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Title

Treatment of patients with primary retroperitoneal sarcoma: predictors of outcome from an Australian specialist sarcoma centre

Running Head

Primary RPS outcomes

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Abstract:

Introduction

Several unanswered questions surround the management of retroperitoneal sarcoma (RPS). Guidelines recommend treatment by a multidisciplinary team at a specialised referral centre. The objective of this study was to describe the management of RPS at an Australian specialist sarcoma centre, comparing outcomes to international standards and analysing for predictors of local failure.

Methods

A retrospective review of a prospectively maintained database was performed on patients with RPS treated between 2008 and 2016. 5-year outcomes analyses focussed on patients undergoing curative-intent surgery for primary, non-metastatic RPS.

Results

88 patients underwent surgery for primary RPS. 5-year overall survival was 66%, 5-year freedom from local recurrence was 65% and 5-year freedom from distant metastasis was 71%. Overall survival was associated with tumour grade (HR=6.1, $p<0.001$) and histologic organ invasion (HR=5.7, $p<0.001$). Variables associated with improved freedom from local recurrence were macroscopically complete resection (HR=0.14, $p<0.001$) and neoadjuvant radiotherapy (HR=0.33, $p=0.014$). Treatment at a specialist sarcoma centre was associated with a higher rate of preoperative

biopsy and neoadjuvant radiotherapy (both p<0.001). There was a trend towards improved local control for patients undergoing surgery at a specialist centre (p=0.055).

Discussion

This is the largest Australian series of RPS and outcomes are comparable to major international sarcoma centres. Patients treated at a specialist centre had higher rates of preoperative diagnosis and tailored therapy which was associated with improved outcomes. Patients with suspected RPS should be referred to a specialist centre for optimal preoperative evaluation and multidisciplinary management.

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Introduction

Retroperitoneal sarcomas (RPS) are rare soft tissue tumours, representing 10-15% of all soft tissue sarcomas, and have an incidence of 0.3-1 new cases per 100,000 population per year[1-3]. They are a heterogeneous group of tumours and, owing to their often-large size and complex anatomical relations, pose a substantial technical surgical challenge. Local recurrence (LR) is common (at least 40-50%) and remains a major cause of morbidity and mortality, with up to 75% of RPS-related deaths attributable to locally recurrent disease[4]. Clearly, optimising therapy to minimise the risk of LR is paramount.

High tumour grade and macroscopically incomplete resection have been consistently identified as predictors of LR[1, 5-7]. However, the rarity and heterogeneity of RPS has led to a relative paucity of high quality, prospective data, resulting in as yet unanswered questions surrounding the utility of radiotherapy and the extent of surgical resection to reduce the local failure rate. Therefore, international guidelines strongly recommend treatment by a multidisciplinary team at a specialised referral centre[2].

The main objective of this study was to describe the experience of managing RPS at an Australian specialist sarcoma centre, comparing outcomes to international standards. Specifically, we compared the treatment of primary RPS managed in a specialist centre with those initially treated at other centres. Predictors of LR,

including the use of radiotherapy, the extent of resection and the experience of the centre performing the surgery were evaluated.

Methods

Setting and patients

Peter MacCallum Cancer Centre (PMCC) is a tertiary referral centre for soft tissue sarcoma. The sarcoma multidisciplinary team comprising from surgical, medical and radiation oncologists, radiologists, nuclear medicine physicians, pathologists, specialist nurses, allied health and administrative support staff. All patients presenting to the sarcoma service with a diagnosis of RPS were retrospectively reviewed from a prospectively maintained database, between October 2008 until December 31, 2016. This included previously untreated patients as well as several patients who had undergone initial surgery at other centres prior to referral. These patients were usually referred for multidisciplinary opinions regarding the use of adjuvant systemic therapy or radiotherapy once a post-operative diagnosis of sarcoma was made.

All patients with primary or recurrent retroperitoneal sarcomas, with both non-metastatic and metastatic disease were identified. Patients with visceral sarcomas (including GIST), gynaecological sarcomas, paediatric sarcomas and desmoid tumours were excluded, as were patients with inadequate follow-up to establish oncologic outcomes (Figure S1).

In subsequent analyses, only those patients with primary, resectable RPS were included, excluding those who underwent non-curative intent resection, as well as those presenting with recurrent tumours as these are known to have a different recurrence profile and worse prognosis compared to patients with primary disease[8]. All RPS specimens from other institutions underwent histopathologic review by an expert sarcoma pathologist. Tumour grade was reported according to the FNCLCC method[9], however 6 were unable to be graded due to tumour subtypes falling outside the FNCLCC definition or cases where external pathology was reviewed and there was insufficient information to establish grade. Pathological margins were classified as macroscopically complete (R0 or R1) or incomplete (R2) due to the inherent difficulties in microscopically analysing large sarcomas and the literature showing no worse outcomes with microscopically incomplete (R1) resections compared with microscopically complete (R0) resections[4, 7, 10]. Radiotherapy and chemotherapy were administered on an individual basis as agreed upon by the sarcoma multidisciplinary team, but, in general, treatment frequently involved neoadjuvant radiotherapy and no chemotherapy. Follow-up regimens included clinical examination 3-monthly and CT scans of the chest and abdomen at 6-monthly intervals for the first 5 years and annually thereafter.

Statistical methods

Recurrences were defined as LR if occurring within the retroperitoneum or peritoneal cavity and distant metastases (DM) if occurring elsewhere. In cases of

macroscopically incomplete resections, LR was considered to have occurred if there was radiological progression of the residual tumour focus.

Endpoints were overall survival (OS), freedom from LR and freedom from DM. OS was defined as the time from date of surgery until date of death or referral to hospice care. Freedom from LR and DM was defined as the time from date of surgery until date of local recurrence or distant metastasis respectively. Dates of last follow-up, local recurrence, distant recurrence, death or referral to hospice care were censoring events.

Overall survival, freedom from LR and freedom from DM were described using the Kaplan-Meier method. Univariable Cox proportional hazards regression modelling was performed for OS and freedom from LR. All statistical analyses were performed in the R statistical software package version 3.4.2 (https://www.r-project.org) using standard and validated statistical procedures.

Results

There were 138 patients who met the criteria for inclusion and form the basis for this report (Table 1). Of these, 50 patients either did not undergo definitive surgery (36, 26.1%) or presented with recurrent tumours (14, 10.1%) (Document S1).

The remaining 88 patients with primary, resectable RPS formed the cohort for the remaining analysis (Table 1). Of this cohort, 62 (70.5%) had surgery at PMCC and 26 (29.5%) had surgery at other centres. Tumours resected at PMCC had higher proportions of well-differentiated liposarcoma (24% vs 8%) and de-differentiated

liposarcoma (39% vs 19%), and lower rates of leiomyosarcoma (15% vs 31%). Reflecting this, tumour grade was lower at PMCC than other centres (20% vs 50% grade 3; 39% vs 27% grade 1). The major differences in treatment modalities between the groups were in the rates of diagnostic core biopsy (92% vs 31%) and use of neoadjuvant radiotherapy (87% vs 12%). Median follow-up was 36 months.

Extent of surgery

The frequency and type of organs resected is shown in Figure S2. The most commonly resected organs were the kidney (43% of cases) and colon (36%), with spleen, pancreas, diaphragm and major vessels resected in < 10% of cases. Resections involved a median of 1 organ per patient (Table S1). Resections at PMCC were macroscopically complete (R0/R1) in 97%(60/62), while resections performed at other centres were R0/R1 in 88% (23/26) (p=0.15).

Local recurrence, distant metastases and overall survival of primary tumours

For patients undergoing resection of primary tumours, the 5-year freedom from LR was 65% (95%CI 52-80%), 5-year freedom from DM was 71% (95%CI 58-86%) and 5-year OS was 66% (95%CI 52-83%) (Figure 1).

In univariable analysis (Table 2), the variables significantly associated with OS were tumour grade (HR 6.1, 95%CI 2.3-16, p<0.001, and shown in Figure 2) and the presence of organ invasion, (HR 5.7, 95%CI 2.0-16, p<0.001).

Three variables were found to be significantly associated with LRFS on univariable analysis (Table 2). Macroscopically complete resection (p=0.001) and neoadjuvant radiotherapy (p=0.014) were both associated with lower rates of LR, while not employing a diagnostic core biopsy (p=0.019) was associated with higher LR rates. Surgical treatment at other centres tended towards higher rates of local recurrence (p=0.055, Figure 2).

Experience of surgical institution

Table 3 stratifies key treatment variables showing significant associations between undergoing surgery at PMCC for: use of neoadjuvant radiotherapy (87% vs 12%, p<0.001), use of diagnostic core biopsy (92% vs 31%, p<0.001) and number of organs resected (1 vs 0.5, p=0.014) compared to other centres. These variables are associated with a trend to reduced LR with surgery at PMCC (p=0.055) but no difference in OS (p=0.95).

Discussion

In 2014, the trans-Atlantic RPS working group published a consensus document describing evidence-based, fundamental aspects of primary RPS management[2]. The current series, representing the largest reported Australian series of RPS, has shown that several of these recommendations, such as preoperative diagnostic biopsy, neoadjuvant radiotherapy and wide resection (including adjacent organs where appropriate) are undertaken more frequently at a specialist sarcoma service (Table

3). Whilst the impact of neoadjuvant radiotherapy remains to be proven (and will be discussed further below), and preoperative biopsy is not universally advocated, thorough pre-operative evaluation allows appropriate patient selection, consistency of treatment approaches and enrolment into clinical studies for patients with this rare disease, emphasising the importance of early referral.

Oncological outcomes:

Tumour biology is known to be the main predictor of DM, with higher grade tumours and particular histological subtypes (leiomyosarcoma and de-differentiated liposarcoma) more prone to distant metastasis[5, 10]. Likewise, the variables in this series associated with worse OS are tumour grade (Figure 2) and histological organ invasion, which are findings consistent with previous studies[11]. By contrast, LR is the main outcome that can be most influenced by surgery and radiotherapy, and certain histological subtypes, such as well-differentiated liposarcoma, are more likely to recur locally. In our series, a significantly higher proportion of tumours treated at the specialist sarcoma centre were well-differentiated liposarcoma (24% vs 8%). Despite this, the hazard ratio for LR trended towards lower LR at the specialist centre.
The 5-year DM (29%), OS (67%) and LR (35%) rates in this series are comparable to other series (Table 4).

Effect of experience of centre and the use of radiotherapy:

The small number of patients in the current study makes meaningful comparison of R0/R1 resection rates between institutions impossible. A recent analysis of 3,141 RPS from the National Cancer Database in the United States found that high volume centres had a 2.5-fold higher likelihood of receiving a R0/R1 resection (p=0.026)[12]. This further supports recommendations that RPS be treated at specialist centres[5, 6, 13, 14].

Treatment at a specialist sarcoma centre was strongly associated with an increased use of neoadjuvant radiotherapy (87% PMCC vs 12% other centres, p<0.001). This reflects a multi-disciplinary team approach, which has been previously shown to predict for improved LR rates[6]. A neoadjuvant approach is preferred as the tumour is readily identifiable and displaces radiosensitive structures such as the small bowel out of the radiation fields, allowing delivery of adequate radiation dose to the tumour, with low toxicity[15] and without significantly increased perioperative morbidity or mortality[16]. The rate of neoadjuvant radiotherapy use in this series was 66% overall and 87% in those treated with initial surgery at PMCC, which is higher than any other series, (range 14-62%)[4, 17-20]. The use of neoadjuvant radiotherapy was associated with reduced rates of LR in our analysis.

However, prospective randomised evidence is needed to clarify the role of radiotherapy in RPS. Results of the EORTC 62092-22092 STRASS trial[21], a prospective randomized trial that has recently completed accrual, are eagerly awaited.

Effect of extent of resection:

Macroscopically incomplete resections have been widely documented to lead to poorer outcomes, with survival similar to unresected patients[5, 6, 10]. An R2 resection was rare in this series and we demonstrate R0/R1 resections to be associated with significantly lower rates of local failure (HR 0.14, p=0.001).

There is controversy surrounding the optimal extent of resection for RPS with some groups strongly promoting the resection of adjacent, uninvolved organs in order to achieve wider resection margins and demonstrating up to 50% reduction in LR[6, 10, 17, 18], while others remain unconvinced, citing limitations including non-standardised evaluations and selection bias[22, 23]. Extended resection also causes significantly higher short-term morbidity with a French series demonstrating a 2.75-fold increased perioperative morbidity when more than 3 organs were resected[17].

Furthermore, RPS encompasses a broad range of histological subtypes, each with a distinctive pattern of behavior and recurrence[5]. The practice at our institution is to limit extended multivisceral resection to histologic subtypes where LR is likely to be the cause of future morbidity (such as low grade, well-differentiated liposarcoma). As such, we resected a median of 1 organ per patient, in contrast to centres performing routine extended resections, where the median number of organs resected is 2[17].

Results from this analysis should be interpreted with caution as it is limited by its retrospective design and small sample size (which is a common issue in studies of rare cancers such as sarcoma). Furthermore, the heterogenous group of tumours,

further dilutes the power of the analysis. The median follow-up of 36 months is relatively short. This is due to the majority of patients (approximately three quarters) being captured in the latter half of the enrolment period.

Conclusion

This is the largest Australian series of RPS and outcomes are comparable to major international sarcoma centres. Treatment of RPS at a specialist sarcoma centre is associated with a higher rate of preoperative diagnostic biopsy and subsequent tailored therapy including consideration of neoadjuvant treatment strategies. Prospective data collection and clinical trials are currently underway to better understand tumour biology to improve patient selection for (neo)adjuvant radiotherapy and systemic therapy.

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Supporting information

Document S1. Reasons for not performing surgery

Table S1. Distribution of number of organs resected per patient

Figure S1. Flow diagram for patient inclusion

Figure S2. Frequency of organs resected

Figure legend

Figure 1. Kaplan-Meier plots for A) overall survival and, B) freedom from local recurrence

Figure 2. Kaplan-Meier plots for A) overall survival and B) freedom from local recurrence, stratified by surgical institution, A) and B), and by grade, C) and D) PMCC, Peter MacCallum Cancer Centre

Table 1 - Baseline demographic and disease characteristics; overall cohort and primary resected RPS only
(RPS, Retroperitoneal sarcoma; PMCC, Peter MacCallum Cancer Centre; ECOG, Eastern Cooperative Oncology Group)

Variable		Overall cohort		Primary resected RPS only	
		No surgery (n = 44)	Surgery (n = 94)	Surgery at PMCC (n=62)	Surgery at other centres (n=26)
Age at diagnosis (years)	Median [range]	67.5 [27 - 79]	59 [18 - 86]	59.5 [18 - 86]	56 [34 - 73]
	Interquartile range	59 - 73.2	47.2 - 65	49 – 65.8	47.5 - 64.8
ECOG score	0	13 (30%)	52 (55%)	33 (53%)	17 (65%)
	1	20 (45%)	40 (43%)	28 (45%)	8 (31%)
	2	7 (16%)	1 (1%)	1 (2%)	0 (0%)
	3	4 (9%)	1 (1%)	0 (0%)	1 (4%)
Sex	Male	26 (59%)	57 (61%)	43 (69%)	11 (42%)
	Female	18 (41%)	37 (39%)	19 (31%)	15 (58%)
Biopsy technique	Diagnostic core	40 (91%)	69 (73%)	57 (92%)	8 (31%)
	No biopsy/surgical biopsy/partial resection	4 (9%)	25 (27%)	5 (8%)	18 (69%)
Size (cm)	Median [range]	150 [50 - 224]	130 [20 - 420]	140 [23 - 420]	120 [20 - 300]
	Interquartile range	120 - 171	76.8 - 190	86.2 – 213.8	70.5 - 162
Focality	Unifocal	29 (66%)	88 (94%)	60 (97%)	23 (88%)
	Multifocal	15 (34%)	6 (6%)	2 (3%)	3 (12%)
Location	Abdomen - left	12 (27%)	31 (33%)	22 (35%)	8 (31%)
	Abdomen - right	21 (48%)	45 (48%)	29 (47%)	14 (54%)
	Pelvis	11 (25%)	18 (19%)	11 (18%)	4 (15%)
Histologic subtype	De-differentiated liposarcoma	6 (14%)	33 (35%)	24 (39%)	5 (19%)
	Well-differentiated liposarcoma	2 (5%)	17 (18%)	15 (24%)	2 (8%)
	Leiomyosarcoma	8 (18%)	17 (18%)	9 (15%)	8 (31%)
	Undifferentiated pleomorphic sarcoma	12 (27%)	7 (7%)	3 (5%)	4 (15%)
	Solitary fibrous tumour	6 (14%)	10 (11%)	6 (10%)	2 (8%)
	Other	10 (23%)	10 (11%)	5 (8%)	5 (19%)
Grade	1	-	31 (36%)	22 (39%)	7 (27%)
	2	-	31 (36%)	23 (41%)	6 (23%)
	3	-	25 (29%)	11 (20%)	13 (50%)

Radiotherapy	Unknown	-	7	6	0
	Neoadjuvant	7 (16%)	62 (65%)	54 (87%)	3 (12%)
	Adjuvant	0 (0%)	6 (6%)	1 (2%)	5 (19%)
	Palliative	22 (50%)	2 (2%)	0 (0%)	2 (8%)
	None	15 (34%)	25 (27%)	7 (11%)	16 (62%)

Table 2 – Univariable Cox proportional hazards regression results for overall survival and freedom from local recurrence.
(PMCC, Peter MacCallum Cancer Centre; HR, hazard ratio; CI, confidence interval)

Predictor	**Level**	**Overall survival**			**Freedom from local recurrence**		
		HR	**HR 95% CI**	**P**	**HR**	**HR 95% CI**	**P**
Age at diagnosis		1.0	[0.98, 1.1]	0.27	1.0	[1.0, 1.1]	0.068
Size		1.1	[0.65, 1.7]	0.80	1.5	[0.97, 2.2]	0.076
Macroscopically complete resection	No : Yes	0.33	[0.076, 1.5]	0.13	0.14	[0.041, 0.51]	0.001
Location	Abdomen - left	-	-	0.066	-	-	0.57
	Abdomen - right	0.29	[0.089, 0.94]		1.8	[0.57, 5.6]	
	Pelvis	1.0	[0.34, 3.0]		1.8	[0.46, 7.3]	
Biopsy technique	Diagnostic core : No biopsy/surgical biopsy/partial resection	1.4	[0.51, 3.6]	0.55	2.8	[1.1, 7.0]	0.019
Surgical institution	PMCC : Other centres	1.0	[0.37, 2.7]	>0.99	2.4	[0.96, 5.8]	0.055
Surgical complication	No : Yes	0.82	[0.23, 2.9]	0.75	0.87	[0.29, 2.6]	0.80
No of organs resected	0 : 1	2.2	[0.62, 7.9]	0.075	1.1	[0.40, 3.2]	0.65
	0 : 2+	2.9	[0.87, 9.8]		0.72	[0.22, 2.4]	
Histologic subtype	De-differentiated liposarcoma	-	-	0.26	-	-	0.38

	Well-differentiated liposarcoma	NA	[NA, NA]		0.36	[0.093, 1.4]	
	Leiomyosarcoma	0.66	[0.19, 2.3]		0.51	[0.13, 1.9]	
	Undifferentiated pleomorphic sarcoma	0.68	[0.14, 3.3]		0.97	[0.25, 3.7]	
	Solitary fibrous tumour	0.99	[0.25, 3.9]		0.28	[0.034, 2.3]	
	Other	0.48	[0.098, 2.4]		0.24	[0.030, 1.9]	
Neoadjuvant radiotherapy	No : Yes	1.0	[0.40, 2.7]	0.93	0.33	[0.13, 0.84]	0.014
Organ invasion	No : Yes	5.7	[2.0, 16]	<0.001	2.0	[0.78, 5.0]	0.15
Grade		6.1	[2.3, 16]	<0.001	1.9	[0.99, 3.6]	0.053

Table 3 – Key characteristics stratified by surgical institution
(PMCC, Peter MacCallum Cancer Centre)

Variable	Statistic / Level	Surgical institution		P
		PMCC (n = 62)	Other centres (n = 26)	
Biopsy technique	Diagnostic core	57 (92%)	8 (31%)	<0.001
	No biopsy/surgical biopsy/partial resection	5 (8%)	18 (69%)	
Macroscopically complete resection	No	2 (3%)	3 (12%)	0.15
	Yes	60 (97%)	23 (88%)	
No. of organs resected	Median [range]	1 [0 - 6]	0.5 [0 - 3]	0.011
	Interquartile range	1 - 2	0 - 1	
Neoadjuvant radiotherapy†	No	8 (13%)	22 (88%)	<0.001
	Yes	54 (87%)	3 (12%)	

† missing neoadjuvant radiotherapy data for 1 patient from Other centres group

Table 4 – Rates of treatment variables and outcomes from major RPS series
(NR, not reported; PMCC, Peter MacCallum Cancer Centre; LR, local recurrence; DM, distant metastasis; OS, overall survival)

Study	Period	No. of patients	Follow-up (months)	Complete (R0/R1) resection (%)	Neo/adjuvant radiotherapy (%)	5-year LR (%)	5-year DM (%)	5-year OS (%)
Bonvalot[6]	1985-2005	382	53	75	NR	49	34	57
Bonvalot[17]	2000-2008	249	37	93	14	22.3	24.2	65.4
Gronchi[18]	1985-2001	140	127	90	31	49	12	48
	2002-2008	191	48	94	30	28	25	66
Gronchi[10]	2002-2011	377	44	96	NR	23.6	21.9	64.6
Lewis[4]	1982-1997	231	72	80	62	41	21	54
Smith[5]	2005-2014	362	26	96	NR	NR	NR	81.2 (3-yr)
Stoeckle[20]	1980-1994	145	47	65	61	42	NR	49
Strauss[1]	1990-2009	200	29	85	NR	45.4	NR	68.6

van Dalen[19]	1989-1994	143	122	63	16	NR	NR	39
Current series	**2008-2016**	**88**	**36**	**94**	**65**	**35**	**29**	**66**
				97 (PMCC only)	87 (PMCC only)			

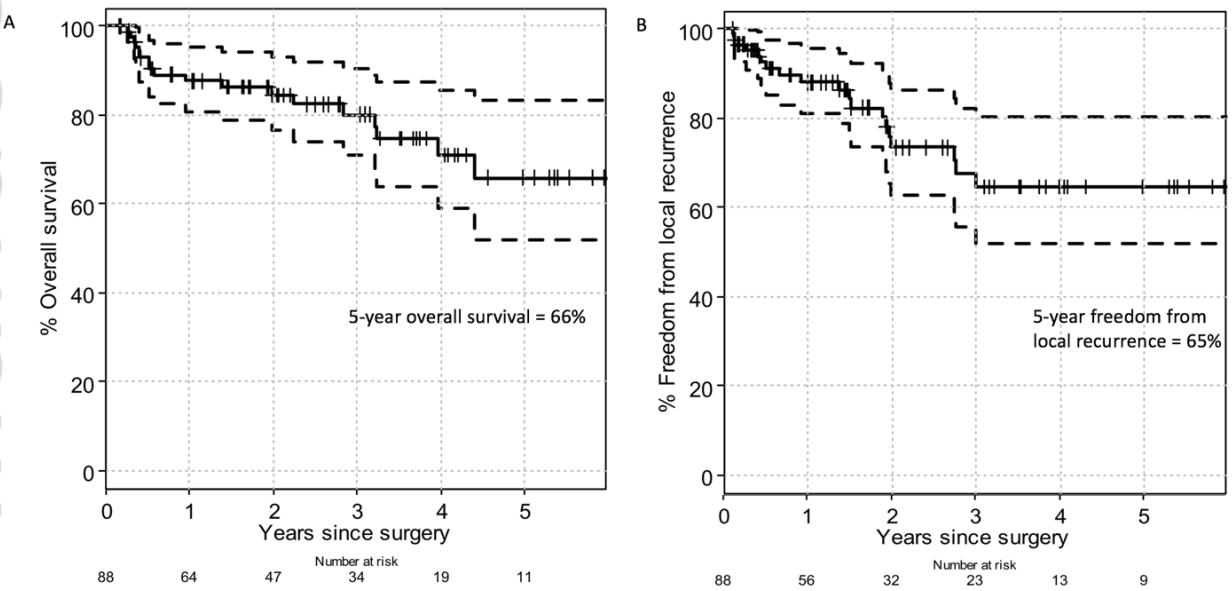

Figure_1.tiff

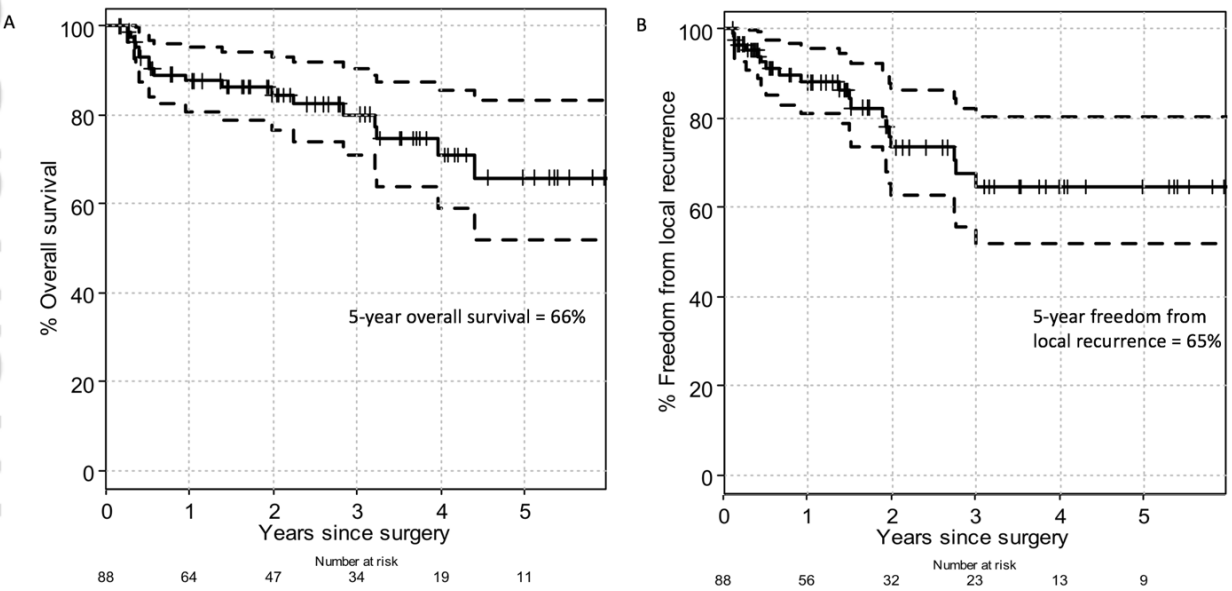

Figure_1.tiff

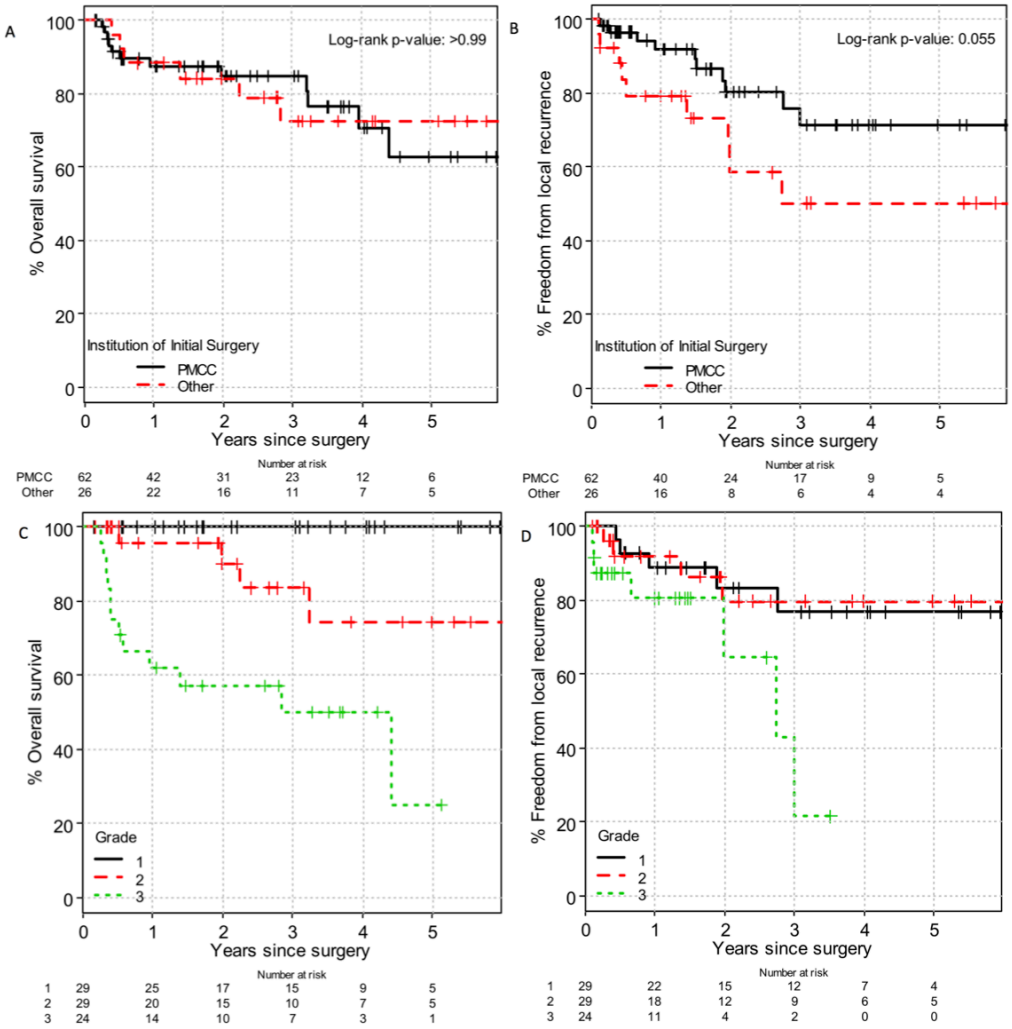

Figure_2.tiff

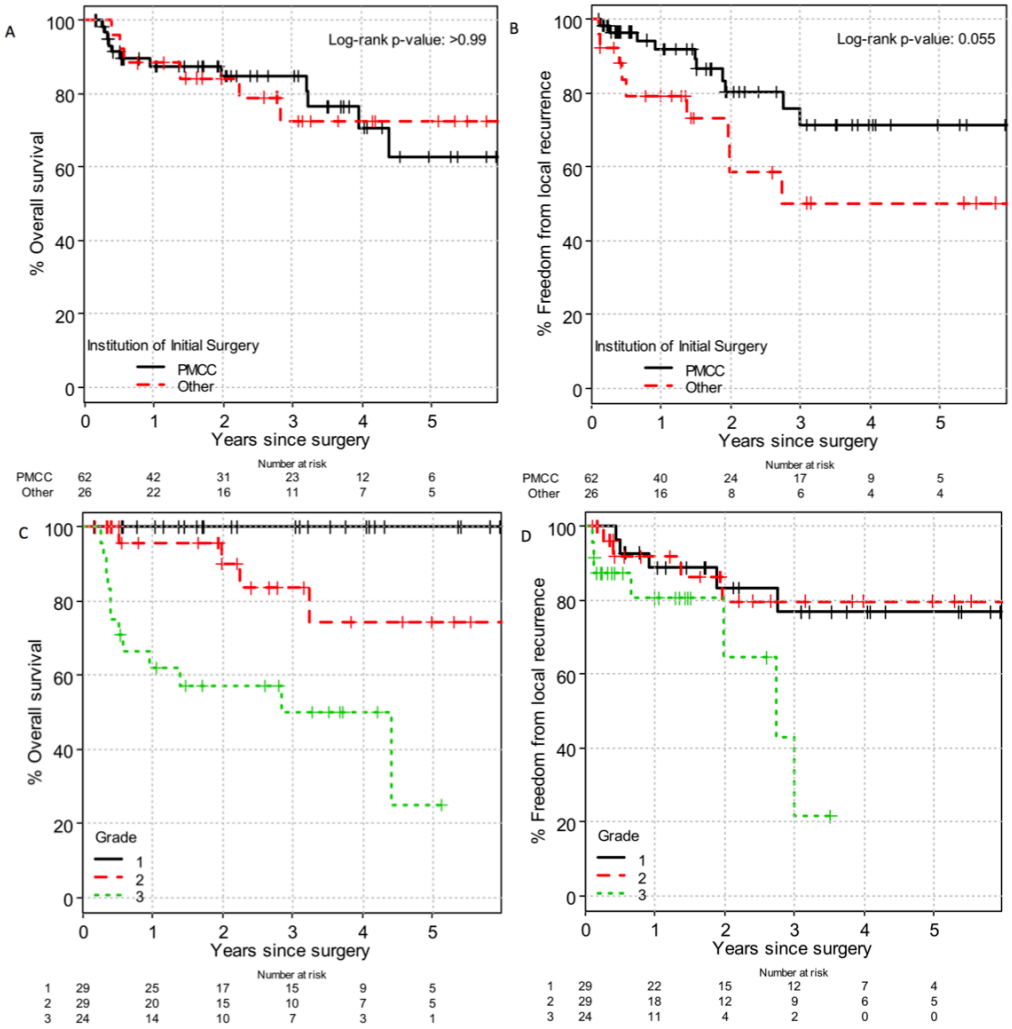

Figure_2.tiff