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Primary mesenteric sarcomas: Collaborative experience from the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG)

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Primary Mesenteric Sarcomas: Collaborative experience from the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG)

Running head

Primary Mesenteric Sarcomas

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Conflict of interests

None

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Synopsis for Table of Contents

Primary mesenteric soft tissue sarcomas are rare with a limited evidence base. Surgical management is challenging and the tumours are commonly high grade. Mesenteric soft tissue sarcoma has a modest survival rate with local recurrence and distant metastatic disease a common feature.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Abstract

Background: Primary mesenteric soft tissue sarcomas (STS) are rare and limited evidence is available to inform management. Surgical resection is challenging due to the proximity of vital structures and a need to preserve enteric function.

Objectives: To determine overall survival (OS) and recurrence-free survival (RFS) for patients undergoing primary resection for mesenteric STS.

Methods: The Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) is an intercontinental collaborative comprising specialist sarcoma centres. Data were collected retrospectively for all patients with mesenteric STS undergoing primary resection between 2000-2019.

Results: Fifty-six cases from 15 institutions were included. The spectrum of pathology was similar to the retroperitoneum, although of higher grade. R0/R1 resection was achieved in 87%. Median OS was 56 months. OS was significantly shorter in higher grade tumours ($p=0.018$) and extensive resection ($p<0.001$). No significant association between OS and resection margin or tumour size was detected. Rates of local recurrence (LR) and distant metastases (DM) at five years were 60% and 41%, respectively. Liver metastases were common (60%), reflecting portal drainage of the mesentery.

Conclusion: Primary mesenteric sarcoma is rare, with a modest survival rate. LR and DM are frequent events. Liver metastases are common, highlighting the need for surveillance imaging.

Keywords

Mesenteric soft tissue sarcoma, sarcoma, surgery

Introduction

The management of soft tissue sarcoma (STS) has evolved over the past ten years with a major drive for centralisation of services and production of international consensus guidelines [1-4]. STS of mesenteric origin is a peculiar entity and is therefore often excluded from comment, principally due to lack of evidence on which to base recommendations [1-4].

The rarity of mesenteric sarcoma, combined with difficulty in developing a standardised definition or description of anatomical location has greatly impeded understanding. Furthermore, the surgical management of mesenteric STS can be challenging with the risk of disruption to vital anatomical structures, potential for short bowel syndrome and anecdotal evidence of multi-focality that can negatively impact upon surgical margins.

Evolution of the Trans-Atlantic Australasian Retroperitoneal Sarcoma Working Group (TARPSWG) presents an opportunity to condense the collective experience of intercontinental specialist sarcoma centres. This multi-centre collaborative approach is important in the study of a rare disease such as mesenteric STS [5]. The primary objective of this study was to determine overall survival (OS), recurrence-free survival (RFS) and rates of recurrence events (LR/DM) after primary resection of mesenteric STS. Secondary outcomes were to identify relevant clinicopathological factors, improve understanding of the natural history of the condition and potentially develop management guidelines.

Materials and methods

A total of 15 institutions across 9 countries participated in the study (Table 1a). All patients with histologically confirmed mesenteric STS, who either received primary surgery at a specialist centre or were referred for on-going management after undergoing resection at a non-specialist centre between 2000 to 2019, were included. Mesenteric STS was pragmatically defined by the TARPSWG research committee as a soft tissue sarcomatous mass clearly arising from the small bowel mesentery, mesocolon, gastro-colic, gastro-hepatic ligaments or where the origin had a degree of uncertainty (abutting the bowel wall but not clearly arising from it). Sarcomas arising from the greater omentum were excluded. Patients less than 18 years at the time of resection, desmoid-type fibromatosis, gastrointestinal stromal tumour, embryonal and alveolar rhabdomyosarcoma and epithelial or haematological malignancy were also excluded. Data were retrospectively collected according to a standardised protocol and subject to Regional Ethics/Institutional Review Board approval and Data Sharing Agreements.

Comorbidities were considered using the Charlson Comorbidity Index [6]. The extent of resection was classified as minor, moderate or extensive. Minor was defined as resection of the tumour alone, and moderate as resection of the tumour and bowel. An extensive resection involved resection of the tumour, bowel and one or more additional solid organs. Resected specimens were used to determine size, histology and French Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade [7].

The primary outcome was OS, with follow up commencing at the time of surgery and patients being censored at the date of last clinic attendance. RFS was also calculated from the time of surgery and censored at the date of last follow up. For RFS, the outcome was a composite of death or recurrence, with the latter comprising either local recurrence (LR) or distant metastases (DM), based on revised-RECIST criteria for identification of “new lesions” [8].

Analysis of RFS excluded those patients with R2 resections or where the R-status was unknown. Rates of LR and DM were also assessed separately using a death-censored approach; those with R2 resections or unknown R-status were excluded from the analysis of LR.

Statistical methods

OS and RFS were assessed using Kaplan-Meier curves. Death-censored LR and DM rates were analysed using the same approach. Associations between OS and both patient- and treatment-related factors were then analysed.

Continuous variables were divided into categories prior to analysis, whilst categories with small sample sizes were combined for nominal variables.

Comparisons across factors were performed using log-rank tests. Cox regression models were used to estimate hazard ratios (HRs) and the associated 95% confidence intervals (CIs).

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p < 0.05$ deemed to be indicative of statistical significance throughout.

Results

Demographics

Data were available for a total of 56 patients from 15 centres, with a median of 3 (range: 1-8) cases per centre (*Table 1a*). The median age at surgery was 59 years (interquartile range [IQR]: 46 – 70) and the majority of patients were male (61%). The median Charlson Comorbidity Index for the cohort was 2 (IQR: 0-4). The most common comorbidity was the presence of a second solid tumour (16%). De-differentiated liposarcoma (DDLPS) was the most common tumour histology (48%) followed by leiomyosarcoma (LMS) (23%) and well-differentiated liposarcoma (WDLPS) (14%). Further demographics are reported in *Table 1b*.

The majority of the cohort underwent open surgery (95%), with most resections being of moderate extent (83%). Macroscopically clear margins (R0/R1) were achieved in 87% of cases with incomplete (R2) resection performed in the remaining 13%. Neoadjuvant treatment was used in 21% of patients and adjuvant therapy in 16%, with chemotherapy being the most common modality in both cases (*Table 1c*). Neoadjuvant therapy was delivered as a combination regimen of either Doxorubicin and Ifosfamide or Gemcitabine and Docetaxel. Intensity-modulated radiation therapy (IMRT) was utilised in four cases where the resection margin against the superior mesenteric artery, in the proximal mesentery, was pre-operatively considered to be at risk (delivered as 50.4-60 Gy to the proximal small bowel mesentery). Adjuvant chemotherapy was again administered as a multi-agent regimen (Doxorubicin in combination with either Ifosfamide, Cisplatin or Olaratumab)

or single agent Pazopanib in one case of synovial sarcoma. IMRT was utilised in three highly selected cases (60-62 Gy), delivered to the root of the small bowel mesentery where the resection margin was compromised (R2). Major perioperative morbidity was low (5%) and related to three incidences of anastomotic leak (two small bowel and one large bowel anastomoses). No cases of perioperative mortality were encountered.

Post-surgical outcomes

Patients were followed up for a median of 19 months (IQR: 11-46) from surgery, during which time there were 17 deaths; 88% (N=15) of these were related to mesenteric STS. The median OS was 56 months from surgery with estimated survival rates of 88%, 70% and 50% at one, three and five years, respectively (*Figure 1a*). For analysis of RFS, those with R2 resections (N=7) or unknown R-status (N=2) were excluded. Of the remainder (N=47), 27 developed recurrence and a further patient died without recurrence. This resulted in a median RFS of 20 months with estimated rates of 66%, 29% and 21% at one, three and five years, respectively (*Figure 1a*).

Recurrence was also analysed separately for LR and DM using a death censored approach. Analysis of LR only included those with R0/R1 resections (N=47), of whom 19 developed LR, giving estimated rates of 21%, 55% and 60% at one, three and five years, respectively (*Figure 1b*). Treatment of LR was most commonly by surgery (42%, N=8) with 37% (N=7) treated with chemotherapy (single agent Doxorubicin and in combination with Olaratumab in one patient). One patient received chemotherapy combined with highly selective IMRT to a bleeding intra-peritoneal tumour deposit, and the

remainder received best supportive care (N=3) or surveillance (N=1). Analysis of DM included all 56 cases, of whom 16 developed DM; six also had prior or simultaneous LR. Estimated rates of DM were 19%, 30% and 41% at one, three and five years, respectively (*Figure 1b*). The most common location for DM was the liver (60%, N=9) with the remainder in the peritoneum (N=2), lung (N=1), bone (N=1) or multiple locations (N=2). The approach to treatment of DM was recorded for 13 cases with the most common modalities being chemotherapy (46%, N=6), best supportive care (23%, N=3) or radiofrequency ablation (15%, N=2).

Post-recurrence outcomes

The 47 patients with R0/R1 resections were then assessed in further detail to classify outcomes after episodes of recurrence (*Figure 2*). Twenty of these patients (43%) remained disease-free during the follow up period, of which one patient subsequently died 13 months post-resection.

The first recurrence was LR in 16 patients (range: 4-68 months post-resection), of whom 3 subsequently died (4, 11, 39 months post-resection, respectively). Of the remainder, 4 patients subsequently developed a second episode of LR. One of these patients died at 139 months post-resection, which was 31 months after their most recent LR diagnosis. A further 3 patients developed DM after an initial episode of LR. One of these (LR: 7 months, DM: 19 months) was alive at the end of follow up. The other two patients developed a further episode of LR (i.e. LR, DM, LR) and subsequently died at 15 and 56 months post-resection, respectively.

Two patients developed simultaneous LR and DM (liver) at 2 and 12 months post-resection, respectively and subsequently died. A further patient developed simultaneous LR and DM (liver) at 4 months, followed by a second DM at 6 months and died 8 months post-resection. Of the 8 patients that presented with DM as the first recurrence (range: 3-38 months post-resection), one subsequently died (18 months). Of the remainder, 3 developed a further DM, of whom one patient subsequently died (DMs at 20 months [liver] and 44 months [gluteus/chest wall], death at 56 months).

Predictors of OS

Associations between OS and a range of patient and treatment-related factors are reported in *Table 2a/b*. Overall survival was found to differ significantly by tumour FNCLCC grade, with no deaths in the 10 patients with grade 1 tumours, compared to a 40% and 0% estimated five year survival rate in those with grade 2 and grade 3 tumours, respectively ($p=0.018$, *Figure 3a*). In addition, OS was found to be significantly shorter in patients undergoing extensive resection with an estimated five year survival rate of 0%, compared to 56% in those with minor-moderate resections ($p<0.001$, *Figure 3b*). OS was not found to differ significantly by R-status ($p=0.085$, *Figure 3c*), although there was a tendency for shorter survival in R2 vs. R0/R1 resections (40% vs. 52% at five years).

Discussion

Primary mesenteric STS is a rare entity, with a median case load in specialist centres of three per centre over a 19-year period. As a result of

intercontinental collaboration, a large series of 56 cases of primary mesenteric STS is described.

The distribution of histology was found to be similar to that seen in retroperitoneal sarcoma (RPS) with a predominance of DDLPS followed by LMS and WDLPS [9,10]. However, the percentage of FNCLCC grade 3 STS was much higher (27% of RPS vs 41% in mesenteric STS) [11]. This may reflect a natural propensity towards higher grade STS arising from the mesentery or a greater tolerance for radiological monitoring of lower grade STS because of anticipated surgical morbidity [11]. In line with the management of STS elsewhere, pre-operative biopsy is mandatory if technically possible. Pre-operative biopsy is particularly important as the treatment of mesenteric desmoid type fibromatosis is likely to have a different threshold for surgical resection [2,10].

Resection margin status was broadly in line with those achieved in RPS with a combined R0/R1 resection rate of 87% and R2 of 13% [9,11]. The distinction between R0 and R1 resection in mesenteric STS is impractical, given the likely exposure of the sarcoma surface to the peritoneal cavity. However, mesenteric STS are highly variable in size and location with a distal location in the mesentery most likely to lend itself to R0/R1 resection, with a lower risk of significant disruption to the mesenteric vasculature and enteric function.

Where R2 resections were performed, the retention of macroscopic disease was likely driven by the desire to preserve critical structures such as the trunk of the superior mesenteric artery. In line with STS in other anatomical locations, debulking surgery is generally to be avoided, although each case

should be considered to achieve a balance between the benefit of organ preservation and the detrimental effect of residual disease.

Although there was a tendency for shorter OS after R2 resection, this difference was not found to be statistically significant (HR: 2.85, $p=0.085$). However, this analysis was limited by low statistical power on account of the small number of R2 resections.

The extent of surgery was found to significantly influence OS with those undergoing more extensive resections at risk of adverse long-term outcomes when compared to lesser resections. However, maximal tumour diameter, which is well known to influence outcome in STS in other anatomical locations, did not significantly influence OS for mesenteric STS. This may imply that the extent of surgery is more associated with proximity of the STS to named vascular structures within the mesentery and the subsequent impact on resection margin, rather than directly related to the dimension of the lesion [12-14]. Sub-analysis to investigate this line of reasoning was precluded by small numbers.

The median follow-up time was 19 months (IQR: 11-46) with an estimated OS of 88%, 70% and 50% at one, three and five years post-resection. These figures confer a slightly worse OS outcome compared to RPS, which has a five year OS of 67% in high volume sarcoma centres [11]. This potentially reflects the higher percentage of high grade STS excised from the mesentery [11-15]. The risk of LR and DM were also relatively high, with estimated five year (death-censored) rates of 60% and 41%, respectively. DM disease occurred in the liver in 60% of cases and only a single patient developed DM

in the lung. The high incidence of DM occurrence in the liver likely reflects the portal venous drainage of the mesentery, compared to systemic venous drainage of RPS, where DM disease of the lungs predominates [11]. This marked difference in pattern of DM has potential implications for post-operative radiological surveillance, and further advocates for contrasted cross-sectional imaging, rather than simple plain chest radiograph [1-4].

Histological subtype was not found to significantly influence OS. The limited number of cases precluded meaningful statistical sub-analysis of histological driven risk of LR and DM. Despite anecdotal evidence of the multi-focal nature of mesenteric STS, this was only seen in 11% of cases and did not appear to impact OS. The number of observed multi-focal STS cases is likely to have been heavily influenced by selection bias, with surgery offered to those with a favourable pathological distribution. The most common site for mesenteric STS was the small bowel mesentery, although location was not found to significantly influence OS. The high incidence (16%) of a secondary malignancy is suggestive of the coincidental manner in which some mesenteric STS are diagnosed with identification on staging imaging or surveillance.

The utility of neoadjuvant and adjuvant therapy is largely tailored to individual sarcoma centre preferences and is not currently widely endorsed for other non-extremity sites of STS, beyond attempts at down-staging to assist marginal clearance of the lesion against critical structures [1,16].

Administration of neoadjuvant or adjuvant therapies was not found to be

significantly associated with OS in this study, although this may be subject to selection bias and lack of uniformity in choice of regimen.

The management of LR was characterised by active intervention with 42% undergoing surgical resection and 37% treated with chemotherapy. One patient had highly selective targeted IMRT for a bleeding peritoneal deposit. Chemotherapy and best supportive care were the predominant treatment strategies for DM. Radiofrequency ablation was utilised in 15%, reflecting the high incidence of liver metastases. The majority of patients did not develop early relapse post-treatment and the majority remained disease-free during the subsequent follow-up period. Active intervention is therefore encouraged, although a complex pattern of further LR, DM or synchronous LR and DM was observed. Evidence from the management of RPS suggests that the vast majority go on to develop recurrent disease with prolonged follow-up.

This study had a number of limitations. The principle limitation was the relatively small sample size that resulted in low statistical power where only large effect sizes are detectable. The other main limitation was the considerable quantity of missing data for some factors of interest which resulted from the retrospective nature of the data collection.

Conclusions

Primary mesenteric STS is rare, with a relatively high incidence of high grade tumours. The spectrum of pathology encountered mirrors that seen in the retroperitoneum. Pre-operative biopsy is mandatory. Attainment of an R0/R1 resection margin is highly recommended. The requirement for extensive

surgery negatively influences OS and is likely to reflect disruption of major mesenteric vasculature in order to obtain a clear margin. Overall survival is worse than that seen in RPS, and LR and DM are common features. The pattern of DM is different from STS in other locations, with a high incidence of liver metastases, reflecting the portal drainage of the mesentery and the requirement for cross-sectional surveillance imaging post-resection. Neoadjuvant and adjuvant therapies did not appear to influence OS. However, utilisation of these modalities is to be considered on the basis of specific histology and potential for down-grading to facilitate resection. Active intervention for the management of relapse is recommended on the basis that early further recurrence was not a particular feature of mesenteric STS in this study.

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Tables and Figures

Table 1a – Contributing Centres

	Number of Cases (%*)
Emory University Hospital, GA, USA	8 (14%)
The Ottawa Hospital, Ottawa, Canada	8 (14%)
Fondazione IRCSS Istituto Nazionale dei Tumori, Milan, Italy	7 (13%)
Mount Sinai Hospital, Toronto, Canada	6 (11%)
Leiden University Medical Centre, Leiden, The Netherlands	3 (5%)
University of Southern California, Los Angeles, CA, USA	3 (5%)
The Netherlands Cancer Institute, Amsterdam, The Netherlands	3 (5%)
Institute of Oncology, Ljubljana, Slovenia	3 (5%)
Candiolo Cancer Institute – FPO, IRCCS, Torino, Italy	3 (5%)
Jackson Memorial Hospital, Miami, USA	3 (5%)

Peter MacCallum Cancer Centre, Melbourne, Australia	3 (5%)
Queen Elizabeth Hospital, Birmingham, UK	2 (4%)
Mayo Clinic Jacksonville, FL, USA	2 (4%)
Sant Pau Hospital, Barcelona, Spain	1 (2%)
Patel Hospital, Karachi, Pakistan	1 (2%)

**Proportion of total cohort recruited by each centre.*

Table 1b – Patient Demographics

	N	Statistic
<i>Patient Demographics</i>		
Age at Surgery (Years)	56	59 (46 - 70)
Gender (% Male)	56	34 (61%)
Ethnicity (% White)	56	50 (89%)
<i>Comorbidities</i>		

Charlson Comorbidity Index*	56	2 (0 - 4)
Second Solid Tumour	56	9 (16%)
Diabetes	56	8 (14%)
COPD	56	3 (5%)
<i>Tumour Details</i>		
Location	56	
<i>Gastric</i>		3 (5%)
<i>Small Bowel</i>		31 (55%)
<i>Large Bowel</i>		19 (34%)
<i>Small and Large Bowel</i>		3 (5%)
Histology**	56	
<i>WDLPS</i>		8 (14%)
<i>DDLPS</i>		27 (48%)

<i>LMS</i>		13 (23%)
<i>Pleomorphic sarcoma</i>		2 (3.6%)
<i>Inflammatory myofibroblastic tumour</i>		2 (3.6%)
<i>Synovial sarcoma</i>		2 (3.6%)
<i>Solitary fibrous tumour</i>		1 (1.8%)
<i>Small round cell tumour</i>		1 (1.8%)
FNCLCC Grade**	46	
1		10 (22%)
2		17 (37%)
3		19 (41%)
Multi-Focal Disease	54	6 (11%)
Width (mm)**	47	160 (100 - 201)
Length (mm)**	45	140 (90 - 210)
Depth (mm)**	33	90 (51 - 108)

Largest Measurement (mm)**	54	178 (100 - 230)
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Data are reported as N (%), or as median (interquartile range), as applicable.

*Includes chronic kidney disease (moderate-severe)(N=2), cerebrovascular disease (N=2), connective tissue disease (N=2), peptic ulcer disease (N=2), liver disease (N=1), leukaemia/lymphoma (N=1), AIDS (N=1), congestive heart failure (N=1), myocardial infarction (N=1), peripheral vascular disease (N=1), dementia (N=0), hemiplegia (N=0).

**As assessed on final histology.

Table 1c - Treatment

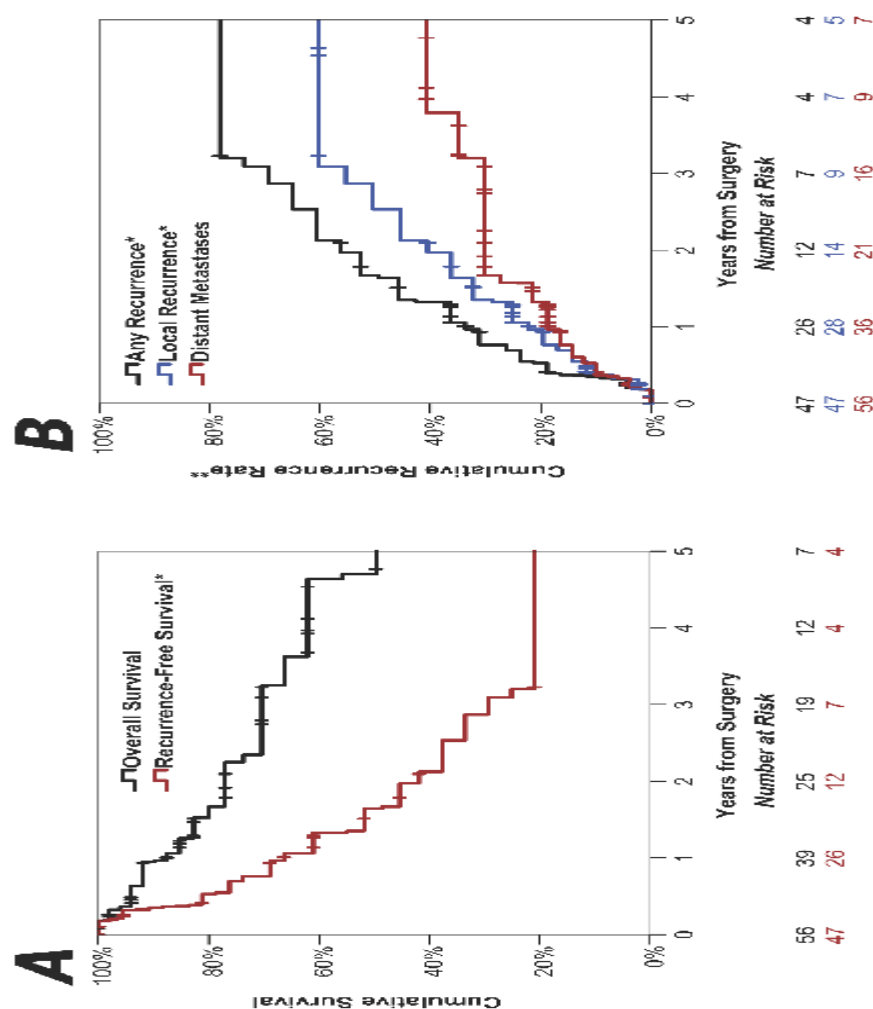
	N	Statistic
Neoadjuvant Treatment	56	
None		44 (79%)
Chemotherapy		8 (14%)
Radiotherapy		4 (7%)
Surgical Management at Reference Centre	56	49 (88%)

Surgery Type (% Open)	56	53 (95%)
Extent of Resection	40	
<i>Minor</i>		1 (3%)
<i>Moderate</i>		33 (83%)
<i>Extensive</i>		6 (15%)
R-status	54	
<i>R0/R1</i>		47 (87%)
<i>R2</i>		7 (13%)
Adjuvant Treatment	56	
<i>None</i>		47 (84%)
<i>Chemotherapy</i>		6 (11%)
<i>Radiotherapy</i>		2 (4%)
<i>Chemotherapy + IMRT</i>		1 (2%)

Data are reported as N (%).

Figures

Figure 1 – Kaplan-Meier curve of survival (Figure 1a) and recurrence outcomes (Figure 1b)



*Analysis of local/any recurrence excludes those with R2 resections or unknown R-status, hence is based on N=47.

**Patients that did not develop recurrence were censored at death in Figure 1b.

Figure 2 – Swimmer plot of patient outcomes

Grey bars represent the follow up periods for individual patients, with points representing the timing of recurrence/death. Only those with R0/1 resections were included in the plot (N=47). Recurrence dates were not recorded for the second instances of recurrence in N=4 cases, hence these were assumed to have occurred half way between the previous recurrence and the end of follow up.

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Table 2a – Associations between patient factors and patient survival

	Total N	Deaths	5 Year*	HR (95% CI)	p-Value
Age at Surgery (Years)					0.967
< 50	16	5	39%	1	-
50 - 69	26	9	54%	0.97 (0.32 - 2.96)	0.950
70+	14	3	59%	0.83 (0.20 - 3.49)	0.802
Gender					0.381
Male	34	10	49%	1	-
Female	22	7	52%	1.55 (0.58 - 4.20)	0.381
Ethnicity					0.239
White	50	17	47%	1	-
Non-White	6	0	100%	NC	NC
Surgical Management at Reference Centre					0.216
No	7	1	67%	1	-

<i>Yes</i>	49	16	48%	3.35 (0.44 - 25.52)	0.216
Diabetes					0.337
<i>No</i>	48	16	50%	1	-
<i>Yes</i>	8	1	50%	0.38 (0.05 - 2.92)	0.337
Second Solid Tumour					0.253
<i>No</i>	47	16	44%	1	-
<i>Yes</i>	9	1	89%	0.33 (0.04 - 2.47)	0.253
Charlson Comorbidity Index					0.741
<i>0-1</i>	23	8	41%	1	-
<i>2-3</i>	16	5	56%	0.63 (0.19 - 2.11)	0.456
<i>4+</i>	17	4	63%	0.77 (0.23 - 2.57)	0.673
Location					0.285
<i>Small Bowel</i>	31	9	52%	1	-
<i>Large Bowel</i>	19	6	48%	1.22 (0.42 - 3.52)	0.715

<i>Small and Large Bowel</i>	3	2	33%	3.61 (0.75 - 17.31)	0.108
<i>Gastric</i>	3	0	100%	NC	NC
Final Histology					0.148
<i>DDLPS</i>	27	8	58%	1	-
<i>WDLPS</i>	8	0	100%	NC	NC
<i>LMS</i>	13	5	38%	1.42 (0.45 - 4.50)	0.552
<i>Other</i>	8	4	0%	1.98 (0.58 - 6.77)	0.279
FNCLCC Grade					0.018
<i>1</i>	10	0	100%	1	-
<i>2</i>	17	7	40%	NC	NC
<i>3</i>	19	8	0%	NC	NC
Multi-Focal Disease					0.341
<i>No</i>	48	15	48%	1	-
<i>Yes</i>	6	1	80%	0.39 (0.05 - 2.95)	0.341

Largest Measurement (mm)					0.955
< 120	16	5	61%	1	-
120-199	17	5	47%	1.15 (0.33 - 4.00)	0.825
200+	21	6	49%	0.96 (0.27 - 3.32)	0.943

Overall *p*-values are from log-rank tests, whilst hazard ratios and pairwise *p*-values are from Cox regression models. Bold *p*-values are significant at $p < 0.05$. *Kaplan-Meier estimated five year survival. NC=Hazard ratio is not calculable, since there are no events in one of the groups.

Table 2b – Associations between treatment-related factors and patient survival

	Total N	Deaths	5 Year*	HR (95% CI)	p-Value
Neoadjuvant Treatment					0.168
No	44	12	56%	1	-
Yes	12	5	29%	2.08 (0.72 - 6.04)	0.168
Surgery Type					0.606
Open	53	16	46%	1	-

<i>Laparoscopic</i>	3	1	67%	0.59 (0.08 - 4.53)	0.610
Extent of Resection					<0.001
<i>Minor-Moderate</i>	34	9	56%	1	-
<i>Extensive</i>	6	4	0%	13.32 (2.84 - 62.39)	<0.001
R-Status					0.085
<i>R0/R1</i>	47	12	58%	1	-
<i>R2</i>	7	4	33%	2.85 (0.87 - 9.36)	0.085
Adjuvant Treatment					0.241
<i>No</i>	47	12	52%	1	-
<i>Yes</i>	9	5	40%	1.87 (0.65 - 5.39)	0.241

Overall *p*-values are from log-rank tests, whilst hazard ratios and pairwise *p*-values are from Cox regression models. Bold *p*-values are significant at *p*<0.05. *Kaplan-Meier estimated five year survival.

Figure 3a – Kaplan-Meier curve of survival by FNCLCC grade. **Figure 3b** – Kaplan-Meier curve of survival by extent of resection. **Figure 3c** – Kaplan-Meier curve of survival by resection status (R-status).

