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A systematic review of population-based studies examining outcomes in primary retroperitoneal sarcoma surgery

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ABSTRACT

Retroperitoneal sarcomas (RPS) are rare mesenchymal tumours. Their rarity challenges our ability to understand expected outcomes. The aim of this systematic review was to examine 30-day morbidity and mortality, overall survival rates and prognostic predictors from population-based studies for patients undergoing curative resection for primary RPS. A systematic literature review of EMBASE, MEDLINE, PUBMED and the Cochrane library was performed using PRISMA for population-based studies reporting from nationally registered databases on primary RPS surgical resections in adults. The main outcomes evaluated were 30-day morbidity and mortality and overall survival rates. The use of additional treatment modalities and predictors of overall survival were also examined. Fourteen studies (n = 12 834 patients) reporting from 3 national databases, (Surveillance, Epidemiology and End Results (SEER), the United States National Cancer Database (US NCDB) and the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP)) were analysed. The reported overall 30-day morbidity and mortality were 23% *(n = 191/846)* and 3% *(n = 278/10 181)* respectively. Reported use of perioperative radiotherapy was 28%. No study reported loco-regional recurrence rates. Overall reported 5-year survival ranged from 52% to 62%. Independent predictors of overall survival were age of the patient, resection margin, tumour grade and size, histological subtype and receipt of radiotherapy. This review of population-based data demonstrated relatively low 30-day morbidity rates in patients undergoing curative surgical resections for primary RPS. Thirty-day mortality rates were similar to other abdominal tumour groups. There remains a paucity of data reporting recurrence rates, however 5-year survival rates ranged from 52 to 62%.

1. Introduction

Retroperitoneal sarcomas (RPS) are a rare heterogeneous group of mesenchymal tumours, representing approximately 15% of soft tissue sarcomas [1,2]. Their relatively late presentation and anatomical location presents a therapeutic challenge. The often close relationship to vital structures in the retroperitoneum can impact on the ability to perform a radical wide resection of the tumour and therefore it may not be possible to obtain a margin of normal tissue around the tumour [3]. Marginal and incomplete resections (R1 or R2) have been reported in up to half of patients undergoing surgery with curative intent [4–9]. Local recurrence is the main cause of treatment failure, ranging from 40 to 80% and approximately 75% of sarcoma-related deaths involve uncontrolled local recurrence [4]. Furthermore, in completely resected RPS, locoregional recurrence is common, occurring in up of 50% of cases [10,11].

Surgical resection currently represents the only possibility for cure, particularly due to the lack of effective systemic treatments, and remains the mainstay of treatment for patients with RPS when it is deemed feasible. There is great interest in strategies that might improve local control, such as radical surgical resection and peri-operative radiotherapy, particularly because this represents the main cause of death after surgery. A radical surgical approach involving en-bloc resection of the tumour with adherent organs or structures has been advocated by many specialist centres with the aim to reduce margin involvement and decrease local recurrence rates [12–15]. Although improved oncological outcomes have been reported, the most common histological subtype of RPS is liposarcoma, which can follow a relatively indolent course and display favourable tumour biology, therefore it has been argued the potential short and long-term morbidity of aggressive multi-visceral resection is not always justifiable [16,17]. Despite the controversy surrounding the optimal surgical management of

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Table 1
Study demographics.

Reference (Author & Year of Publication)	Region	Database	Study Period	Number of Patients	Primary Aim of Study	Risk of Bias
Porter et al., 2006 [25]	North America	SEER	1973–2001 29 years	2348 1654 resections	Incidence, treatment & use of RT	Moderate
Nathan et al., 2009 [26]	United States of America	SEER	1988–2005 27 years	1365	Predictors of OS	Good
Tseng et al., 2011 [27,36]	United States of America	SEER	1988–2004 26 years	1535	Effect of RT on OS	Good/moderate
Bates et al., 2015	United States of America	SEER	1973–2010 37 years	480	Efficacy of Adjuvant RT in high-grade RPS	Good/moderate
Giuliano et al., 2016 [29]	United States of America	SEER	2002–2012 10 years	2920	Predictors of improved OS	Moderate/poor
Wang et al., 2017 [30]	United States of America	SEER	1988–2013 25 years	908	IntraopRT v PreRT/PostRT alone & OS	Moderate/poor
Kashtan et al., 2016 [31]	United States of America	US NCDB	1998–2015 17 years	100	Age disparity in treatment & outcomes (OS) in rhabdomyosarcoma	Moderate/poor
Ecker et al., 2016 [32]	United States of America	US NCDB	2004–2013 9 years	2082	PreRT v Surgery alone & OS in liposarcoma	Good
Nussbaum et al., 2016 [33]	United States of America	US NCDB	2003–2011 8 years	9068	PreRT v PostRT v Surgery alone & OS	Good
Klooster et al., 2016 [34]	United States of America	US NCDB	1998–2011 13 years	395	OS in R2 margin status & predictors	Moderate
Stahl et al., 2017 [35]	United States of America	US NCDB	1998–2011 13 years	4015	R0 v R1 margin status & OS	Good
Tseng et al., 2011 [27,36]	United States of America	ACS-NSQIP	2005–2007 2 years	156	30-day Morbidity & Mortality, predictors of poor perioperative outcome	Moderate
Bartlett et al., 2014 [37]	United States of America	ACS-NSQIP	2005–2011 6 years	696	30-day Morbidity & Mortality PreRT v no PreRT	Good/moderate
Park et al., 2017 [38]	United States of America	ACS-NSQIP	2007–2012 5 years	846	mFI as predictor of 30-day Morbidity & Mortality	Good

RT: radiotherapy. PreRT: pre-operative radiotherapy. IntraopRT: intra-operative radiotherapy. PostRT: post-operative radiotherapy. OS: overall survival. SEER: Surveillance, Epidemiology & End Results. US NCDB: United States National Cancer Database. ACS-NSQIP: American College of Surgeons National Surgical Improvement Program.

RPS, limited data exists on the short-term peri-operative outcomes following resection of RPS. Peri-operative radiotherapy is the most widely utilised multimodality strategy directed at decreasing locoregional recurrence in RPS, but at present, data supporting the use is also limited and the increasing use of radiotherapy has largely been extrapolated from its established role for soft tissue extremity sarcomas [18,19].

The majority of data available on primary RPS surgical resection is from single specialist institutions or small collaborative centres reporting outcomes for RPS. Furthermore, variations in practice regarding reporting of resection margins, histology and post-operative surveillance can make it difficult to compare outcomes. Consequently, findings from these studies have inherent biases and therefore may not be generalisable to a broader population. Recently, there have been a growing number of population-based studies of RPS trying to address these issues. We therefore sort to systematically review these studies to examine the 30-day morbidity and mortality, overall survival rates and predictors of this from population-based studies utilising large national databases for patients undergoing curative resection for primary RPS.

2. Methods

2.1. Search strategy

A systematic review of published work was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20] statement for the conduct of a review study. The study team developed a concept table and built a search strategy with a medical librarian to identify articles reporting outcomes from primary retroperitoneal sarcoma surgery. Three concepts were developed: retroperitoneal sarcoma, post-operative morbidity and mortality (30-days) and surgery. Exploded medical subject heading (MeSH) terms were combined with text word searching using the Boolean operator 'OR' for each concept. Each concept was combined with 'AND'. Variation in spelling were accounted for using '*' in the search to represent wildcard characters. Search limits were confined to the English language. Four databases were searched (Ovid Medline, 1946 to present; Ovid EMBASE, 1980 to present; PubMed and Cochrane database) and the search strategy was adapted to each database. The final search was performed on 8th November 2017. Reference lists of included articles were also searched and further articles included if appropriate. The full search strategy used is summarised in Appendix 1.

2.2. Inclusion and exclusion criteria

To minimise selection, reporting and publication bias, any case reports or series and cohorts from single or combined centres were excluded. Only population-based studies using nationally recognised central databases were included. The criteria were also refined to human adults (≥18 years) only. The anatomical region for included tumours was defined as being inclusive of the retroperitoneal and abdominopelvic space. Reports that did not focus on surgical resection as the main treatment option, and without curative intent were also omitted. *Any articles focusing on benign or recurrent disease, or those not originating from soft tissues were excluded.*

2.3. Selection of articles

Using pre-defined data fields, two authors independently assessed the study titles and abstracts for inclusion. They discussed and resolved any differences in title selection between them, with a third assessor independently reconciling any differences in abstract selection. Full-text versions of potentially eligible studies were retrieved, which were further assessed by two independent study authors against the inclusion/exclusion criteria and a consensus was reached.

2.4. Data extraction & outcomes

One author extracted information from the studies using a standardised spreadsheet. Data extracted included study year, study design and purpose, patient demographics, 30-day morbidity and mortality, type of surgical resection, histological factors, additional treatment modalities including chemotherapy and radiotherapy, overall survival data and predictors of survival. The specific International Classification of Diseases (ICD) codes used were also recorded.

2.5. Assessment of risk of bias in included studies

Two study authors assessed risk of bias independently and a third author resolved any discrepancies. The Quality Assessment Tool for observational cohort or cross-sectional studies, developed by the National Heart, Lung, and Blood Institute [21]. Data recorded included incomplete outcome data, clearly defined outcome measures and other sources of bias. Studies were assigned good, fair or poor quality (low, moderate, high risk of bias) using the published criteria and is outlined in Table 1.

2.6. Data synthesis

The heterogeneous nature of the methodology and data collected from this systematic review did not allow meta-analysis to be conducted. *When publications referred to the same population database and reported the same outcome, the largest study was described.*

2.7. Description of national databases

The Surveillance, Epidemiology and End Results (SEER) database is published by the National Cancer Institute and is a coordinated system of cancer registries strategically located across the US [22]. The database covers 28% of the US population and draws data from 20 states [22]. One of the aims of the database is to evaluate the quality of cancer care.

The US National Cancer Data Base (US NCDB) is a nationwide clinical oncology database, which is jointly administered by the American College of Surgeons and the American Cancer Society. The US NCDB currently includes records for more than 30 million patients and contains data from over 1500 Commission on Cancer-associated institutions in the USA [23]. The Commission on Cancer estimates the US NCDB captures approximately 70% of newly diagnosed cancer cases in the USA [23].

The American College of Surgeons National Surgical Improvement Program (ACS NSQIP) is a national initiative that began in 2004 to collect validated, risk-adjusted 30-day perioperative outcome data from a variety of hospital facilities [24]. This national database evaluates the quality of care at institutions and improves surgical outcomes [24].

3. Results

3.1. Search results

One thousand and seventeen studies were identified from the literature search of the electronic databases, which, following screening (inclusion/exclusion criteria and removal of duplicates), resulted in 14 full articles for inclusion in this qualitative synthesis (Fig. 1). All studies were assessed using the Quality Assessment Tool for observational cohort or cross-sectional studies (Table 1).

3.2. Demographics of included studies

Of the 14 included studies reporting on 3 nationally recognised central databases, one was from Canada and the USA[25] and the others were all from the USA [26–38] (Table 1). Six studies used The Surveillance, Epidemiology and End Results (SEER) database [25–30], five studies reported from the United States National Cancer Data Base (US NCDB) [31–35] and the final three used the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP) [36–38]. The 14 studies span over four decades of surgical treatment for retroperitoneal sarcomas, with the earliest studies reporting data from 1973 [25,28] and the most recent from 2015 [31]. Overlapping of data in studies occurred across all the specific databases, therefore the largest dataset was used for that particular database, unless the study did not report a specific outcome, when the next largest sample study to report a specific outcome was used. The number of patients varied across the studies, but it equated to a total of 12 834 patients from the largest series from each database [29,33,38]. Table 1 outlines the characteristics of the 14 studies included, published between 2006 and 2017, which were all conducted as retrospective data analyses. Table 2 summarises the aim of each study, the main reported outcomes pertinent to this review and the basic reported demographic data, which varied depending on the database analysed. The inclusion and exclusion criteria for each study is outlined in Appendix 2.

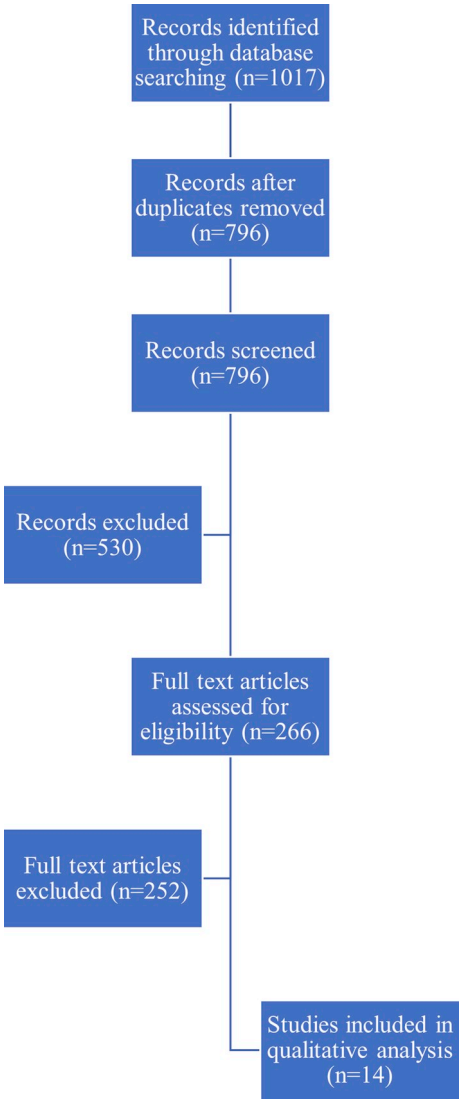

Fig. 1. PRISMA flow diagram.

3.3. Frequency and type of surgical resection

The overall frequency of reported radical resections for RPS was

Table 2
Main reported outcomes, basic patient demographic data and histology subtypes.

Reference (Author & Year of Publication)	Main reported outcomes pertinent to review	Patient Demographics	Histology Types
SEER Subgroup			
Porter et al., 2006 [25]	Patient demographics Treatment modalities Use of RT Geographical factors	N = 2348 Male 1121 (48%) Age < 60 932 (40%) Caucasian 1977 (84%)	All types of RPS Histological subtypes not specified
Nathan et al., 2009 [26]	Patient demographics Histological Factors Lymph Node & Metastatic disease Use of RT AJCC staging Overall survival Predictors of overall survival	N = 2500 Curative surgery = 1365 (55%) N = 1365 Female 754 (55%) Median Age 63 Caucasian 1135 (83%)	All types of RPS Liposarcoma (50%) Leiomyosarcoma (26%) Malignant fibrous histiocytoma (11%) Fibrosarcoma (2%) Rhabdomyosarcoma (1%) Malignant peripheral nerve sheath tumour (1%) Sarcoma not specified (7%) Others (2%)
Tseng et al., 2011 [27,36]	Patient demographics Histological Factors Perioperative variables Use of RT RT v surgery alone Overall and disease specific survival Predictors of overall and disease-specific survival	N = 1535 Male 723 (47%) Mean Age 61.5 (14.8 SD) Caucasian 1157 (75%)	All types of RPS Liposarcoma (49%) Leiomyosarcoma (28%) Malignant fibrous histiocytoma (10%) Sarcoma not specified (7%) Others (6%)
Bates et al., 2015	Patient demographics Use of RT Surgery & PostRT v Surgery alone Overall survival Predictors of overall survival	N = 480 Male 241 (50%) Age ≤ 65 279 (58%) Caucasian 404 (84%)	All types of high grade RPS Leiomyosarcoma (29%) Dedifferentitated Liposarcoma (28%) Malignant fibrous histiocytoma (10%) Sarcoma not specified (%)
Giuliano et al., 2016 [29]	Patient demographics Histological factors Lymph node & Metastatic disease Treatment modalities Use of RT Overall and cause-specific mortality Predictors of overall survival	N = 2920 Female 1506 (51.6%) Median Age 63 (52–73 IQR) Caucasian 2360 (81%)	All types of RPS Liposarcoma (47%) Leiomyosarcoma (25%) Sarcoma not specified (14%) Others (14%)
Wang et al., 2017 [30]	Patient demographics Histological factors Use of RT IntraopRT v PreRT/PostRT alone Overall survival Predictors of overall survival	N = 908 Female 432 (48%) Age ≤ 65 608 (67%) Caucasian 715 (79%)	All types of RPS Liposarcoma (42%) Leiomyosarcoma (31%) Rhabdomyosarcoma (2%) Fibrosarcoma (2%) Malignant fibrous histiocytoma (8%) Sarcoma not specified (15%)
US NCDB Subgroup			
Kashtan et al., 2016 [31]	Patient demographics Histological factors Institutional factors Perioperative factors Use of RT & Chemo Age based disparity Overall Survival Predictors of overall survival	N = 100 Male 51 Age < 65 65 Caucasian 79 Charlson Deyo Score 0 52 Private Insurance 50 Median income > $46000 40	Rhabdomyosarcoma (100%)
Ecker et al. 2016 [32]	Patient demographics Histological factors Institutional factors Use of Chemo Pre-RT v Surgery alone (Propensity score matching) Overall survival Predictors of overall survival	N = 2082 Male 1092 (52%) Age ≤ 63 1000 (48%) Caucasian 1849 (89%) Charlson Deyo Score 0 1631 (78%) Private Insurance 939 (45%) Median Income ≥ $48000 1350 (65%)	Liposarcoma (100%)
Nussbaum et al., 2016 [33]	Patient Demographics Histological factors Institutional factors 30-day mortality Pre-RT or Post-RT v Surgery alone (Propensity Score Matching) Overall Survival Predictors of Overall Survival	N = 9068 Male 4390 (48%) Mean Age 60 Caucasian 7713 (85%) Charlson Deyo Score 0 7276 (80%) Insurance 8568 (94%) Above median income 5481 (60%)	All types of RPS Liposarcoma (47%) Leiomyosarcoma (30%) Haemangiosarcoma (1%) Malignant fibrous histiocytoma (5%) Malignant peripheral nerve sheath tumour (2%) Fibrosarcoma (2%) Spindle Cell sarcoma (3%) Giant cell sarcoma (4%) Sarcoma not specified (6%)

(*continued on next page*)

Table 2 (*continued*)

Reference (Author & Year of Publication)	Main reported outcomes pertinent to review	Patient Demographics	Histology Types
Klooster et al., 2016 [34]	Patient demographics Histological factors Institutional factors Use of RT & Chemo R2 Resection Margin Overall survival Predictors of overall survival	N = 395 Male 173 (44%) Age < 65 218 (55%) Charlson Deyo Score 0 180 (46%)	All types of RPS Liposarcoma (41%) Leiomyosarcoma (18%) Undifferentiated pleomorphic sarcoma (19%) Fibrosarcoma (1.5%) Malignant peripheral nerve sheath tumour (1.5%) Sarcoma not specified (19%)
Stahl et al., 2017 [35]	Patient Demographics Histological Factors Use of RT & Chemo R0 v R1 Resection Margins (Propensity Score Matching) Overall Survival Predictors of Overall Survival	N = 4015 Female 2201 (55%) Age < 60 1920 (48%) Caucasian 3348 (83%) Charlson Deyo score 0 2293 (57%)	All types of RPS Liposarcoma (59%) Further histological subtypes not specified
ACS-NSQIP Subgroup			
Tseng et al., 2011 [27,36]	Patient Demographics Perioperative variables Use of PreRT 30-day Overall Morbidity 30-day Serious Morbidity 30-day Mortality Predictors of 30-day overall & serious morbidity	N = 156 Female 82 (53%) Mean Age 59.5 (± 15.2SD) Caucasian 117 (75%) ASA 1/2 78 (50%) Mean BMI 29.8 (± 7.4SD) Hypertension 65 (42%) Smoker 20 (13%) Diabetes Mellitus 19 (12%)	All types of RPS Histological subtypes not specified
Bartlett et al. 2014 [37]	Patient Demographics Perioperative variables Length of Hospital Stay Use of PreRT 30-day Morbidity 30-day Mortality Predictors of Morbidity & Mortality	N = 696 Male 342 (49%) Median Age 60 (19–90) Independent Functional Status 678 (98%) BMI > 25 532 (77%) Hypertension 304 (44%) Smoker 78 (11%) Diabetes 82 (12%)	All types of RPS Histological subtypes not specified
Park et al., 2017 [38]	Patient Demographics Perioperative Variables 30-day Overall Morbidity 30-day Serious Morbidity 30-day Mortality Predictors of 30-day overall morbidity, serious morbidity & mortality	N = 846 Female 437 (52%) Mean Age 59 (± 14SD) Caucasian 667 (79%) Mean BMI 28.7 (± 2.6SD) ASA 1/2 302 (36%) Independent Functional status 824 (97%) mFI score 0 410 (49%)	All types of RPS Histological subtypes not specified

40% *(4528/11 449)* [27,33,38]. Giuliano et al. reported *2208 patients from a total of 2920 (76%)* underwent surgical resection for primary RPS, but did not specify the type of resection [29]. Tseng et al. utilised the SEER database and specified the type of surgical resection performed. *From 1535 patients, 660 (43%) underwent a complete resection (total removal or radical surgery), 223 (15%) had incomplete resection (biopsy, debulking and destruction), 600 (39%) had simple resection (excision or simple resection) and finally 52 (3%) were unknown* [27].

Nussbaum et al. reported on neo-adjuvant or adjuvant radiotherapy versus surgery alone for RPS in *9068 patients* from the US NCDB. Following imputation for missing variables and exclusion of neo-adjuvant radiotherapy patients, as this data (not known at the time of pre-operative radiation) was not recorded (563 patients), *3501 (41%) underwent radical resection (concomitant resection of neighbouring organ), 2398 (28%) had simple resection and 2606 (31%) had local excision (includes excisional biopsy)* [33]. Between 2004 and 2013, Ecker et al. reported on the use of neo-adjuvant radiotherapy in the management of retroperitoneal liposarcoma versus surgery alone from data acquired from the US NCDB [32]. *This study identified a total of 8975 patients with RPS in the US NCDB for this time period, which revealed 3587 (40%) patients did not have surgery* [32].

Park et al. reported *846 patients* that underwent surgical resection for a primary RPS from the ACS NSQIP database [38]. *A multi-visceral resection (concomitant adjacent organ resection) was reported in 367* (43%) patients, but did not specify the type of organ resected. Bartlett et al. reported on the early outcomes of *696 patients* from the use of neo-adjuvant therapy versus surgery alone for RPS from the ACS NSQIP between 2005 and 2011 and specified the type of organ resected. A major organ resection was performed in 371 (53%) patients, with 161 colonic (23%) and 134 kidney (19%) resections being the commonest organs removed [37].

3.4. 30-day morbidity & mortality

Park et al. is the largest study of *846 patients* from the ACS NSQIP database to report these outcomes. *The overall (any ACS NSQIP complication) and serious (defined as Clavien-Dindo ≥ 3) reported 30-day morbidity were 23% (n = 191/846) and 13% (109/846) respectively* [38]. Univariate analysis demonstrated 30-day serious morbidity were greater among males (18% versus 8%; $p < 0.0001$), those that underwent multi-visceral resections (18% versus 9%; $p = 0.0001$), higher wound classification scores ($p = 0.01$) and those with lower pre-operative albumin scores ($p = 0.04$). Rates of serious 30-day morbidity were not significantly different among patients who underwent neo-adjuvant chemotherapy (8% versus 13%; $p = 0.46$) or radiotherapy (9% versus 13%; $p = 0.56$), this was also the case for overall 30-day morbidity [38]. Significant predictors of 30-day serious morbidity on multivariate analysis were multi-visceral resection (OR 1.86; 95% CI 1.19–2.89; $p = 0.006$) and a modified frailty index (mFI: contains 11

variables) ≥3 compared with non-frail patients (OR 2.93; 95% CI 1.22–7.03; p = 0.02) [38].

Studies from the SEER and US NCDB databases did not report 30-day morbidity rates [25–35]. However, Ecker et al. did report a hospital readmission rate within 30-days of 6.9% for the neo-adjuvant radiotherapy group *(12/174 patients)* and 6.3% for the surgery alone group *(120/1908 patients)*, with no statistical difference [32]. Bartlett et al. (n = 696 patients) described a median length of hospital stay for primary RPS surgery of 7 days (range 1–78 days) [37].

Nussbaum et al. [33] *excluded 267 patients* from their study because they died within 30-days of surgery (exclusion criteria), whilst there were 11 (1%) deaths within 30-days of surgery in Park et al. series *(n = 846 patients)* [38]. Therefore, the overall reported 30-day mortality rate for primary RPS surgery was 3% *(278/10 181 patients)* [33,38]. Univariate analysis of the Park et al. series demonstrated increase rates of 30-day mortality among males (2.2% versus 0.2%; p = 0.0009), patients with impaired functional status (18% versus 1%; p < 0.0001) and lower mean haematocrit and albumin levels (p < 0.01) [38]. Significant predictors of mortality on multivariate analysis were male gender (OR 0.11; 95% CI 0.01–0.93; p = 0.04) and impaired functional status (OR 44.17; 95% CI 5.65–345.20; p < 0.0001) [38]. Studies from the SEER database did not report 30-day mortality rates [25–30].

3.5. Histological factors

The proportion of histological subtypes are outlined in Table 2, demonstrating a wide variety of subtypes. *The important reported histological factors in the management of primary RPS are outlined in* Table 3. This shows a general trend towards the majority of tumours being > 10 cm in size and of a higher grade. Metastatic disease was present in 15% of patients *(2424/16 379)* [29,35], *but the majority were excluded from individual studies*.

3.6. Resection margins

Positive resection margins were reported in the adjuvant radiotherapy (n = 2215) and surgery alone (n = 6290) groups in 874 (40%) and 1851 (29%) patients respectively [33] *from the US NCDB*. Klooster et al. evaluated the long-term survival of patients after margin-positive resections of RPS using the US NCDB and demonstrated a R2 resection rate of 3% *(395/12 028 patients)* between 1998 and 2011 [34]. The reported R2 resection rate was 5% in 1998 versus 2.5% in 2011 [34]. R2 resection margins were more likely to be associated with higher grade (OR 1.80: 95% CI 1.10–3.20; p = 0.03), tumour size ≥20 cm (OR 2.10; 95% CI 1.10–4.20; p = 0.03) and a Charlson/Deyo score of 2 (OR 3.5; 95% CI 1.60–7.50; p = 0.001). Neither the SEER nor the ACS NSQIP databases report resection margins.

3.7. Additional treatment modalities

3.7.1. Radiotherapy

A total of 3598 patients (28%) across the largest studies from each of the 3 databases *(n = 12 834)* received some form of radiation therapy as part of their treatment for primary RPS [29,33,38]. *A detailed breakdown of the frequency of neo-adjuvant, intra-operative and adjuvant radiotherapy reported across these population studies is outlined in* Table 4.

Nussbaum et al. report the use of neo-adjuvant or adjuvant radiotherapy versus surgery alone for RPS [33]. Factors associated with the use of radiotherapy were estimated in logistic regression models. Variables associated with the use of neo-adjuvant radiotherapy included age, sex, year of diagnosis, histological subtype, tumour grade and treatment facility type. Variables associated with adjuvant radiotherapy were age, tumour size, histological subtype, tumour grade, extent of resection, margin status and treatment facility type. *Notably, treatment at academic medical centres versus treatment at local community hospitals was associated with increased use of neo-adjuvant radiotherapy (OR 7.98: 95% CI 3.53-18.06; p < 0.0001) and decreased use of adjuvant radiotherapy (OR 0.58: 95% CI 0.48-0.71; p < 0.0001)*. Furthermore, use of neo-adjuvant radiotherapy was more frequent in 2007–2011 than in 2003–2006 (OR 1.40; 95% CI 1.19–1.74; p = 0.0002), whilst the use of adjuvant radiotherapy was unrelated to treatment period [33].

3.7.2. Chemotherapy

Studies from the US NCDB and ACS NSQIP databases reported *606 (12%) from a total of 5256 patients* received a form of chemotherapy [34,35,38]. *A summary of the use of chemotherapy in primary RPS is provided in* Table 5. Data for chemotherapy use is not available from the SEER database.

Table 3
A summary of the reported histological factors. SD: standard deviation.

Reference	Tumour Grade	Tumour Size	Local Extension	Lymph Nodes	Metastasis
SEER					
Giuliano et al., 2016 [29] (n = 2920)	Grade 1 719 (24%) Grade 2 286 (10%) Grade 3&4 1189 (41%) Unknown 726 (25%)	< 10 cm 754 (26%) ≥10 cm 1804 (62%) Unknown 362 (12%)	Confined to primary 558 (19%) Localised 640 (22%) Adjacent connective tissue 348 (12%) Adjacent organ/structure 1152 (40%) Unknown 222 (7%)	Yes 133 (5%) No 2396 (82%) Unknown 391 (13%)	Yes 425 (15%) No 2309 (79%) Unknown 186 (6%) Metastatic patients: 191 (45%) no treatment 147 (35%) Surgery alone 37 (9%) Surgery & Radiotherapy 43 (10%) Radiotherapy only 7 (1%) Not reported
US NCDB					
Nussbaum et al., 2016 [33] (n = 9068)	Grade 1 3351 (37%) Grade 2 1174 (13%) Grade 3 4543 (50%)	No Radiotherapy Group: Mean 16 cm (± 12.5 SD) Neo-adjuvant Radiotherapy Mean 15.4 cm (± 11.9 SD) Adjuvant Radiotherapy Mean 12.7 cm (± 11.5 SD)	Not reported [32] Ecker et al., 2016 reported adjacent organ invasion independent predictor of risk of death HR1.50 (1.25-1.81 p < 0.001)	Not reported	Excluded from study Stahl et al., 2017 [35] reported 1999 patients (15%) excluded due to metastatic disease from total 13459 patients with RPS in US NCDB
ACS NSQIP					
Park et al., 2017 [38] (n = 846)	Not reported	≤5 cm 158 (19%) 5.1–10 cm 129 (15%) > 10 cm 442 (52%) Unknown 117 (14%) No association on univariate analysis with 30-day morbidity/mortality	Not reported	Not reported	Not reported

Table 4
The reported use of radiotherapy in the treatment of primary RPS.

Study	Use of Radiotherapy		
	Neo-adjuvant Radiotherapy	Intraoperative Radiotherapy	Adjuvant Radiotherapy
SEER			
Giuliano et al., 2016 [29] (n = 2920)	All Radiation therapy (timing not specified) 756 (26%) Radiation therapy alone (no surgery) 125 (4%)		
[25] Porter et al., 2006 (n = 1654 patients undergoing surgical resection)	20 (1%)	22 (1%) Wang et al., 2016 (n = 908 patients) IORT alone 33 (4%) IORT & EBRT 32 (4%)	366 (22%)
US NCDB			
Nussbaum et al., 2016 [33] (n = 9068)	563 (6%)	Excluded from study Stahl et al., 2017 [35] IORT 57/4015 (1%)	2215 (24%)
ACS NSQIP			
Park et al., 2017 [38] (n = 846)	64 (8%)	Not recorded in any study	Not recorded in any study

IORT: Intra-operative radiotherapy. EBRT: External beam radiotherapy (peri-operative). Porter et al. is reported in this table because Giuliano et al. did not report the specific timings of the radiotherapy.

3.8. Local recurrence

No studies across the three population-based databases reported loco-regional recurrence rates [25–38].

3.9. Overall survival

Reported overall survival rates for primary RPS ranged between 52% and 62%. Giuliano et al. reported overall survival rates in *2920 patients* diagnosed with primary RPS that had varying treatment modalities (no treatment, surgery alone, radiotherapy alone and surgery & radiotherapy). The overall 5-year and 10-year survival rates in this study were 58% and 45% respectively [29].

Propensity scores were calculated for the use of neo-adjuvant and adjuvant radiotherapy and were independently matched to the surgery alone group in the Nussbaum et al. study. The 1:2 matching for neo-adjuvant radiotherapy versus surgery alone resulted in *1126 matched pairs and a sample size of 1689 patients*, whilst the 1:1 matching for adjuvant radiotherapy versus surgery alone resulted in *2196 matched pairs and a sample size of 4392 patients*. In the matched neo-adjuvant radiotherapy group versus surgery alone survival analysis, the median follow-up time was 42 months (IQR 27–70) and 43 months (IQR 25–64) respectively. The median overall survival was 110 months for the neo-adjuvant group versus 66 months in the surgery alone group ($p < 0.0001$). The 5-year overall survival rate was 62% in the neo-adjuvant radiotherapy group versus 54% in the surgery alone group (HR 0.70; 95% CI 0.59–0.82; $p < 0.0001$). In the propensity matched adjuvant radiotherapy group versus surgery alone, the median follow-up time was 54 months (IQR 32–79) and 47 months (IQR 26–72) respectively. Median overall survival was 89 months for patients in the adjuvant radiotherapy group versus 64 months in the surgery alone group ($p < 0.0001$). The 5-year overall survival rate was 60% for the adjuvant radiotherapy group and 52% for the surgery alone group (HR 0.78; 95% CI 0.71–0.85; $p < 0.0001$) [33].

Overall 5-year survival rates for R2 resections *were 24% (n = 64; based on 272 cases with available survival data)* and the median overall survival for RPS with R2 resections was 21 months [34].

Studies from the ACS NSQIP do not report overall survival rates [36–38].

3.10. Predictors of overall survival

Ten out of the 14 studies reported predictors of overall survival. No study based on the ACS NSQIP database report predictors of overall survival [36–38] as this is a database based on validated risk-adjusted 30-day peri-operative outcome data.

On multi-variate survival analysis, Giuliano et al. *(n = 2920)* showed increasing age, histological subtype, increasing tumour grade and size, local advancement of the tumour, lymph node positivity and presence of distant metastasis were associated with shorter survival time (Table 6). Operative resection was also an independent predictor of survival versus no surgery and radiation therapy was a positive predictor for survival against no radiation therapy. A combination of surgery and radiation therapy were also a positive predictor of survival versus surgery alone (TR 1.31; 95%CI 1.06–1.61; $p = 0.011$) [29].

A secondary outcome of Nussbaum et al. study *(n = 9086)* were factors associated with overall survival, which were calculated using proportional hazards models in unmatched datasets, following imputation for missing variables. The use of neo-adjuvant (HR 0.67: 95% CI 0.57–0.78; $p < 0.0001$) and adjuvant radiotherapy (HR 0.77; 95% CI 0.71–0.83; $p < 0.0001$) were independently associated with improved overall survival compared with surgery alone. Other independent

Table 5
The reported use of chemotherapy in the treatment of primary RPS.

Study	Use of Chemotherapy
SEER	
Giuliano et al., 2016 [29] (n = 2920)	Not reported No study reported Chemotherapy use (data unavailable in SEER)
US NCDB	
Nussbaum et al., 2016 [33] (n = 9068)	Not reported
Stahl et al., 2017 [35] (n = 4015)	445 (11%) patients received chemotherapy in total R0 resection (n = 2593): 258 patients (10%) received chemotherapy R1 resection (n = 1422): 187 patients (14%) received chemotherapy
Klooster et al., 2016 [34] (n = 395)	122 (31%) patients with R2 resection received chemotherapy
ACS NSQIP	
Park et al., 2017 [38] (n = 846)	39 patients (5%) received pre-operative chemotherapy

Table 6
Predictors of overall survival in RPS.

Study			
SEER			
	Predictors of Overall Survival	Multi-variate Analysis Time Ratio (95% CI)	
Giuliano et al., 2016 [29] (n = 2920)	Age	TR 0.98 (0.97–0.98) p < 0.001	
	Grade 3 or 4	TR 0.26 (0.20–0.33) p < 0.001	
	Tumour size ≥ 10 cm	TR 0.59 (0.49–0.71) p < 0.001	
	Extension to adjacent organs	TR 0.56 (0.51–0.70) p < 0.001	
	Lymph node positive	TR 0.64 (0.46–0.89) p = 0.007	
	Distant metastasis positive	TR 0.43 (0.34–0.53) p < 0.001	
	Surgery	TR 2.45 (2.02–2.98) p < 0.001	
	Radiation therapy	TR 1.34 (1.12–1.61) p = 0.001	
US NCDB			
	Predictors of Overall Survival	Neo-adjuvant radiotherapy versus surgery alone Hazard Ratios (95% CI)	Adjuvant radiotherapy versus surgery alone Hazard Ratios (95% CI)
Nussbaum et al., 2016 [33] (n = 9068)	Age per 5 years	1.15 (1.13–1.17) p < 0.0001	1.14 (1.12–1.15) p < 0.0001
	Male Sex	1.11 (1.02–1.20) p = 0.013	1.11 (1.03–1.19) p = 0.0069
	Charlson/Deyo Comorbidity Score ≥2	1.70 (1.44–2.02) p < 0.0001	1.61 (1.38–1.88) p < 0.0001
	Income above median	0.91 (0.84–0.98) p = 0.015	0.88 (0.82–0.95) p = 0.0004
	Patient insured	0.76 (0.59–0.97) p = 0.025	0.75 (0.61–0.92) p = 0.0068
	Tumour size per 5 cm	1.07 (1.05–1.08) p < 0.0001	1.06 (1.05–1.07) p < 0.0001
	Grade 3	2.16 (1.92–2.44) p < 0.0001	2.13 (1.86–2.43) p < 0.0001
	Simple surgical resection	–	1.12 (1.03–1.22) p = 0.011
	R1 resection margin	–	1.51 (1.39–1.64) p < 0.0001
ACS NSQIP			
Park et al., 2016 [38] (n = 846)	Predictors of overall survival not reported in this study Data not available from ACS NSQIP database		

predictors of overall survival were age, sex, Charlson/Deyo comorbidity score, income status, insurance status, tumour size, histological subtype and tumour grade. Extent of the surgical resection and surgical margin status were also independent predictors of overall survival (Table 6). Notably, adjuvant radiotherapy effect was not dependent on surgical margin status for overall survival (HR 0.93: 95%CI 0.79–1.10; p = 0.38).

Predictors of overall survival for RPS with R2 resections were age ≥65, histological subtype and grade of tumour [34]. Regarding overall survival in RPS with R2 resections, only poorly differentiated grade was an independent predictor of survival (HR 2.43; 95% CI 1.54–3.85; p < 0.01) [34].

4. Discussion

This systematic review identified 14 population-based studies reporting outcomes from primary RPS surgical resection. *This population-based data demonstrated relatively low overall 30-day morbidity and mortality of 23% (191/846 patients) and 3% (278/10 181 patients) respectively in patients undergoing surgical resection for primary RPS.* The reported use of peri-operative radiotherapy was variable across the studies at 28%, reflecting the inconsistent and equivocal evidence that exists currently for systemic therapy in the management of RPS. *No study reported loco-regional recurrence rates, which is a reflection of the population-based databases evaluated for outcomes for primary RPS surgical resections.* Overall reported 5-year survival ranged from 52% to 62%. Independent predictors of overall survival were age of the patient, comorbidity status, resection margin, tumour grade and size, histological subtype and receipt of radiotherapy. These predictors for overall survival are similar to other smaller studies [3,39].

There are several limitations to this study, which need to be considered. Firstly, the study is retrospective, albeit based on data collected from prospectively maintained databases. *Interpretation of these results are limited by heterogeneity, both within and between the included studies, which prevented a meta-analysis being conducted. The majority of studies reflect the large heterogeneity of the condition, featuring numerous histological subtypes, gradings and resection margins, whilst a small number focussed on smaller but more homogenous patient cohorts.* There were also large variations in treatment strategies reported across the studies, partly reflected by the paucity of therapeutic guidelines [40] and the differing treatment centres performing these cases. *Variations in definitions also existed between databases, for example surgical resection type of excision versus radical resection, so it is difficult to objectively ascertain the true extent of the resection.* There are also variations in the data collected between databases, because they have different objectives, so not all variables are available from each data set, for example the reported use of chemotherapy. *However, in the absence of randomised controlled studies, this systematic review of population-based studies provides large qualitative estimates of the clinical outcomes for the management of primary RPS.*

The serious morbidity rate of 13% *(109/846)* described by Park et al. [38] is comparable to the 16.4% from the Trans-Atlantic RPS working group, which is an international collaborative of 8 specialist sarcoma centres detailing the combined experience of 1007 patients [41]. However, 87% (876/1007) of patients underwent en-bloc resection of one or more organs[41] in this series compared with 43% *(367/846)* in the Park et al. study [38]. The 30-day mortality rate reported in this review of 3% is also comparable with other recent large studies, but these focussed predominately on multi-visceral resections [3,13,41,42] as already outlined. Maurice et al. recently evaluated the US NCDB for non-metastatic RPS cases to investigate the volume-outcome relationship in RPS surgery [43]. From the 3141 cases identified, hospital volume was an independent predictor for receiving surgical management (OR 1.91; CI 1.37–2.68; p < 0.001), a R0/R1 versus R2 resection (OR 2.47; CI 1.12–5.47; p = 0.026) and a R0 versus R1 resection (OR1.79; CI 1.30–2.46; p < 0.001). High-volume centres were significantly associated with improved surgical outcomes and suggests further centralisation of RPS care [43]. *Centralisation of services to reference centres for RPS surgery may eradicate or reduce some of the variabilities in treatment strategies highlighted by this review, as the management requires specific expertise and is advocated by other studies also* [44–50].

Locoregional recurrence was not reported in any of the 14 included

studies. The Trans-Atlantic RPS Working Group are the largest series to report recurrent RPS, with 408 patients (41%) developing local recurrence, distant metastasis or both from an initial 1007 consecutive patients with primary RPS [51]. The median follow-up after surgery from the primary tumour to local recurrence, distant metastasis or both were 76 (range 49–107), 59 (41–89) and 70 (59–104) months respectively. The 5-year overall survival for local recurrence, distant metastasis or both were 29%, 20% and 14% respectively. Predictors of overall survival after local recurrence were the time interval to local recurrence and resection of local recurrence, whilst predictors for distant metastasis were time interval and histological subtype [51]. Local control might also be optimised further by the use of pre-operative radiotherapy [51]. The Trans-Atlantic Retroperitoneal Sarcoma Working Group aims to develop consensus treatment standards based on the strength of available evidence. With the paucity of supporting data, the 2015 consensus approach established that post-operative radiotherapy is of "no study-proven value" and that pre-operative radiotherapy should only "be considered after careful review by a multi-disciplinary sarcoma tumour board"[40]. However, there is growing evidence from more recent non-randomised observational studies, included in this review, supporting the use of perioperative radiotherapy [32,33] and a recent meta-analysis [52]. This hypothesis is being evaluated in Europe with an ongoing multicentre randomised controlled trial assessing pre-operative radiotherapy versus resection alone for primary RPS (EORTC 62092-22092; NCT01344018), but has not completed recruiting at present [53]. The use of pre-operative radiotherapy is advantageous because the tumour provides a defined target area and avoid unnecessary irradiation of normal tissue and may also improve surgical margin negative resection [6,54].

This review highlights the importance of an individualised discussion and treatment plan for patients with primary RPS. The morbidity and mortality associated with surgical resection remains significant, which increases with the complexity of resection, with multi-visceral resection being an independent predictor of morbidity and this also has been demonstrated by an association of weighted organ score and severe adverse events in other studies [13,41]. Elderly patients, male sex and a Charlson/Deyo comorbidity score ≥ 2 are also associated with poorer outcomes and patients must be counselled accordingly when considering surgical intervention. Furthermore, thoughtful consideration of the relative risks involved in achieving local control in the context of overall tumour extent and anticipated disease biology is required [40], particularly as resection margin, tumour grade and histological subtype are independent predictors for overall survival. The choice of treatment strategies should be tailored to the specific histology [44]. Finally, there is limited evidence regarding long-term functional outcomes following primary RPS resections, with sparse quality of life data [55], which should also be highlighted when counselling patients regarding treatment options.

To our knowledge, this systematic review is the first attempt to pool the data from nationally registered databases on this rare, but important condition, to assess surgical outcomes, use of systemic therapies, overall survival and predictors of survival. The majority of previous studies are single-centre or small collaborative data, which have their own inherent biases. This study provides an important and necessary summary of the current data, enabling clinicians to better inform patients of the potential short and long-term outcomes in the management of primary RPS.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.03.002.

Appendix 1

Ovid MEDLINE/PubMed/EMBASE/Cochrane search strategy

1	retroperitoneal sarcoma*.mp.
2	malignant neoplasm*.mp.
3	retroperitoneal.mp.
4	abdominopelvic.mp.
5	3 or 4
6	2 and 5
7	1 or 6
8	post?op* or morbidity or mortality or illness or death or complication* or retrospective follow up.mp.
9	morbidity.mp.
10	mortality.mp.
11	illness.mp.
12	death.mp.
13	complication*.mp.
14	retrospective follow up.mp.
15	8 or 9 or 10 or 11 or 12 or 13 or 14
16	surgery.mp.
17	15 and 16
18	7 and 17

Ovid MEDLINE MeSH search

1	exp Soft Tissue Neoplasms/or exp Sarcoma/or exp Retroperitoneal Neoplasms/or exp Leiomyosarcoma/or exp Liposarcoma/
2	exp Retroperitoneal Space/
3	exp Mortality/
4	1 and 2 and 3

Appendix 2. Inclusion & Exclusion Criteria

Study	Inclusion Criteria	Exclusion Criteria
Porter et al., 2006 [26]	All patients with primary RPS ICD-O-2 coding	Age < 18
Nathan et al., 2009 [26]	Surgical resection of primary RPS Curative intent ICD-O-3 coding	Biopsies & local ablative therapies
Tseng et al., 2011 [27,36]	Surgical therapy of RPS ICD-O-3 coding	Age < 18 Metastatic disease Non-surgical patients Cases identified by death certificate or autopsy alone
Bates et al., 2015	Surgical resection of primary RPS High grade Non-metastatic ICD-O-3 coding Known post-operative Radiotherapy status	Age < 18 Rhabdomyosarcoma, adenosarcomas Incomplete diagnostic/treatment data Non-surgical patients Preop RT & IORT
Giuliano et al., 2016 [29]	All patients with primary RPS ICD-O-3 coding	Not recorded
Wang et al., 2017 [30]	Surgical resection of RPS & Intraoperative radiotherapy and/or External Beam Radiotherapy Site specific and histology coding	Surgical resection of RPS & no RT therapy
Kashtan et al., 2016 [31]	All patients with primary retroperitoneal rhabdomyosarcoma ICD-O-3 coding	Not recorded
Ecker et al., 2016 [32]	Surgical resection of Primary retroperitoneal liposarcoma Non-metastatic Curative intent ICD-O-3 coding	Age < 18 Surgery not performed Palliative resection No preop radiotherapy but received IORT or postoperative RT, < 45GY preop therapy, palliative radiation therapy
Nussbaum et al., 2016 [33]	Surgical therapy of Primary RPS Non-metastatic Known radiotherapy status ICD-O-3 coding	Age < 18 Intraoperative radiotherapy Pre and post-operative radiotherapy received Unknown facility type Unknown time to surgery Surgery > 30 weeks from diagnosis Radiotherapy > 37 weeks after surgery Death within 30-days
Klooster et al., 2016 [34]	Surgical resection of Primary RPS with R2 margins ICD-O-3 coding	R0 or R1 margins Resection margin unavailable
Stahl et al., 2017 [35]	Surgical resection of Primary RPS with R0 or R1 margins International classification of diseases for oncology 3rd edition(ICD-O-3) coding	Age < 18 Prior cancer diagnosis Metastatic RPS Surgery not performed R0/R1 resection margin not available Diagnosis in 2012 (insufficient follow-up)
Tseng et al., 2011 [27,36]	Surgical resection of Primary RPS CPT and ICD-9 coding	None recorded
Bartlett et al., 2014 [37]	Surgical resection of Primary RPS CPT and ICD-9 coding	None recorded
Park et al., 2017 [38]	Surgical resection of Primary RPS Current procedural terminology (CPT) & International classification of disease (ICD-9) coding	Beyond 2012 ≥1 missing variable from mFI

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