective	Median 54 (25–91)	51/67	12	TNM stages I-III: CAP/ 5FU (n=5), or FLOX (n=4). Stage IV: n/s (n=1), FOLFOX (n=5), CAP (n = 1), or FOLFIRI +/- bevacizumab (n=3)	5-yr OS 68 (*56–77) %	Median 82.6 (*60–107) m	CRH recommended for TNM stage I–III. CRS-HIPEC may improve survival in metastatic disease.
Madsen et al, 2018[24]	48 (18M, 30F)	Retrospective (Grouped by carcinomatosis- 1: None (n=6) 2: High risk (n=8) 3: Limited (n=27) 4: Extensive (n=7)	Median 52 (32–75)	16/21	21	Grp 1-3 (Adjuvant): CAPOX or FLOX (n=16). Grp 4 (Palliative): carboplatin + etoposide, or CAPOX (n=23)	Grp 1 & 2= 5-yr OS 100%, Grp 3= Median OS 3.2 (*2.3–4.1) yrs, Grp 4= Median OS 1.3 (*0.6–2.0) yrs	Median in yrs- Grp 1= 4.6 (3.2–7.4), Grp 2= 3.5 (0.9–5.4),Grp 3= 2.6 (0.9–8.0), Grp 4= 1.1 (0.1–1.7)	CRS-HIPEC improves outcome if at-risk-of or with actual peritoneal spread
Clift et al, 2018[19]	21 (9M, 12F)	Retrospective	Median 55 (32–77)	8/12	1	Adjuvant CAPOX (n=6)	Mean OS 80.3 m. 1-, 3-, and 5-yr OS 79.4, 60 & 60%.	Median 30 (2.5–123) m	Poor outcome despite CRH and CRS-HIPEC

Yu et al, 2017[21]	15 (9M, 6F)	Retrospective (carcinomatosis patients only)	Median 52 (36–74)	not relevant	15[£]	Adjuvant paclitaxel (n=1)	Median OS 28 (6.5–56) m	n/s	CRS-HIPEC and adjuvant chemotherapy improve survival, especially when cytoreduction is complete

Authors, study year	**N (M,F)**	**Type**	**Age (range) in years**	**CRH (done/ eligible)**	**CRS-HIPEC (n)**	**Chemotherapy**	**Overall (OS) or Disease-specific Survival (DSS) (range or *95% CI)**	**Follow-up (range or *95% CI)**	**Key message(s)**
Shaib et al, 2016[14]	1582 (814M, 768F)	SEER database 1973-2011	Median 55 (10-99)	n/s	n/s	n/s	n/s	n/s	No survival difference comparing CRH with appendicectomy
Lamarca et al, 2016[4]	74 (34M, 40F)	Retrospective	Median 56 (26–83)	36/56	25	Adjuvant FOLFOX (n=18). Palliative FOLFOX (n=24)	Median OS 52.1 (*29.4–90.3) m	Median 27.6 (3.8–217) m	CRH does not affect relapse rate or disease-free survival
Taggart et al, 2015[17]	74 (42M, 32F)	Retrospective. Grouped by content of adenocarcinoma: 1= < 25%, 2= 25-50%, 3= > 50%	Mean 50 (23-79)	Grp 1= 14/20, Grp 2= 11/19, Grp 3= 5/12	n/s	n/s	Grp 1: Mean OS 83.8 (SD, 34.6) m; Grp 2: Mean OS 60.6 (SD, 30.3) m; Grp 3: Mean OS 45.6 (SD, 39.7) m	n/s	Adenocarcinoma content in aGCC correlates with disease stage and survival

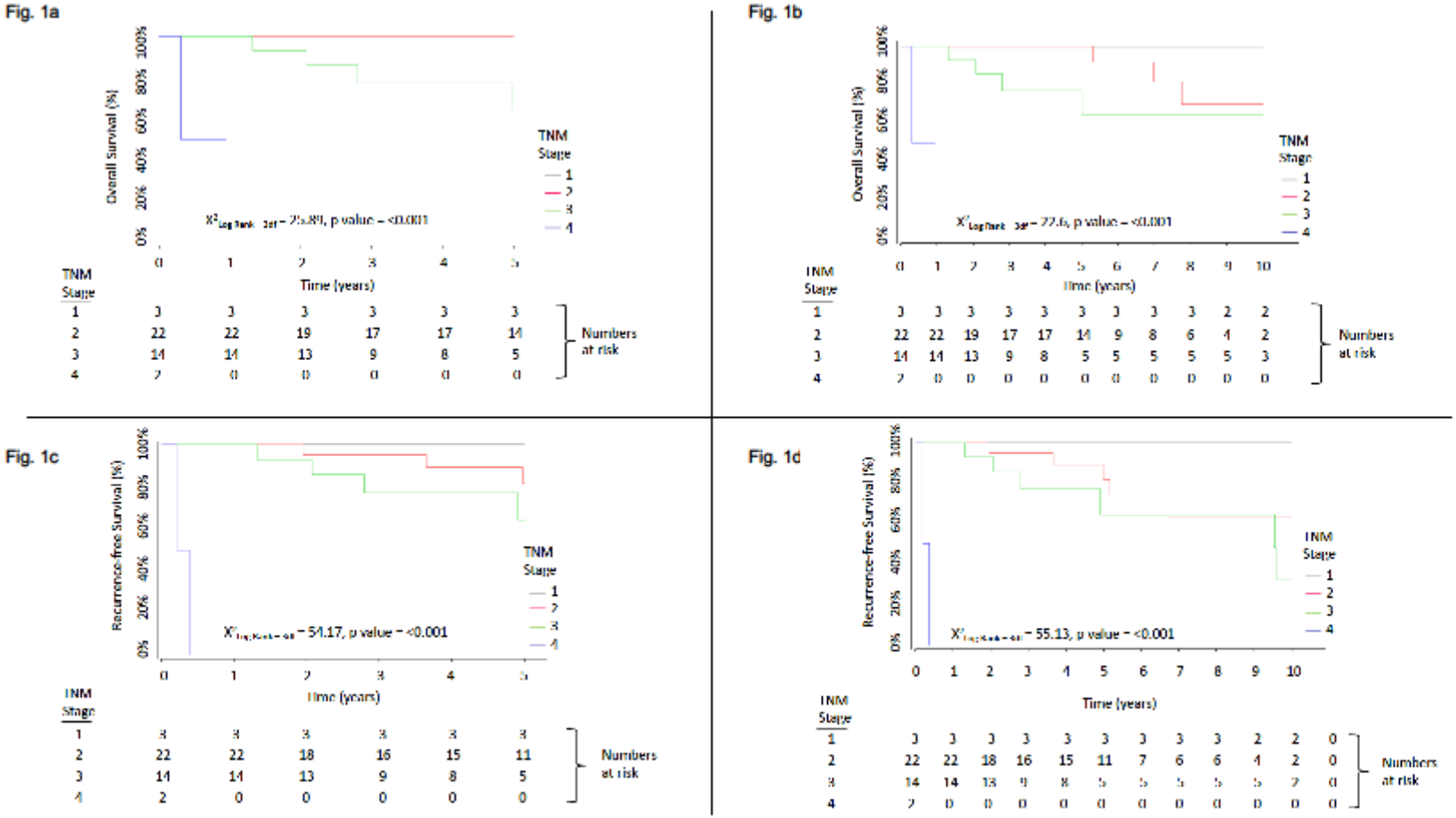
Tang et al, 2008[15]	63 (20M, 43F)	Retrospective	Mean 50 (SE ±1)	16/22	8	Adjuvant 'colonic adenocarcinoma-type' regimens (n=33)	Mean OS 43 (SE ±7) m. DSS 77%.	Mean 49 (SE ±5) m	CRH +/- oophorectomy if TNM T3-4/ Tang B & C/ perforated. Adjuvant FOLFIRI/ FOLFOX if TNM stage III-IV. CRS-HIPEC & chemotherapy if TNM stage IV/ Tang C
Toumpanakis et al, 2007[25]	15 (8M, 7F)	Retrospective	Median 53 (32–64)	7/7	nil	TNM Stage 4 (Palliative): Etoposide + cisplatin (n=2), 5FU + cisplatin + STZ (n=2)	n/s	Median 30 m	High Ki67 indicates metastases. CRH may reduce risk of developing metastases. Benefit of chemotherapy uncertain for metastatic disease.
Authors, study year	**N (M,F)**	**Type**	**Age (range) in years**	**CRH (done/ eligible)**	**CRS-HIPEC (n)**	**Chemotherapy**	**Overall (OS) or Disease-specific Survival (DSS) (range or *95% CI)**	**Follow-up (range or *95% CI)**	**Key message(s)**
O'Donnell et al, 2007[26]	2 (2F)	Retrospective	Mean 61 (SE ± 15)	1/1	nil	nil	n/s	Mean 63 (1–125) m	Right hemicolectomy is recommended
Pham et al, 2006[16]	57 (21M, 36F)	Retrospective	Mean 55 (SE ± 13)	n/s	nil	Systemic 5FU + LV (n=27)	Mean OS 47 (SE ± 3) m	n/s	Appendectomy alone for TNM stage I. CRH for TNM stage II-III. Adjuvant chemotherapy with 5FU + LV is minimally effective. CRS has uncertain benefit

Byrn et al, 2006[13]	16 (7M, 9F)	Retrospective	Mean 50 (31-80)	7/9	nil		Mean OS 16 m	Mean 12 m	CRH should not be offered to all but customized to individual patients
McGory et al, 2005[1]	369 (188M, 181F)	SEER database 1973-2001	Mean 52 (SD ± 16)	not stated	n/s	n/s	n/s	n/s	Despite guidelines, 30% of all non-carcinoids (GCC included) underwent appendectomy alone
Bucher et al, 2005[12]	7 (6M, 1F)	Retrospective	Median 72 (27-81)	3/6	nil		n/s	Median 60 (24–108) m	Appendicectomy alone if aGCC < 1cm, within adventitia, G1, and R0. Otherwise for CRH
McCusker et al, 2002[3]	227 (117M, 110F)	SEER database 1973-1998	Mean 52 (SD ± 16)	n/s	n/s	n/s	n/s	n/s	aGCC have worse survival than malignant carcinoids

Authors, study year	**N (M,F)**	**Type**	**Age (range) in years**	**CRH (done/ eligible)**	**CRS-HIPEC (n)**	**Chemotherapy**	**Overall (OS) or Disease-specific Survival (DSS) (range or *95% CI)**	**Follow-up (range or *95% CI)**	**Key message(s)**
Li et al, 2002[27]	11 (7M, 4F)	Retrospective	Mean 57 (35–76)	2/5	nil		n/s	Mean 4.5 yrs	Appendicectomy for T1 tumours. CRH if cell proliferation index >3%.

Kanthan et al, 2001[28]	7 (5M, 2F)	Retrospective	Median 61 (34-82)	6/6	nil		n/s	n/s	Key aim is complete local excision with negative margins. All had right hemicolectomy as primary or secondary procedure.
Ramnani et al, 1999[29]	22 (M:F n/s)	Retrospective	n/s	n/s	n/s	n/s	n/s	n/s	aGCC are variants of typical carcinoids: both express CgA & p53 but not K-ras mutations
Butler et al, 1994[30]	9 (2M, 7F)	Retrospective	Median 58 (31-73)	1/4	nil	nil	n/s	n/s	aGCC are more aggressive than classic carcinoids. CRH + bilateral oophorectomy may be beneficial but should not be guided by tumour size alone

***Table 4*: Summary of published aGCC studies**. *m (months), yrs (years), n/s (not stated), Grp (Group)*



Kaplan-Meier graph showing how overall and recurrence-free survival of aGCC patients are affected by TNM stage. 5-year and 10-year overall survival were both significantly reduced by increasing TNM stage (p<0.001) (Figs 1a and 1b respectively). The 5-year and 10-year recurrence-free survival were also both significantly reduced by increasing TNM stage (p<0.001) (Figs 1c and 1d respectively).

Fig. 2a

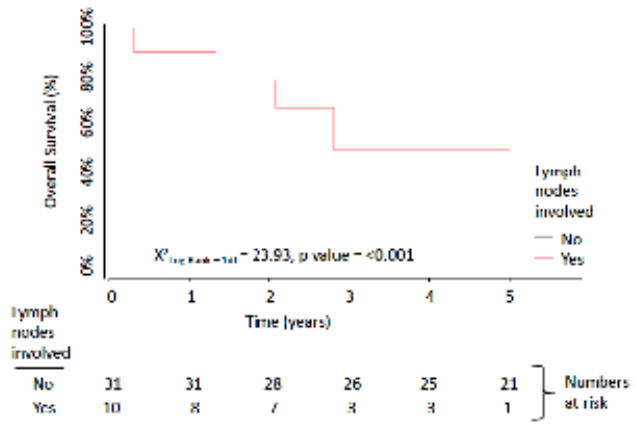


Fig. 2b

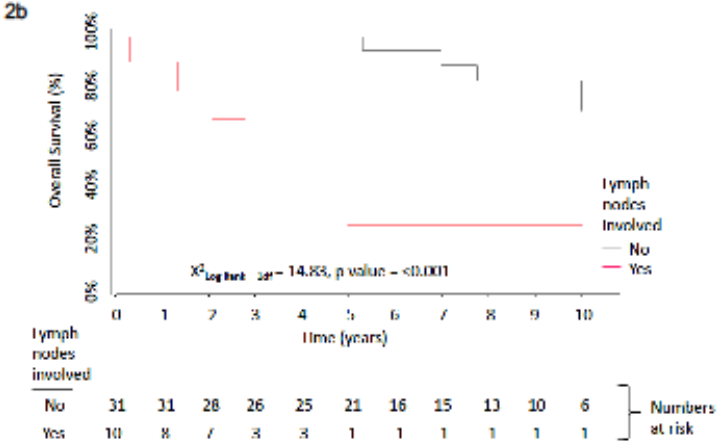


Fig. 2c

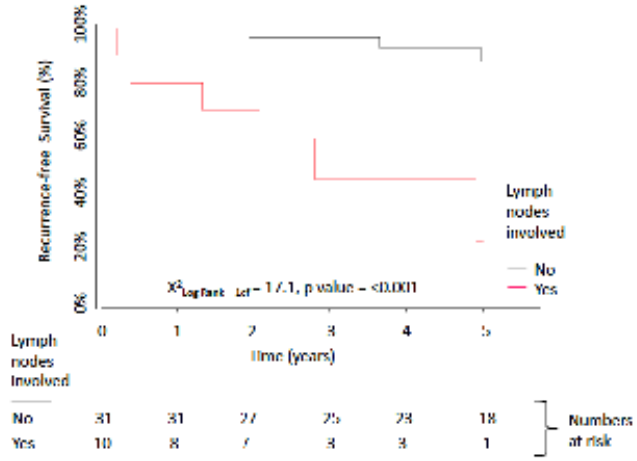
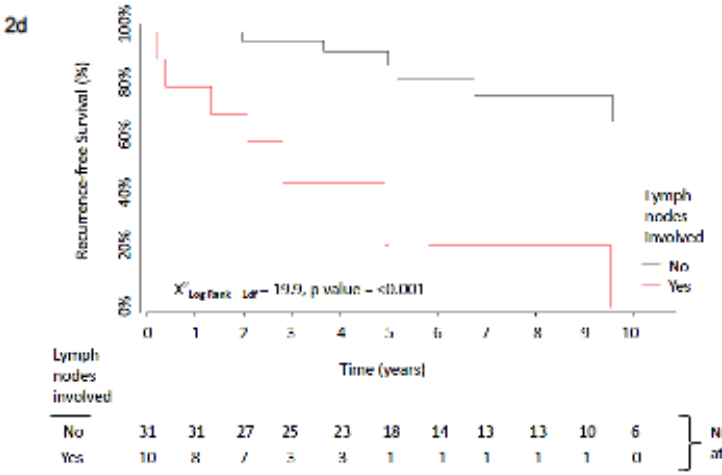


Fig. 2d



Kaplan-Meier graph showing how overall and recurrence-free survival of aGCC patients are affected by tumour invasion of lymph nodes. 5-year and 10-year overall survival were both significantly reduced if lymph nodes were invaded by tumour (p<0.001) (Figs 2a and 2b respectively). Similarly, 5-year and 10-year recurrence-free survival were both also significantly reduced if lymph nodes were invaded by tumour (p<0.001) (Figs 2c and 2d respectively).

Fig. 3a

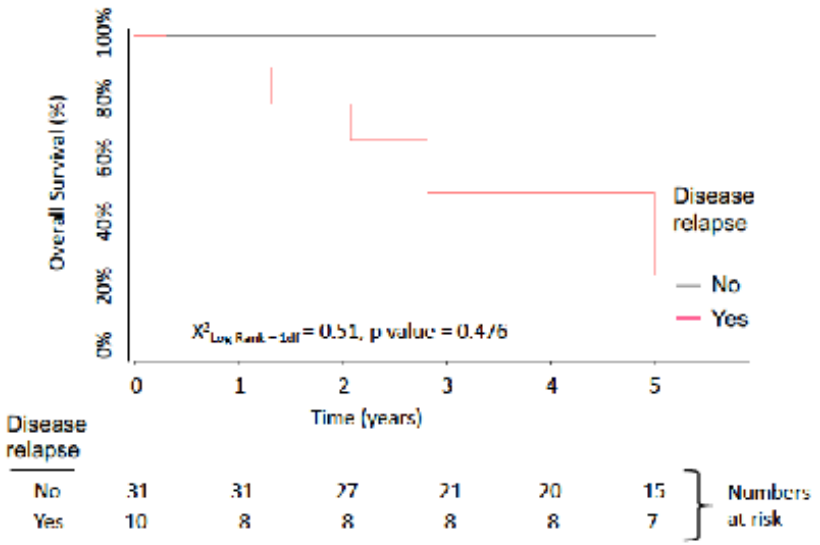
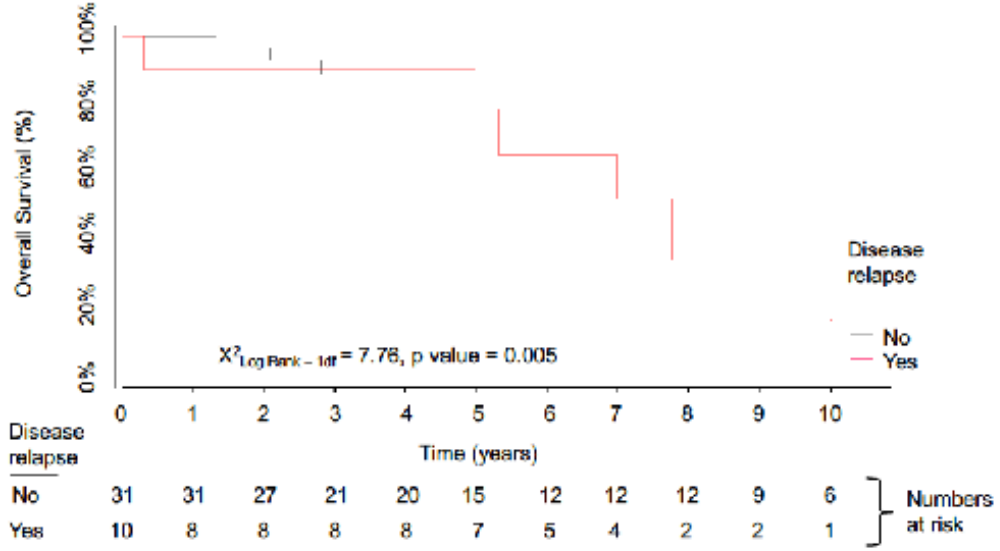


Fig. 3b



Kaplan-Meier graph showing how overall survival of aGCC patients is affected by disease recurrence. 5-year overall survival was not significantly affected but 10-year overall survival was significantly (p=0.005) reduced in patients who experienced disease recurrence (Figs 3a and 3b respectively).