A systematic review of margin status in retroperitoneal liposarcomas: Does the R0 margin matter?

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Retroperitoneal liposarcomas (RPLPSs) are a rare tumor group for which current guidelines recommend aggressive en bloc resection to attain microscopically negative (R0) margins. To ensure R0 margins, resection of adherent or adjacent organs is often required. However, it is still unclear if R0 margins confer any additional benefit to patients over a grossly negative but microscopically positive (R1) margin. We performed a systematic search of PubMed and Embase databases for studies including patients receiving R0 or R1 resection for RPLPS. Nine retrospective cohort studies, one prospective cohort study, and 49 case reports/case series were included. A total of 552 patients with RPLPS were evaluated: 346 underwent R0 resection and 206 underwent R1 resection. In the R0 group, 5-year overall survival (OS) ranged from 58.3% to 85.7%; local recurrence (LR) ranged from 45.5% to 52.3%. In the R1 group, 5-year OS ranged from 35% to 55.3%; LR ranged from 66.7% to 91.7%. Among cohort studies, OS, disease-free survival (DFS), LR rate, and LR-free survival (LRFS) were significantly associated with R0 resections. Assessment of case series and reports suggested that the R0 margin led to a slightly higher morbidity than that of R1. In conclusion, this review found the R0 margin to be associated with reductions in LR rates and improved OS when compared with the R1 margins, though accompanied by slight increases in morbidity. The roles of tumor histotype and perioperative chemotherapy or radiotherapy were not well-elucidated in this review.

KEYWORDS

liposarcoma, margin, retroperitoneal, sarcoma, R0
1 Introduction

Retroperitoneal soft tissue sarcomas are uncommon and affect less than 0.1% of the population (1). Among them, a multitude of histological subtypes exist, with liposarcomas (LPSs) representing the most common histotype (2). Favorable survival profiles and lower propensity for distant metastases in LPS, especially in the well-differentiated (WDLPS) and low-grade dedifferentiated (DDLPS) patients (3), have generated great interest among sarcoma surgeons. For once, when tumor biology is “favorable,” the surgeon is now at the helm to possibly dictate patient outcomes via strategies to lower local recurrence (LR) rates.

Up-front extended resection (ER) to achieve microscopically clear (R0) margins was introduced by Gronchi et al. (4) and has been shown to significantly lower rates of LR with acceptable morbidity and mortality profile. While adopted by most of Europe and the Trans-Atlantic group (TARPSWG) (5), differing opinions continue to exist regarding the utility of such an aggressive surgical approach in the management of retroperitoneal sarcomas (RPS). Few would argue for the preservation of involved or encased organs; as such, the debate lies mainly in the en bloc removal of adherent or adjacent organs in which the suspicion of histological invasion is low (6, 7).

The addition of perioperative radiation therapy (RT) to the armamentarium of tools aimed at minimizing LR rates further adds complexity to the subject matter (8). It is unknown if a planned R1 (microscopically positive) margin in the context of neoadjuvant RT is of equivalence to the R0 margin. In the subset of patients with LPS, however, exploratory analysis from the STRASS trial appears to suggest a potential benefit of preoperative RT (9).

To date, data on the optimal surgical margins in retroperitoneal LPS (RPLPS) have been limited to retrospective cohort studies or case series/reports. As such, our study aims to provide a summative analysis on patients with RPLPS in an attempt to shed light on the effects of margins status, RT, chemotherapy (CT), and histotype on survival and recurrence outcomes.

2 Materials and methods

A literature search of PubMed, OvidSP, Embase, and Cochrane databases was conducted for studies reporting on the surgical management of RPLPS up to March 2020. The medical search headings (MeSH) “retroperitoneal liposarcoma,” “well-differentiated liposarcoma,” “de-differentiated liposarcoma,” “R0,” “R1,” “resection,” “extended resection,” “microscopic,” and “margin” were used. Additional relevant studies were identified by screening the references cited in shortlisted articles. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1) (10).

2.1 Criteria for inclusion of study

Articles were included if they 1) were original articles published in English in peer-reviewed journals; 2) included patients with RPLPS identified via imaging modalities such as computed tomography or magnetic resonance imaging scans; 3) included patients with biopsy-proven RPLPS; 4) unambiguously reported margin status, patient survival, and morbidity outcomes.

Articles were excluded if they 1) did not report the margin status of the resections; 2) included patients presenting with metastatic disease at initial diagnosis; 3) reported all outcomes for R0 and R1 resections collectively. Studies that presented data on RPS patients with other non-LPS histotypes were included only if data of patients with RPLPS could be extracted independently. For example, the retrospective cohort study of RPS patients from the Memorial Sloan-Kettering Cancer Center could not be included because survival and recurrence data for R1 or R0 resections were merged with other non-LPS histotypes (11). Similarly, the TARPSWG 2020 study evaluating a large cohort of RPS patients was excluded, as outcomes for R1 and R0 resections were reported together (12).

2.2 Data extraction and analysis

Data were extracted using standardized forms, which recorded patient and study characteristics, the radicality of resection performed (R0 or R1), histologic subtype (well-differentiated, dedifferentiated, pleomorphic, or myxoid), tumor grade (FNCLCC), postoperative morbidity and mortality, the use of neoadjuvant and/or adjuvant chemotherapy (CT) or radiotherapy (RT), number of additional organs removed and other perioperative outcomes, by two independent reviewers. Where appropriate, data that were reported for R0 and R1 collectively were extracted but were not considered in further analysis.

All studies were assessed for their level of evidence using the Oxford Centre for Evidence-Based Medicine Levels of Evidence (13). The authors elected to perform a descriptive review of the data as opposed to a meta-analysis due to the heterogeneity of the studies assessed.

2.3 Definitions

In accordance with residual tumor classification (R-classification) guidelines laid out by the American Joint Committee on Cancer (AJCC), an R1 resection was defined as microscopic tumor cells present at the border of the specimen, while an R0 resection was defined as the absence of tumor cells at the inked resection surface (14).
An "R+1" margin was defined as having >1 mm of normal tissue between the tumor and the inked resection margin (15).

3 Results

The search identified 59 relevant articles published between 1996 and 2019 (Tables 1A, B).

3.1 Quality of evidence

3.1.1 R0-margin resection

A total of 52 studies reported on the outcomes of RPLPS patients who received R0 resection (Tables 2A, 3A).

Eight were retrospective cohort studies evaluating the relationship between margin status and recurrence and survival outcomes (16–23). R0-margin patients receiving adjuvant or neoadjuvant CT/RT were included in these studies, but data on their recurrence and survival outcomes were reported together with R1-margin patients and hence could not be extracted. Of note, three studies (16, 20, 21) adopted the stricter R+1 margin classification system that classifies margins as R0 only if the resection margins are surrounded by >1 mm of tumor-negative tissue.

Of the remaining 44 studies, 4 were case series (26–29) and 40 were case reports (30–69), both documenting the recurrence and survival outcomes of RPLPS patients receiving R0-margin resection for RPLPS.

3.1.2 R1-margin resection

A total of 16 studies reported on the outcomes of RPLPS patients who received R1 resection (Tables 2B, 3B). R1-margin patients receiving adjuvant or neoadjuvant CT/RT were included in these studies, but data on their recurrence and survival outcomes were reported together with R0-margin patients and hence could not be extracted.

Ten were retrospective cohort studies evaluating the relationship between margin status (R0/R1) with recurrence and survival outcomes (16–25). One study (19) was a prospective cohort study examining the effect of preoperative irradiation by high-dose helical tomotherapy with a total dose of 54 Gy over 30 fractions.

Of the remaining six studies, one was a retrospective case series (26) and five were case reports (70–74), both documenting

### TABLE 1A List of cohort studies reporting on retroperitoneal liposarcomas.

| Study | Year | Design       | Study Duration | Level of Evidence | R0 | R1 | Outcomes reported                                                                                   | Description |
|-------|------|--------------|----------------|-------------------|----|----|---------------------------------------------------------------------------------------------------|-------------|
| Sanchez-Hidalgo et al. (16) | 2018 | Cohort study | 2004-2015       | 2b                | 27 | 8  | DFS, OS, early (<12 mo) recurrence, late (>12 mo) recurrence                                      | Analyses influence of tumor size, stage, grade, histology, contiguous resection, BMI, age and adjuvant therapy on OS and DFS. |
| Nathenson et al. (17)       | 2018 | Cohort study | 2000-2013       | 2b                | 12 | 11 | PFS, OS                                                                                           | Analyses influence of tumor size, stage, grade and histology and margin on OS and PFS. |
| Zhao et al. (18)            | 2015 | Cohort study | 2000-2007       | 2b                | 39 | 22 | OS                                                                                               | Analyses the prognostic factors of postoperative outcomes. Margin status, tumor grade, ascites, postop metastasis and age were significant predictors of OS. |
| Sargos et al. (19)          | 2012 | Cohort study | 2007-2008       | 2b                | 4  | 4  | RR, DFS, OS, OS*                                                                                  | Case series documenting the effect of pre-op tomotherapy on RPLPS patients. |
| Lee et al. (20)             | 2011 | Cohort study | 1990-2005       | 2b                | 11 | 10 | OS, DFS, mortality*                                                                               | Analyses influence of tumor size, grade, histology, margin status, and age on OS and DFS. |
| Milone et al. (21)          | 2011 | Cohort study | 1990-2011       | 2b                | 21 | 6  | OS, LRFS, RR                                                                                      | Case series documenting the overall survival and recurrence rate for R0 and R1 |
| Singer et al. (22)          | 2003 | Cohort study | 1982-2001       | 2b                | 77 | 66 | DSS, LRFS, DRFS                                                                                  | Analyses factors predicting recurrence patterns and OS. De-differentiated histology and the need for contiguous organ resection increases risk for LR, margin is prognostic for survival. |
| Linehan et al. (23)         | 2000 | Cohort study | 1982-1998       | 2b                | 105| 54 | DSS, LR, DR*                                                                                     | Analyses influence of anatomic site, margin status, tumor size and grade on LR and DSS. |
| Wu et al. (24)              | 2018 | Cohort study | 2005-2015       | 2b                | 15 | 15 | DSS, LR*                                                                                          | Assesses the utility of vimentin and Ki-67 as prognostic biomarkers. R1 margins were not a prognostic factor for DSS, while gross margins were. |
| Rhu et al. (25)             | 2017 | Cohort study | 1998-2016       | 2b                | 6  | 6  | OS, DFS                                                                                          | Reports the influence of tumor grade and histology, sex, age, margin status, adjuvant therapy on OS and DFS, and compares the postop outcomes of RPLPS and inguinoscrotal LPS. |

BMI, body mass index; DFS, disease-free survival; DR, distant recurrence; DRFS, distant recurrence-free survival; DSS, disease specific survival; LR, local recurrence; LRFS, local recurrence-free survival; LPS, liposarcoma; OS, overall survival; PFS, progression-free survival; DFS, disease-free survival; RPLPS, retroperitoneal liposarcoma; RR, recurrence rate.

*Outcomes were collectively reported for R0/R1.
| Study                      | Year | Margin status | Description                                                                                                                                                                                                 |
|----------------------------|------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fernandez-Ruiz et al. (26) | 2010 | 4 R0          | Case series documenting the evolution of RPLPS patients                                                                                                                                                     |
| Han et al. (27)            | 2010 | 2 R0          | Case series of 1) RPLPS abutting the left kidney and adrenal gland removed via en bloc resection with removal of those organs; 2) RPLPS encausing left kidney removed via en bloc resection with nephrectomy |
| Crisan et al. (28)         | 2015 | 2 R0          | Case report of 2 patients with primary LPS of the kidney. Patient 1 is a 65 y/o man with a giant RPLPS occupying the right hemi-abdomen and compressing various abdominal organs but treated with organ-sparing complete resection of tumor. Patient 2 is a 70 y/o man with LPS in the right perirenal area displacing the right kidney and colon toward the midline, treated by en bloc excision together with kidney. |
| Daldoul et al. (29)        | 2017 | 2 R0          | Case series of 1) a giant RPLPS with colonic involvement removed by hemicolectomy and nephrectomy; and 2) a giant RPLPS removed by R0 resection with nephrectomy                                                   |
| Yaman (30)                 | 1996 | R0            | Case report of RPLPS removed via complete resection with nephrectomy                                                                                                                                         |
| Susini et al. (31)         | 2000 | R0            | Case report of a 27 y/o pregnant woman with RPLPS extending from the left adnexa to the epigastric region but removed sparing the left ovary, uterus, and right adnexa                                               |
| Sener et al. (32)          | 2004 | R0            | Case report of a 44 y/o woman with 2.0 cm cystic mass abutting the right kidney, treated by radical nephrectomy, adrenalectomy, and en bloc resection of the tumor.                                                                            |
| Mehrotra et al. (33)       | 2006 | R0            | Case report of giant inflammatory RPLPS abutting the left kidney and pushing the IVC, aorta, and the left ureter                                                                                               |
| Calé et al. (34)           | 2007 | R0            | Case report of primary mesenteric LPS removed without intestinal resection or small bowel devascularization                                                                                                 |
| Gaston et al. (35)         | 2007 | R0            | Case report of a patient whose kidney was encased by RPLPS and extended into the diaphragm, treated with en bloc resection with partial diaphragmatic resection                                                        |
| Gupta and Yadav (36)       | 2007 | R0            | Case report of a patient with RPLPS invading the kidney, treated by complete resection of the tumor with wedge resection of the renal parenchyma. (This is a case series of 2 patients but only 1 had margin specified)         |
| Perez-Ponce et al. (37)    | 2008 | R0            | Case report of RPLPS with paravertebral involvement removed via en bloc resection                                                                                                                          |
| Yildirim et al. (38)       | 2008 | R0            | Case report of a 61 y/o man with RPLPS filling the pelvic cavity and extending to the epigastric region displacing intestines and pancreas, treated by organ-sparing complete excision.                                         |
| Benseler et al. (39)       | 2009 | R0            | Case report of RPLPS removed via en bloc resection including the left kidney and descending colon                                                                                                           |
| Goertz et al. (40)         | 2009 | R0            | Case report of RPLPS dimensions 45 cm × 35 cm × 19 cm and weighed 15.5 kg, resected via en bloc resection with partial diaphragmatic resection                                                               |
| Salemis et al. (41)        | 2011 | R0            | Case report of a 73 y/o man with RPLPS extending into the thigh                                                                                                                                             |
| Coleblunders et al. (42)   | 2011 | R0            | Case report of recurrent RPLPS invading the thoracoabdominal wall but sparing the peritoneum, treated by an en bloc wide margin excision caudally down to the iliohypogastric muscle and cranially up to the left adrenal. |
| Makni et al. (43)          | 2012 | R0            | Case report of a 60 y/o man with primary RPLPS extending from the epigastrum to the pelvic region, treated with complete but organ-sparing resection. (This paper is actually a case series, but only 1 case had sufficient data suitable for review) |
| Bansal et al. (44)         | 2013 | R0            | Case report of giant RPLPS with adherent ileum and ureter removed by wide excision along with ileum and ureter                                                                                              |
| Sharma et al. (45)         | 2013 | R0            | Case report of inflammatory WD RPLPS removed by wide excision                                                                                                                                             |
| Nagy et al. (46)           | 2013 | R0            | Case report of recurrent RPLPS displacing the left kidney. Although the RPLPS recurred multiple times, only the results from the resection of the primary tumor are presented in this review.              |
| Hoshi et al. (47)          | 2014 | R0            | Case report of recurrent RPLPS removed via complete resection with partial nephrectomy                                                                                                                    |
| Caizzone et al. (48)       | 2015 | R0            | Case report of a huge RPLPS involving the vena cava and iliac vessels removed via en bloc resection with nephrectomy                                                                                         |
| Kasahima et al. (49)       | 2015 | R0            | Case report of a 34 y/o woman with RPLPS after first delivery                                                                                                                                              |
| Reznichenko (50)           | 2016 | R0            | Case report of giant RPLPS involving small bowel and mesentery removed by en bloc resection with small intestine                                                                                            |
| Kobyashi et al. (51)       | 2016 | R0            | Case report of recurrent RPLPS managed via re-resection                                                                                                                                                   |
| Machado et al. (52)        | 2016 | R0            | Case report of DDLPS of the pancreas treated with distal pancreatectomy with splenectomy and regional lymphadenectomy.                                                                                |

(Continued)
the recurrence and survival outcomes of RPLPS patients receiving R1-margin resection for RPLPS.

In total, our systematic review evaluated a total of 552 patients with RPLPS of whom 346 underwent R0-margin resection and 206 underwent R1-margin resection.

### 3.2 Outcomes of the R0 margin for retroperitoneal liposarcoma (RPLPS)

A total of 346 patients achieved R0 resections, of whom 296 patients came from cohort studies and 50 from case series/case reports.

#### 3.2.1 Cohort studies (R0)

A total of 296 patients from eight cohort studies received R0-margin resection (Table 2A). The rates of LR ranged from 45.5% to 52.3%. The 3-year OS and DFS ranged from 87% to 87.5% and 22.2% to 62.5%, respectively. The 5-year OS ranged from 58.3% to 85.7%. From the study by Sargos et al. (19), the recurrence rate among R0-margin patients who received preoperative RT was 0%.

Due to the heterogeneity of the data, there is little basis for comparison between studies that adopted an “R+1” margin definition (16, 20, 22) vs. studies using the “R” margin
3.2.2 Case series and case reports (R0)

A total of 50 patients from 44 case series/case reports received R0-margin resection. The data extracted from the case series and case reports for RPLPS patients receiving R0 resection are shown in Table 3A and are summarized as follows. The median follow-up duration was 22 months. The histological distribution was as follows: 58% WDLPS (n = 29), 20% DDLPS (n = 10), 10% myxoid (n = 5), 6% pleomorphic (n = 3), and 6% mixed or unreported (n = 3). Moreover, 32% (n = 16) of tumors were low-grade (G1), 12% (n = 5) were high-grade (G2/G3), and 56% (n = 28) did not report tumor grade. In addition, 54% of patients (n = 27) received multivisceral resection, of whom 28% (n = 14) of patients had one additional organ resected, 24% (n = 12) had two additional organs resected, and 2% (n = 1) had five additional organs resected. The most common organ removed was the kidney (78%, n = 21) followed by the adrenal gland (15%, n = 4), diaphragm (11%, n = 3), colon (8%, n = 2), and pancreas (8%, n = 2). Regarding adjuvant CT and RT, 32% (n = 16) of tumors were low-grade (G1), 12% (n = 5) were high-grade (G2/G3), and 56% (n = 28) did not report tumor grade.

3.2.2.1 Comparing well-differentiated liposarcoma (WDLPS) vs. dedifferentiated liposarcoma (DDLPS) Patients (R0)

LR among WDLPS patients was 24% (n = 7/29) while that among DDLPS patients was 40% (n = 4/10).

3.2.2.2 Comparing outcomes of adjuvant chemotherapy (CT) radiotherapy (RT) vs. no CT/RT (R0)

LR among patients who received no CT or RT, only adjuvant CT, only adjuvant RT, and adjuvant CT and RT was 31% (n = 14), 50% (n = 5), 50% (n = 1), and 0% (n = 0), respectively.

### Table 2A: Summary of cohort studies which included patients receiving R0-margin resection.

| Study                  | Year | No. cases | CT/RT      | Post-op Morbidity | OS                  | DFS                  | LRFS                 | RR                   | Margin definition in study |
|------------------------|------|-----------|------------|-------------------|---------------------|----------------------|----------------------|------------------------|-----------------------------|
| Sanchez-Hidalgo et al. (16) | 2018 | 27        | Unable to extract | Clavien-Dindo ≥ III: 17.1% | Median: 93 mos (95%CI: 44-141) | 1-yr: 81% | 3-year: 22.2% | Median: 22 mos | Early recurrence (<12mos) = 45.5% | R+1                        |
| Nathenson et al. (17)   | 2018 | 12        | Adjuvant CT: n=1 | Adjuvant/neoadjuvant RT: n=10 | NR | 2-yr: 100% | 2-yr: 62% | NR | LR: 50% | R                        |
| Zhao et al. (18)        | 2015 | 39        | Intraop RT: n=2 | adjoint CT: n=7 | adjoint CT+RT: n=11 | 0% | Median: 114 mos | NR | NR | RR: 59/61 | R                        |
| Sargos et al. (19)      | 2012 | 4         | Neoadjuvant RT | Unable to extract | Unable to extract | NR | NR | 0% | R                          |
| Lee et al. (20)         | 2011 | 11        | NR         | 28.6% | 3-yr: 87.5% | 3-yr: 58.3% | NR | 52% | R+1                       |
| Milone et al. (21)      | 2011 | 21        | NR         | 0% | 5-yr: 85.7% | NR | NR | 52.3% | R                        |
| Singer et al. (22)      | 2003 | 77        | CT 0%      | NR | 3-yr: 87% | NR | 3-yr: 55% | 50% | R+1                       |
| Linehan et al. (23)     | 2000 | 105       | NR         | NR | 5-yr: 65% | NR | 5-yr: 42% | 25% | R                        |

CT, chemotherapy; DFS, disease-free survival; LR, local recurrence; LRFS, local recurrence-free survival; RR, not reported; OS, overall survival; CI, confidence interval.

* reported collectively for R0/R1.

** reported collectively for R1/R2.

** reported collectively for R0/R1/R2.

** reported collectively with RPLPS of the extremity and trunk.
3.3 Outcomes of the R1 margin for retroperitoneal liposarcoma (RPLPS)

A total of 206 patients in this review received resections leading to an R1 margin, of whom 196 patients came from cohort studies and 10 from case series or case reports.

3.3.1 Cohort studies (R1)

A total of 196 patients from 10 cohort studies received R1-margin resection. The rates of LR ranged from 66.7% to 91.7% (Table 2B). The 3-year OS ranged from 70% to 88.9%. The 5-year OS ranged from 35% to 55.3%. The 3-year LRFS was 50%, and the 5-year LRFS was 47%.

Due to the heterogeneity of the data, there is little basis for comparison between studies that adopted an “R+1” margin definition (16, 20, 22) vs. studies using the “R” margin definition.

3.3.2 Case series and case reports (R1)

A total of 10 patients from six case series/case reports received R1-margin resection. The data extracted from the case series and case reports for RPLPS patients receiving R1 resection are shown in Table 3B and are summarized as follows.

The median follow-up duration was 15.5 months. The histological distribution was as follows: 30% WDLPS (n = 3), 50% DDLPS (n = 5), 10% myxoid (n = 1), and 10% unreported (n = 1). In addition, 20% (n = 2) of tumors were low-grade (G1) and 70% (n = 7) were high-grade (G2/G3), with 10% (n = 1) unreported grade. Moreover, 70% of patients (n = 7) received multivisceral organ resection, of whom 20% (n = 2) had one additional organ resected, 30% (n = 3) had two additional organs resected, 10% (n = 1) had four additional organs resected, and 10% (n = 1) had six additional organs resected. Of the patients who received multivisceral resection, the most common organ...
TABLE 3A Summary of 4 case series and 40 case reports which included patients receiving R0-margin resection.

| First Author | Year | Histology (FNCLCC) | Grade | CT/RT | Post-op Mortality reported | Clavien-Dindo Grade | Additional organs removed | No. of organs removed | Recurrence at last followup (Yes/No) | Follow-up duration | Patient alive at last followup? |
|--------------|------|---------------------|-------|-------|-----------------------------|---------------------|--------------------------|----------------------|--------------------------------------|-------------------|-------------------------------|
| Fernandez-Ruiz et al. (26) | 2010 | WDLPS 1 | none given | No | NA | None | 0 | No | 50.4mo | Yes |
| Han et al. (27) | 2010 | WDLPS NR | none given | No | NA | kidney, adrenal gland | 2 | No | 1.5y | Yes |
| Crisan et al. (26) | 2015 | Myxoid 2 | Adjuvant CT | No | NA | kidney | 1 | No | 3y | Yes |
| Daldoul et al. (29) | 2017 | DDLPS NR | none given | No | NA | kidney | 1 | Yes | 3 y | Yes |
| Yaman (30) | 1996 | WDLPS NR | none given | No | NA | kidney | 1 | No | 42 mo | Yes |
| Susini et al. (31) | 2000 | WDLPS NR | none given | No | NA | fallopian tube | 1 | No | 2y | Yes |
| Sener et al. (32) | 2004 | WDLPS 1 | none given | No | NA | kidney, adrenal gland | 2 | No | 12mo | Yes |
| Mehrotra et al. (33) | 2006 | WDLPS NR | none given | No | NA | None | 0 | No | 24 mo | Yes |
| Calo et al. (34) | 2007 | WDLPS NR | Adjuvant CT | No | NA | None | 0 | No | 33 mo | Yes |
| Gaston et al. (35) | 2007 | NR 1 | none given | No | NA | left hemidiaphragm | 1 | No | 22mo | Yes |
| Gupta and Yadav (36) | 2007 | WDLPS NR | none given | No | NA | None | 0 | No | 6mo | Yes |
| Perez-Ponce et al. (37) | 2008 | WDLPS low | none given | No | NA | kidney, ureter | 2 | No | 7y | Yes |

(Continued)
| First Author et al. | Year | Histology | Grade (FNCLCC) | CT/RT | Post-op Mortality reported | Clavien-Dindo Grade | Additional organs removed | No. of organs removed | Recurrence at last followup (Yes/No) | Follow-up duration | Patient alive at last followup? |
|---------------------|------|-----------|----------------|-------|-----------------------------|---------------------|--------------------------|------------------------|--------------------------------------|------------------|-----------------------------|
| Yildirim et al. (38) | 2008 | WDLPS     | NR             | none given | No                           | NA                  | None                     | 0                      | No                                   | 3mo              | Yes                         |
| Benseler et al. (39) | 2009 | WDLPS     | I              | none given | No                           | NA                  | kidney, descending colon | 2                      | Yes                                  | 10y              | Yes                         |
| Goertz et al. (40)  | 2009 | WDLPS     | NR             | none given | No                           | NA                  | None                     | 0                      | Yes                                  | 2y               | No (died of disease)       |
| Salemis et al. (41) | 2011 | WDLPS     | NR             | none given | No                           | NA                  | None                     | 0                      | No                                   | 18mo             | Yes                         |
| Coleblanders et al. (42) | 2011 | DDLPS     | NR             | none given | No                           | NA                  | diaphragm, iliopsoas muscle | 2                      | Yes                                  | 7mo              | Yes                         |
| Makni et al. (43)   | 2012 | DDLPS     | NR             | none given | No                           | NA                  | ileum, ureter            | 2                      | Yes                                  | 1.5y             | Yes                         |
| Bansal et al. (44)  | 2013 | Mixed     | NR             | none given | No                           | NA                  | none                     | 0                      | No                                   | 63mo             | Yes                         |
| Sharma et al. (45)  | 2013 | WDLPS     | NR             | none given | No                           | NA                  | none                     | 0                      | No                                   | 6m               | Yes                         |
| Nagy et al. (46)    | 2013 | DDLPS     | low            | none given | No                           | NA                  | kidney                   | 1                      | Yes                                  | 8mo              | Yes                         |
| Hoshi et al. (47)   | 2014 | WDLPS     | NR             | none given | No                           | NA                  | kidney                   | 1                      | No                                   | 10y              | Yes                         |
| Caizzone et al. (48) | 2015 | Pleomorphic | NR             | none given | No                           | NA                  | kidney                   | 1                      | No                                   | 24mo             | Yes                         |
| Kasashima et al. (49) | 2015 | WDLPS     | NR             | none given | No                           | NA                  | kidney, adrenal gland    | 2                      | No                                   | 3y               | Yes                         |
| Reznichenko et al. (50) | 2016 | Myxoid     | NR             | none given | No                           | NA                  | small intestine, kidney  | 2                      | Yes                                  | 7y               | Yes                         |
| Kobayashi et al. (51) | 2016 | DDLPS     | high           | none given | No                           | Grade III           | None                     | 0                      | Yes                                  | 4y               | Yes                         |
| Machado et al. (52) | 2016 | DDLPS     | high           | adjuvant CT,RT | No | NA                  | pancreas, spleen         | 2                      | No                                   | 5y               | Yes                         |
| Zeng et al. (53)    | 2017 | WDLPS     | I              | adjuvant RT | No                           | Grade IV            | None                     | 0                      | No                                   | 8mo              | Yes                         |
| Tsiao et al. (54)   | 2017 | NR        | low            | none given | No                           | Grade III           | none                     | 0                      | No                                   | 6m               | Yes                         |
| Singal et al. (55)  | 2018 | Myxoid     | NR             | none given | No                           | NA                  | none                     | 0                      | Yes                                  | 16mo             | Yes                         |

(Continued)
| First Author                  | Year | Histology | Grade (FNCLCC) | CT/RT | Post-op Mortality reported | Clavien-Dindo Grade | Additional organs removed | No. of organs removed | Recurrence at last followup (Yes/No) | Follow-up duration | Patient alive at last followup? |
|------------------------------|------|-----------|----------------|-------|---------------------------|---------------------|--------------------------|----------------------|-------------------------------------|-------------------|-------------------------------|
| Ioannidis et al. (56)        | 2018 | WDLPS     | NR             | none given | No                       | NA                  | None                     | 0                    | No                                  | 4 y               | Yes                           |
| Agrusa et al. (57)           | 2019 | DDLPS     | NR             | none given | No                       | NA                  | kidney, adrenal gland   | 2                    | No                                  | 12 mo             | Yes                           |
| Argadjendra et al. (58)      | 2019 | WDLPS     | NR             | none given | No                       | NA                  | None                     | 0                    | No                                  | 12 mo             | Yes                           |
| Huo et al. (59)              | 2015 | Myxoid    | low            | none given | No                       | NA                  | None                     | 0                    | No                                  | 6 mo              | Yes                           |
| Clar et al. (60)             | 2009 | WDLPS     | 1              | none given | No                       | Grade I             | kidney                   | 1                    | No                                  | 3 y               | Yes                           |
| Hashimoto et al. (61)        | 2010 | DDLPS     | 2              | none given | No                       | NA                  | kidney                   | 1                    | No                                  | 12mo              | Yes                           |
| Akhoondinasab and Omranifar (62) | 2011 | WDLPS     | 1              | none given | No                       | Grade I             | None                     | 0                    | Yes                                 | 2y                | Yes                           |
| Bhat et al. (63)             | 2013 | WDLPS     | NR             | none given | No                       | NA                  | None                     | 0                    | No                                  | 8 mo              | Yes                           |
| Oh et al. (64)               | 2016 | WDLPS     | 1              | none given | No                       | NA                  | None                     | 0                    | Yes                                 | 28 mo             | Yes                           |
| Tanaka et al. (65)           | 2017 | DDLPS     | NR             | none given | No                       | NA                  | kidney, head of pancreas, duodenum, IVC, abdominal aorta | 5                    | No                                  | 16 mo             | Yes                           |
| Abufkaidaand Alsalamneh (66) | 2019 | WDLPS     | low            | none given | No                       | NA                  | none                     | 0                    | Yes                                 | 22 mo             | Yes                           |
| Montenegro et al. (67)       | 2019 | Pleomorphic | NR             | none given | No                       | NA                  | kidney, spleen           | 2                    | No                                  | 6 mo              | Yes                           |
| Herzberg et al. (68)         | 2019 | DDLPS     | low            | none given | No                       | NA                  | kidney, part of diaphragm | 2                    | No                                  | 2 y               | Yes                           |
| Yang et al. (69)             | 2016 | WDLPS     | NR             | adjuvant CT, RT | No                       | NA                  | None                     | 0                    | No                                  | 6 mo              | Yes                           |

All time-points are taken with respect to the date of initial operation.
CT, chemotherapy; DDLPS, dedifferentiated liposarcoma; DM, distant metastasis; LR, local recurrence; MO, months; NA, not applicable NR, not reported; RT, radiotherapy; WDLPS, well-differentiated liposarcoma; Y, years.
removed was the kidney (58%, n = 4), followed by the ovary (29%, n = 2). Regarding adjuvant CT/RT, seven patients had neither CT nor RT, one patient had adjuvant CT, and two patients had adjuvant RT.

At a median follow-up of 15.5 months (range 2.6–50.7), two out of 50 patients had demised (26). Only one patient experienced minor Clavien-Dindo Grade 1 postoperative complications.

### 3.3.2.1 Comparing well-differentiated liposarcoma (WDLPS) vs. dedifferentiated liposarcoma (DDLPS) patients (R1)

LR among WDLPS patients was 33% (n = 1/3) while that among DDLPS patients was 40% (n = 2/5).

### 3.3.2.2 Comparing outcomes of adjuvant chemotherapy (CT)/radiotherapy (RT) vs. no CT/RT (R1)

LR among patients who received neither CT nor RT was 43% (three out of seven patients), LR among patients who received only CT was 0% (zero out of one patient), and LR among patients who received only RT was 100% (two out of two patients).

### 3.4 Outcomes of patients who received neoadjuvant or adjuvant radiotherapy (RT) chemotherapy (CT)

In the cohort studies, survival and recurrence outcomes of patients receiving neoadjuvant or adjuvant CT/RT were reported collectively as R0/R1 and could not be extracted independently for aggregation across studies. However, three retrospective cohort studies individually reported on the effects of neoadjuvant or adjuvant CT/RT upon univariate or multivariate analysis, with differing results. Sánchez-Hidalgo et al. (16) reported that administering adjuvant CT or RT to patients with dedifferentiated tumor histology neither improved

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**TABLE 3B** Summary of 1 case series and 5 case reports that included patients receiving R1-margin resection.

| First Author | Year | Histology | Grade (FNCLCC) | CT/RT | Postop Mortality | Clavien-Dindo Grade | Additional organs removed | No. of organs removed | Recurrence at last follow-up (Yes/No) | Follow-up duration | Patient alive at last follow-up? |
|--------------|------|-----------|----------------|-------|------------------|---------------------|--------------------------|-----------------------|-------------------------|-------------------|-----------------------------|
| Fernandez-Ruiz et al. (26) | 2010 | WDLPS | 1 | adjuvant CT | None | NA | None | 0 | No | 31.2 mo | Yes |
| | | myxoid | 2 | none given | None | NA | kidney | 1 | Yes | 7.7 mo | No (died of disease after 7.7 mo) |
| | | WDLPS | 1 | none given | None | NA | Left ovary and fallopian tube | 2 | Yes | 35 mo | Yes |
| | | DDLPS | 2 | none given | None | NA | Left kidney and adrenal gland | 2 | No | 50.7 mo | No (death due to unknown cause at 50.7 mo) |
| | | DDLPS | 2 | none given | None | NA | None | 0 | Yes | 2.6 mo | Yes |
| McCallum et al. (70) | 2006 | DDLPS | high | none given | None | NA | Uterus, cervix, both ovaries, both fallopian tubes | 6 | No | 35 mo | Yes |
| Keil et al. (71) | 2008 | NR | 3 | adjuvant RT | NR | NR | None | 0 | Yes | 1 y | Yes |
| Sato et al. (72) | 2014 | WDLPS | NR | none | None | NA | Right kidney, right colon | 2 | No | 19 mo | Yes |
| Bruce et al. (73) | 2018 | DDLPS | high | no | None | NA | Splenic bed, external iliac vessel, renal fascia, colonic mesentery | 4 | No | 9 mo | Yes |
| Ghose et al. (74) | 2018 | DDLPS | high | adjuvant RT | None | NA | Right kidney | 1 | Yes | 8 mo | Yes |

All time points are taken with respect to the date of initial operation.

CT, chemotherapy; DDLPS, dedifferentiated liposarcoma; DM, distant metastasis; LR, local recurrence; mo, months; NA, not applicable; NR, not reported; RT, radiotherapy; WDLPS, well-differentiated liposarcoma; y, years.
DFS/OS nor reduced LR rates. Similarly, Nathenson et al. (17) reported that none of adjuvant CT, neoadjuvant RT, or adjuvant RT had a significant influence on OS and PFS, regardless of tumor histology and grade. Zhao et al. (18) reported a lower median survival for patients receiving adjuvant therapy (intraoperative/postoperative RT or CT) than those who did not undergo adjuvant therapy (p = 0.03) but acknowledged selection bias due to adjuvant therapy being arranged only for patients with high-grade tumors.

4 Discussion

RPS accounts for 15% of all soft tissue sarcomas and represents a rare class of tumors occurring in approximately 5 per 100,000 people in Europe (76). To date, the impact of microscopic margin status (R0 vs. R1 margin) has never been validated in RPS. While few would defend the preservation of involved or encased organs, much of the debate lies in whether an en bloc approach to remove all adjacent or adherent organs should override intraoperative assessment of suspected histopathologic organ invasion (HOI). To further complicate the matter, it has been shown that up to 26% of patients in whom there was no suspicion of organ involvement actually demonstrate pathologically identified HOI; this underscores the need for a more aggressive and extended resection regardless of intraoperative assessment (7). Hence, while groups like the TARPSWG (77) and EORTC-STBSG (78) recommend en bloc resection to maximize the chances of achieving an R0 margin, so far, there is limited evidence to conclude if the elusive R0 margin even makes a difference to patient outcomes. As such, the role of the R0-margin status is controversial in RPS.

The results of our systematic review provide some clarity on this matter. As shown in Tables 2A, B, although the numerical values for OS and DFS vary considerably between cohort studies, the R0 margin demonstrated benefits over the R1 margin with regard to these outcomes in most individual studies. For OS, the R0 margin was prognostic for increased OS in the studies by Nathenson et al. (17), Zhao et al. (18), Milone et al. (21), Singer et al. (22), and Linehan et al. (23), while studies by Sánchez-Hidalgo et al. (16) and Lee et al. (20) did not find a statistically significant correlation between the R0/R1 margin and OS. For DFS, the R0 margin was prognostic for increased DFS in studies by Sánchez-Hidalgo et al. (16) and Nathenson et al. (17), but the study by Lee et al. (20) did not find a statistically significant correlation between the R0/R1 margin and DFS. Among the case series and case reports included in our review, the follow-up duration varied tremendously and follow-up data were limited, hence preventing any formal assessment of the benefits of the R0 margin on survival outcomes.

Additionally, while different studies adopted the R+1 classification system that requires at least 1 mm of healthy tissue around the tumor margin to qualify as R0 (in essence, an R0+1 margin), there was no obvious superiority over the standard R0 margin.

One of the biggest arguments for aggressive surgical approaches, such as frontline extended resection, is the reduction in the LR rate and hence an increase in local control. Gronchi et al. (79) showed that the 5-year LR rate was
lower at 28% with the frontline extended approach compared to 48% with standard less aggressive approaches. The French Sarcoma Group (80) also cited a 3.29-fold reduced LR rate for an aggressive extended approach compared to patients who underwent simple complete resection.

The studies included in our analysis showed that the R0 margin led to a lower LR rate compared to that of the R1 margin. The LR rate for the R0 margin ranged from 45.5% to 52.3%, lower than the LR rate of the R1 margin that ranged from 66.7% to 91.7%. In particular, Sánchez-Hidalgo et al. (16) found that the R1 margin was strongly correlated with early recurrence (<12 months) on univariate analysis, and in the series by Milone et al. (21), the R0-margin LR rate was lower than the R1-margin LR rate, although no statistical significance analysis was done to reinforce these findings. The limited data for LRFS appear to corroborate the above findings. Only the studies by Singer et al. (22) and Linehan et al. (23) presented LRFS data for the R0 and R1 margin separately for comparison between R0 and R1 to be done. While Singer et al. (22) reported that the R0 margin led to longer LRFS and longer distant recurrence-free survival, the benefit over the R1 margin was not statistically significant. On the other hand, Linehan et al. (23) reported that the R1 margin paradoxically led to a longer LRFS (albeit not statistically significant).

From our analysis, there were hardly any extractable data from the cohort studies concerning survival and LR data stratified by RPLPS subtypes (WDLPS/DDLPS), although the case series and reports suggest that the R0 margin benefits LR in WDLPS patients (R0, 24%; R1, 33%) but offers no additional benefit in DDLPS patients (R0, 40%; R1, 40%). At the same time, while a more aggressive multivisceral resection would increase the chance of attaining R0 margins (77, 78), the final margin status attained potentially also depends on underlying tumor biology because more dedifferentiated RPLPS tends to be more locally invasive (6) and hence has a higher inherent tendency to invade the tumor capsule to increase the chance of margins being positive on final histopathology. It is therefore possible that despite a multivisceral resection, the margin status may end up as R1. In our dataset, out of the R0 patients, majority were WDLPS histotype, whereas of the R1 patients, majority were DDLPS histotype. Yet, the more common margin status attained in each of the WDLPS and DDLPS was still R0, suggesting that R1-margin cases are grossly underrepresented in the available literature. Hence, it is challenging to conclude regarding the extent that tumor biology and extent of resection contribute to the margin status attained just based on these limited data from case series and reports. The patients with pleomorphic and myxoid RPLPS were too few to be adequately represented, and no further analysis on their outcomes was done.

That being said, proponents of aggressive resection argue that it offers the best chances of local control that in turn drives oncologic outcomes in WDLPS and <G2 DDLPS. However, aggressive resection does not offer further benefit in high-grade DDLPS patients in whom distant metastases are the main driver of outcomes (3).

Existing large-scale studies on RPS in general are not unanimous on whether aggressive resections increase morbidity and mortality. While studies by Gronchi et al. (79) argue that aggressive resections do not increase morbidity and mortality, this is refuted by groups such as the TARPSWG (81) that argues that the removal of major organs when resecting aggressively puts patients at 1.5 times greater risk of morbidity.

In our analysis, postoperative morbidity/mortality data could only be extracted from case series and case reports; where it was extractable from cohort studies, the morbidity rate for R0 and R1 was equal (Tables 2A, B). Among the case series and reports, although there were more incidences of morbidity among R0 than R1 patients, the percentage morbidity in both patient groups was roughly equal (R0 = 12% vs. R1 = 10%) due to the different total numbers of patients. It is however valid to say that R0 has slightly higher morbidity as evidenced by the presence of Clavien–Dindo Grade 3, 4, and 5 complications. Postoperative mortality was low in both R0 and R1 patients, with there being only one case of mortality in R0 and none among R1 patients. On the whole, our analysis suggests that postoperative morbidity and mortality are only slightly higher for the R0 margin than those for the R1 margin in the context of RPLPS.

While the precise role of each of CT and RT in survival and LR outcomes in RPLPS is not well-established due to most studies being conducted on RPS in general, it has been reported elsewhere that standard chemotherapy has a marginal role in WDLPS due to the very low mitotic rate (82), and its use is therefore limited to metastatic and recurrent tumors (83). Furthermore, within the retroperitoneal space, the presence of radiosensitive organs, such as the pancreas, and kidney, in close proximity to the primary tumor limits the effectiveness and delivery of radiotherapy (be it neoadjuvant or adjuvant) (84).

Among the studies included in our review, analysis in studies performed by Sánchez-Hidalgo et al. (16), Nathenson et al. (17), and Zhao et al. (18) failed to find any statistically significant influence of CT/RT on survival and LR outcomes. As these are retrospective studies, there is expected to be some selection bias, since CT/RT would be offered more to patients with high-grade tumors or inherently aggressive tumor biology. Furthermore, the regimen of CT and RT was not standardized among the cohort studies and, in some instances, not specified at all. The limited follow-up data from case series and reports do not show any improvement of CT/RT to survival and LR in both R0 and R1 patients nor is there any definitive proof to address the question of whether R1 with CT/RT is of equivalence to the R0 margin.

The findings of our systematic review support and allude to the latest general consensus management guidelines for RPS published by the TARPSWG in 2021 (85). Our review showed that the R0-margin resection for RPLPS increased OS and reduced LR. Indeed, the TARPSWG recommends an extended approach to resect adherent organs regardless of expected microscopic infiltration, with removal of all ipsilateral
resection on survival or recurrence outcomes. Regarding the effect of CT/RT, tumor histotype, or extent of extent. Therefore, it is difficult to make definitive conclusions stemming from publication bias. As such, data for short case series and case reports were simply presented in a descriptive manner. Therefore, it is difficult to make definitive conclusions regarding the effect of CT/RT, tumor histotype, or extent of resection on survival or recurrence outcomes.

5 Conclusion

Among the publications included in our systematic review, there was unanimity that the R0 margin delivered statistically significant improvements to OS, and there was fairly strong evidence that the R0 margin led to increased DFS. Data heterogeneity and collective reporting of R0 and R1 outcomes prevented a direct comparison of the differences in LRFS and RR, but the evidence points toward decreased RR from R0-margin resection. A modest amount of evidence points to a roughly equal postoperative morbidity rate between R0 and R1 resection.

To date, there have been no systematic reviews on the impact of the R0 margin in the treatment of RPLPS or even RPS for that matter. On the whole, our review suggests that the R0 margin benefits survival and LR in RPLPS patients without compromising postoperative morbidity. The role of other factors such as tumor biology and the role of CT/RT, while important, have yet to be delineated. At this juncture, our review emphasizes the need for larger-scale multicenter cohort studies assessing the effect of histotype, CT/RT, and extent of resection on survival and recurrence outcomes.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: JSMW. Data curation: BP, JSMW. Formal analysis: BP, CJS, JW-ST, WKDJ, JSMW. Funding acquisition: JSMW. Investigation: BP, CJS, JW-ST, WKDJ, JSMW. Methodology: JSMW. Project administration: CC, CO. Resources: KCS, CC, C-AJO, JSMW. Supervision: KCS, C-AJO, CC, JSMW. Validation: BP, CS JW-ST, WKDJ, JSMW. Visualization: BP, CS. Roles/Writing - original draft: BP, JSMW. Writing - review and editing: BP, CJS, JW-ST, WKDJ, KCS, CC, C-AJO, JSMW. All authors contributed to the article and approved the submitted version.

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**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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