Clinical benefit and residual kidney function of en bloc nephrectomy for perirenal retroperitoneal sarcoma

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Abstract
Aim: The purpose of this study was to evaluate the efficacy of en bloc nephrectomy for perirenal retroperitoneal sarcoma (RPS) with respect to postoperative kidney function and oncological benefits.

Methods: We performed a comparative study of 114 patients undergoing surgery for primary RPS, classifying cases as nephrectomy (NPX, n = 65) versus no nephrectomy (no-NPX, n = 49). The Δ and % change between preoperative and postoperative estimated glomerulus filtration rate (eGFR) were analyzed to compare renal function changes after surgery. Kaplan–Meier analysis was performed to verify the incidence of local relapse between the two groups.

Results: During a median follow-up of 29 months, median postoperative GFR of 65 patients in the NPX group decreased to 73.5% of preoperative eGFR. Although 38 patients (58%) in the NPX group experienced a progression in chronic kidney disease stage after nephrectomy, no patients progressed to end-stage renal disease (ESRD). In French Federation of Cancer Centers Sarcoma grade 2, the NPX group had statistically significant local control benefits, compared with the no-NPX group (P = 0.048).

Conclusions: Residual renal function after en bloc nephrectomy was stabilized without progression to ESRD. Moreover, en bloc nephrectomy for perirenal RPS might secure a complete resection margin for local tumor control.

Keywords
en bloc nephrectomy, local tumor control, residual kidney function, retroperitoneal sarcoma

1 | INTRODUCTION

Retroperitoneal sarcoma (RPS) is a rare tumor with a mean annual incidence of approximately 2.7 cases per 106 persons. Since RPS has a tendency to be locally advanced and involves adjacent organs and major vascular structures at presentation, it is difficult to determine the optimal extent of surgery for complete resection of RPS. Retroperitoneal liposarcoma (LPS) originating from perinephric fat tissue is usually a huge mass that encases or abuts an adjacent kidney. Thus, there is an ongoing debate regarding the necessity to perform en bloc nephrectomy for complete surgical resection of perinephric LPS. Some surgeons claim that contiguous organ resection is safe and improves loco-regional tumor control. However, others oppose en bloc nephrectomy because of the potential long-term risk of chronic kidney disease (CKD) requiring dialysis and limitations in systemic chemotherapy.

There have been some reports regarding kidney function changes after nephrectomy performed for various reasons, including RPS. To our knowledge, there have been no comparative studies that simultaneously analyzed oncological outcome and residual kidney function after en bloc nephrectomy for RPS compared with surgical resection without nephrectomy. We compared residual renal functional outcomes after nephrectomy as a part of extended surgery for RPS with the renal function of patients who underwent surgical resection...
without nephrectomy and assessed progression of CKD stage in terms of renal adaptation. We also studied whether en bloc nephrectomy for RPS achieved a better oncological outcome through evaluation of local recurrence and cancer-specific survival compared to conventional excision of perirenal RPS without nephrectomy.

2 | METHODS

2.1 | Study design and population

After approval by the Institutional Review Board, all patients who underwent a primary operation for complete resection of RPS at a single institution between October 1996 and September 2015 were retrospectively analyzed. Over a 20-year period at our institute, 149 patients underwent primary surgical resection for RPS located in the perirenal space or with suspected ureter invasion. Exclusion criteria included no medical record of renal function test at least 30 days after surgery (n = 28), bilateral nephrectomy (n = 2), history of previous nephrectomy (n = 1), concomitant evidence of distant metastases (n = 2) and diagnosed with end-stage renal disease (ESRD) before surgery (n = 2). In total, 114 patients were included in this study. The median follow-up duration of the studied cohort was 29 months after surgery (interquartile range [IQR], 16–59 months). Patients were divided into two groups: nephrectomy (NPX) group (n = 65) and no nephrectomy (no-NPX) group (n = 49) (FIGURE 1). Patients in the NPX group underwent the aggressive surgical procedure of en bloc resection. En bloc resection consisted of removing the surrounding connective tissues and organs located within 1 cm of the tumor surface. This included adjacent kidney, colon, adrenal glands, psoas muscle or inferior vena cava if abutting the tumor and loco-regional peritonectomy. Patients in the no-NPX group underwent simple resections or en bloc resection only if there was definite direct involvement of adjacent organs in the operative field.

The following characteristics of 114 patients were reviewed: demographic factors (age, gender, body mass index and American Society of Anesthesiologists grade), pathologic factors (tumor size, French Federation of Cancer Centers Sarcoma Group [FNCLCC] grade, histologic diagnosis and completeness of resection margin) and renal functional factors (preoperative and postoperative ultimate values of serum creatinine [sCr] and estimated glomerular filtration rate [eGFR], and history of acute kidney injury [AKI]).

EgFR was calculated using the modification of Diet in Renal Disease (MDRD) study equation for GFR (in mL per minute per 1.73 m²) = 186×sCr−1.154×age−0.203×(0.742 if female).10,11 Ultimate sCr and GFR were defined as the new steady state baseline of the lowest sCr and highest GFR measured 30 days or more after surgery.8

AKI was defined as an increase in sCr to 1.5 times or more of baseline within 7 days after surgery. The stages of CKD were defined according to the definition of the National Kidney Foundation.12,13

It is well known that GFR declines as a consequence of aging. To evaluate the progression of CKD stage in NPX and no-NPX groups, expected GFR at patient’s last follow-up was calculated based on each individual patient’s age, preoperative GFR and follow-up duration. The results were compared with postoperative CKD stage according to ultimate GFR. CKD progression was defined as the condition when ultimate GFR exceeded expected GFR.7

2.2 | Statistical analysis

The primary endpoint was residual renal function. We compared CKD stage progression between the NPX and no-NPX groups. We compared the proportion of CKD progression in NPX and no-NPX groups with the Chi-square test. The secondary endpoint was reduction of ultimate GFR to 60% or less of preoperative GFR based on residual renal adaptation after unilateral nephrectomy. Regarding oncologic outcomes, the primary endpoint of the study was incidence of local recurrence, and the secondary endpoint was cancer-specific survival.

Continuous data were represented as median and IQR. Categorical data were specified as numbers and percentages. Statistical analysis was conducted using independent-samples T or Mann–Whitney tests for continuous values and the Chi-square or Fisher’s exact tests, especially when expected cell frequencies were below 5 for categorical values. The incidence of local recurrence and overall survival rate were analyzed by the Kaplan–Meier method. The log-rank test was used to compare curves produced from the NPX and no-NPX groups. A P value < 0.05 was considered statistically significant. Data handling and analysis were carried out using Statistical Package for Social Sciences for Windows release 22.0 (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Demographic, histological and treatment-associated characteristics of NPX and no-NPX groups

In the study cohort of 114 patients as shown in Table 1, median age at operation was 57 years (IQR 49–64 years). Male to female proportion was 50:50, with 57 patients each. Tumors in the NPX group were significantly larger than those in the no-NPX group, as median tumor size was 26 and 12 cm, respectively (P < 0.001). The majority (73%) of tumors in both groups were high-grade RPS (FNCLCC grades 2 and 3), and 59 patients (89%) in the NPX group were diagnosed with LPS, whereas 28 patients (57%) in the no-NPX group were diagnosed with LPS (P < 0.001). Although there was no difference in macroscopic completeness of resection between the two groups, patients in the NPX group underwent statistically more contiguous organ resections (NPX: 35 cases [53%] vs no-NPX: 11 cases [22%], P = 0.002). The NPX group underwent more combined resection of adjacent organs such as the colon (P = 0.002), pancreas (P = 0.042) and spleen (P = 0.005) compared to the no-NPX group. Although chemotherapy was applied with no specific difference between the two groups, patients in the NPX group more frequently underwent tissue expander insertion (41% vs 16%, P = 0.004) and adjuvant radiation therapy (RT) (61% vs 37%, P = 0.011).
Comparison of renal function changes after surgical resection between NPX and no-NPX groups

As shown in TABLE 2, median preoperative values of GFR in the NPX versus no-NPX groups were 88.8 versus 86.8 mL/min/1.73 m², respectively, with no statistical difference ($P = 0.882$). Median postoperative ultimate GFR was 62.3 mL/min/1.73 m² and significantly decreased more than that in the no-NPX group ($P = 0.004$). The median value of decline between preoperative and ultimate GFR was 26.5%. Postoperative measurements of GFR ($\Delta$ change and % change) decreased remarkably in the NPX group compared to the no-NPX group ($P = 0.001$ and $P = 0.001$, respectively).

Progression of CKD stage and residual renal function in terms of renal adaptation

TABLE 3 shows the expected CKD stages according to postoperative CKD stage in individual patients of both groups. Of 46 patients who were expected to have CKD stage 1, 22 patients (76%) in the NPX group progressed in CKD stage and 6 patients (35%) in the no-NPX group progressed in CKD stage ($P = 0.012$). Of 62 patients who were expected to have CKD stage 2 (GFR of 60–89 mL/min) in both groups, there was no significant difference in CKD stage progression ($P = 0.310$). Only two patients in the NPX group had a final CKD stage of 4 (GFR of 15–29 mL/min), but no patients required dialysis. Six patients in both groups with expected CKD stage 3 (GFR 60 < mL/min) did not experience CKD stage progression after nephrectomy. Of the total studied patients, 38 patients (59%) in the NPX group experienced significant progression of CKD stage after nephrectomy compared to 16 patients (33%) in the no-NPX group ($P = 0.008$).

As shown in Figure 1, there were 35 patients (54%) in the NPX group and 12 patients (25%) in the no-NPX group with ultimate GFR reduced to 75% or less of preoperative GFR. Six patients in both groups with expected CKD stage 3 (GFR 60 < mL/min) did not experience CKD stage progression after nephrectomy. Of the total studied patients, 38 patients (59%) in the NPX group experienced significant progression of CKD stage after nephrectomy compared to 16 patients (33%) in the no-NPX group ($P = 0.008$).

Local recurrence and cancer-specific survival

This analysis was applied in 84 patients (74%) who underwent complete macroscopic resection in the total cohort of 114 patients. Median follow-up duration for survival was 36 months (IQR 20–69 months). The 5-year cumulative incidence of local recurrence for the 84 studied patients was not different between the NPX and no-NPX groups ($P = 0.429$; FIGURE 2A). Subgroup analysis according to FNCLCC grade showed the 5-year local recurrence rate for grade 2 patients in the NPX group was 55%, whereas it was 63% for those in the no-NPX group. This difference was statistically significant ($P = 0.048$; FIGURE 2C). However, the 5-year local recurrence rate for grade 1 and grade 3 patients was not different between the NPX and no-NPX groups ($P = 0.456$; FIGURE 2B and $P = 0.5418$; FIGURE 2D, respectively).

The 5-year cancer-specific survival rates in the NPX and no-NPX groups were 75% and 71%, respectively ($P = 0.554$). Subgroup analysis of FNCLCC grade 2 showed the 5-year cancer-specific survival for 25 patients who underwent en bloc nephrectomy was 88%, compared with 43% for 19 patients in the no-NPX group. There was a trend toward better cancer-specific survival for grade 2 tumors in the NPX group ($P = 0.077$).

DISCUSSION

The predominant type of RPS developing in the perirenal space is LPS originating from perirenal fat. LPS is likely to be indistinguishable from perirenal fat tissue, and surgeons may find it difficult to confirm involvement of the renal parenchyma in the operative field. For this reason, surgeons usually perform en bloc nephrectomy for cases of RPS with kidney encasement to guarantee complete macroscopic resection. However, some surgeons are reluctant to conduct simultaneous resection of kidneys encased by RPS because there is limited evidence regarding the oncological benefit of en bloc nephrectomy and the long-term risk of CKD in patients following nephrectomy. To address these two questions, we performed comparative analysis of postoperative kidney function and long-term oncological outcomes in the same cohort of 114 patients classified into NPX ($n = 65$) and no NPX ($n = 49$) groups.

Compared to the postoperative renal function of the no-NPX group, NPX patients had statistically significant decreases in $\Delta$ change
| Characteristics                              | Total (n = 114) | No nephrectomy (n = 49) | Nephrectomy (n = 65) | P value |
|---------------------------------------------|-----------------|-------------------------|----------------------|---------|
| Age (years), median (IQR)                  | 57 (49–64)      | 56 (49–63)              | 57 (48–65)           | 0.937   |
| Gender, n (%)                              |                 |                         |                      |         |
| Male                                        | 57 (50%)        | 24 (49%)                | 33 (51%)             | 1.000   |
| Female                                      | 57 (50%)        | 25 (51%)                | 32 (49%)             |         |
| BMI (kg/m²)                                 | 23.2 (20.8–25.2)| 23.9 (20.9–26.1)        | 22.7 (20.4–24.7)     | 0.071   |
| ASA score 1:2:3, n (%)                      | 36:73:5 (32:64:4%) | 16:30:3 (33:61:6%)      | 20:43:2 (31:66:3%)   | 0.751   |
| Tumor size (cm), median (IQR)              | 18 (12–31)      | 12 (9–19)               | 26 (16–36)           | < 0.001 |
| FNCLCC grade, n (%)                         |                 |                         |                      |         |
| 1                                           | 30 (27%)        | 13 (27%)                | 17 (26%)             | 1.000   |
| 2                                           | 55 (48%)        | 26 (49%)                | 31 (48%)             |         |
| 3                                           | 29 (25%)        | 12 (24%)                | 17 (26%)             |         |
| Histology, n (%)                            |                 |                         |                      |         |
| Liposarcoma                                 | 87 (77%)        | 28 (57%)                | 59 (89%)             | < 0.001 |
| Leiomyosarcoma                              | 15 (13%)        | 9 (19%)                 | 6 (9%)               |         |
| UPS                                         | 5 (4%)          | 5 (10%)                 | 0 (2%)               |         |
| Fibrosarcoma                                | 2 (2%)          | 2 (4%)                  | 0                    |         |
| MPNST                                       | 5 (4%)          | 5 (10%)                 | 0                    |         |
| Macroscopic complete resection, n (%)       |                 |                         |                      |         |
| Yes                                         | 84 (74%)        | 36 (74%)                | 48 (74%)             | 1.000   |
| No                                          | 30 (26%)        | 13 (26%)                | 18 (26%)             |         |
| Contiguous organ resection other than kidney, n (%) |         |                         |                      |         |
| No                                          | 69 (61%)        | 38 (78%)                | 31 (47%)             | 0.002   |
| Yes                                         | 45 (39%)        | 11 (22%)                | 35 (53%)             |         |
| Combined resected organ                     |                 |                         |                      |         |
| Colon                                       | 29 (25%)        | 5 (10%)                 | 24 (37%)             | 0.002   |
| Adrenal gland                               | 15 (13%)        | 3 (6%)                  | 12 (19%)             | 0.091   |
| Small bowel                                 | 12 (11%)        | 3 (6%)                  | 9 (14%)              | 0.228   |
| Pancreas                                    | 10 (9%)         | 1 (2%)                  | 9 (14%)              | 0.042   |
| Spleen                                      | 10 (9%)         | 0 (0%)                  | 10 (15%)             | 0.005   |
| Radiation therapy, No                       | 45 (40%)        | 26 (53%)                | 19 (29%)             | 0.011   |
| Neoadjuvant                                 | 3 (2%)          | 0 (0%)                  | 3 (5%)               |         |
| Adjuvant                                    | 57 (50%)        | 18 (37%)                | 39 (61%)             |         |
| Palliative                                  | 8 (8%)          | 5 (10%)                 | 3 (5%)               |         |
| Tissue expander insertion                   |                 |                         |                      |         |
| No                                          | 79 (69%)        | 41 (84%)                | 38 (59%)             | 0.004   |
| Yes                                         | 38 (31%)        | 8 (16%)                 | 27 (41%)             |         |
| Chemotherapy                                |                 |                         |                      |         |
| No                                          | 85 (75%)        | 36 (74%)                | 49 (75%)             | 1.000   |
| Neoadjuvant                                 | 3 (3%)          | 1 (2%)                  | 2 (3%)               |         |
| Adjuvant                                    | 13 (11%)        | 6 (12%)                 | 7 (11%)              |         |
| Palliative                                  | 13 (11%)        | 6 (12%)                 | 7 (11%)              |         |

BMI: body mass index; ASA: American Society of Anesthesiologists; IQR: interquartile range; UPS: undifferentiated pleomorphic sarcoma; MPNST: malignant peripheral nerve sheath tumor.
One interesting result of our study is that the median GFR at 5 years postoperative of the no-NPX group also declined to 60 mL/min/1.73 m². Despite preserving a kidney, the decrease in renal function may result from other factors such as radiation-induced nephropathy or administration of nephrotoxic chemotherapeutic agents. Another report demonstrated that dialysis dependency after nephrectomy may be associated with presentation of de novo renal disease, not post-nephrectomy condition or administration of nephrotoxic chemotherapeutic agents. Another report demonstrated that dialysis dependency after nephrectomy may be associated with presentation of de novo renal disease, not post-nephrectomy condition or administration of nephrotoxic chemotherapeutic agents after surgery. Therefore, the renal function of RPS patients after surgery should be closely monitored regardless of nephrectomy.

Unfortunately, there was a difference in tumor size between the NPX and no-NPX groups. The NPX group underwent more combined resections of adjacent organs such as colon, pancreas and spleen than the no-NPX group. Because en bloc nephrectomy could be part of achieving complete macroscopic resection as well, tumor size in the

and % change between pre and postoperative ultimate GFR. The NPX group had the lowest and highest GFR measurements at a median of 2 and 4 days after nephrectomy, respectively, but renal function stabilized within 6 weeks postnephrectomy. This tendency curve reflects the routine course of renal adaptation after nephrectomy, similar to previous studies of donor nephrectomy and partial nephrectomy.

After nephrectomy, renal adaptation and residual kidney function have been well-established in a study regarding patients who underwent donor nephrectomy. Generally, after kidney donation, there is an initial decline in GFR of 25–35%. This is followed by a small increase in GFR, which is then maintained at 60–75% of prenephrectomy GFR. There might be some controversy, but we compared kidney function changes after RPS surgery including nephrectomy with the result after donor nephrectomy in order to explain renal adaptation after unilateral nephrectomy. There were 65 patients who underwent nephrectomy that showed a 26.5% reduction of preoperative GFR during a follow-up period of over 2 years. However, this result does not completely reflect our study since some patients received nephrotoxic chemotherapy. Thus, to assess the postoperative renal function of patients who underwent en bloc nephrectomy for RPS, we performed a comparative analysis with those who underwent surgery without nephrectomy. In these two groups, there was no significant difference in the proportion of patients who underwent adjuvant chemotherapy as a potential confounding factor of postoperative renal function. Although progression of CKD stage occurred in nearly 60% of NPX patients within 2 years after operation, no patient required dialysis or had a restriction in systemic chemotherapy, even with progression to CKD stage 4, similar to results of a previous report. Moreover, despite the perceived high risk of nephrectomy in patients with preoperative compromised kidney function, none of the six patients in both groups with estimated CKD stage 3 (GFR 60 < mL/min) who underwent nephrectomy experienced postoperative progression of CKD stage. There were 16 (25%) patients in the NPX group and 5 (10%) in the no-NPX group who showed decreased renal function in relation to renal adaptation with 60% or less of prenephrectomy GFR. This difference was not statistically significant (P = 0.086). Therefore, the decreased renal function of the NPX group might be clinically acceptable compared with that of the no-NPX group based on the level of renal adaptation.

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NPX group might be larger than those in no-NPX group. Since this selection bias was inevitable to perform this small retrospective study, we did not adjust for tumor size. This is a drawback of this study. However, Keung et al. reported that predictors affecting outcomes in RPS were tumor integrity (intact vs fragmented), multifocality, macroscopic completeness and FNCLCC grade.17 Unlike extremity sarcoma, tumor size was not a prognostic factor. In our study, although there was a difference in tumor size between two groups, FNCLCC grade and macroscopic complete resection were not different between the two groups.

It is well known that an aggressive surgical strategy improves local control of RPS.4,18 However, there is insufficient evidence regarding RPS located in the perirenal space to ensure that en bloc nephrectomy improves long-term survival and locoregional tumor control.

Our study demonstrated that the trend toward better local control for patients who underwent en bloc nephrectomy was more pronounced for grades 2–3. In particular, there was a statistically significant difference in the 5-year incidence of local recurrence for patients with grade 2 tumors in the NPX versus no-NPX groups. However, a larger population of patients is needed to confirm the local control benefits in NPX patients and no-NPX patients with grade 3. Kaplan-Meier analysis for cancer-specific survival showed no difference for patients with grade 1 tumors in both groups. Generally, grade 1 patients underwent reoperation for recurrence, and they survived relatively longer compared to patients with higher grade tumors. A 5-year time span is not enough to demonstrate any survival difference for these patients, who have a survival rate of roughly 80%. A trend toward better survivals in the NPX group was somewhat remarkable for grade 2 tumors. Conversely, the number of grade 3 patients was not sufficient to evaluate the survival difference between the NPX and no-NPX groups, as mentioned above.

Our study has several limitations. First, the follow-up duration for renal function was not enough to confirm long-term outcomes of kidney function after nephrectomy due to recently starting routine laboratory check-ups of blood chemistry at the outpatient clinic. The second limitation is that our study consisted of a small cohort, especially for FNCLCC grade 3 patients. We will report the kidney function change and oncological outcomes after en bloc nephrectomy for RPS with larger populations and longer follow-up in a subsequent study. The third limitation is comparing kidney function changes after RPS surgery including nephrectomy with results after donor nephrectomy. Finally, more patients in the NPX group underwent RT compared with no-NPX patients.

In conclusion, kidney function changes after en bloc nephrectomy for RPS may be acceptable because no patient progressed to ESRD, required dialysis or had systemic treatment limitations despite the progression of CKD stage. Although a larger cohort of RPS patients is necessary to definitely confirm these oncological outcomes, an aggressive surgical approach including nephrectomy for perinephric RPS enables complete macroscopic resection and improves local tumor control and survival. Therefore, when surgeons encounter RPS abutting the kidney, en bloc nephrectomy may be helpful to obtain complete resection margins.
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