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ORIGINAL ARTICLE

Clinical characteristics and surgical outcomes of retroperitoneal tumors: a comprehensive data collection from multiple departments

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Abstract

Background There are only a limited number of comprehensive reports for retroperitoneal tumors (RPTs). The aim of this study was to perform an interdepartmental data collection for RPTs and to comprehensively clarify the clinical characteristics of this rare disease.

Methods All patients who were diagnosed with RPT from January 2005 to July 2018 in a single institution were included. The analyzed factors included demographics, clinical features, treatment methods, pathological diagnosis, and prognosis.

Results A total of 422 patients (215 males and 207 females) with primary RPTs were identified. Biopsy for RPT was performed in 180 patients (43%). Among the 422 patients, 239 (57%) underwent surgery. The most common tissue origin was mesodermal ($n=99$, 41%), followed by neurogenic ($n=54$, 23%), extragonadal ($n=27$, 11%), and metastatic tumors ($n=13$, 5%). Among the 99 resected mesodermal tumors, the most common pathological subtypes were liposarcoma ($n=55$, 56%) and leiomyosarcoma ($n=16$, 16%). The long-term outcomes after surgery were analyzed in patients with intermediate and malignant sarcomas (including liposarcoma, leiomyosarcoma, and others combined, $n=71$). The 3- and 5-year disease-free survival rates in the intermediate tumors were 68.2% and 54.2%, respectively, whereas those in the malignant tumors were 48.6% and 28.9%, respectively. The 3- and 5-year overall survival rates in the intermediate tumors were 100% and 94.1%, respectively, whereas those in the malignant tumors were 78.4% and 72.8%, respectively ($p=0.009$).

Conclusions The clinical manifestations of RPTs were extremely variable. Recurrence after repeating resection is commonly observed in patients with malignant retroperitoneal sarcoma.

Keywords Interdepartmental data collection · Retroperitoneal sarcoma · Repeating resection · Retroperitoneum · Clinical characteristics · Sarcoma · Recurrence

Introduction

Retroperitoneal tumors (RPTs) are rare tumors that develop from soft tissues found in the retroperitoneal space, which is a compartmentalized space bounded anteriorly by the posterior parietal peritoneum and posteriorly by the transversalis fascia [1]. RPTs arise from various tissues, and their

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malignant potential ranges from benign tumor to high-grade malignancy. It sometimes involves retroperitoneal organs such as the kidney, adrenal gland, pancreas, and intrapelvic organs (bladder, uterus, ovary, prostate, etc.). Invasive RPTs also involve major retroperitoneal lumen structures such as the abdominal aorta, inferior vena cava, and ureter [2].

Pathological findings of RPTs are extremely variable. The malignant potential of RPT ranges from benign tumor, borderline malignancy, and low-grade malignancy to high-grade malignancy [2]. The tissue origin of RPT includes fat, muscle, fibrous tissue, nerve, lymph node, bone, and blood or lymphatic vessels. Because of these complicated characteristics, the clinical manifestation of RPT is extremely variable. In this regard, the surgical approach to RPT should be arranged depending on the original location of the tumor, malignant potential of the tumor, and the status of other organ/structure involvement [3–5]. Moreover, surgery for RPT is not only performed by gastrointestinal surgeons but is also performed by urologists, orthopedic surgeons, pediatric surgeons, gynecologists, and surgeons in other departments [6–9]. Nevertheless, there are a limited number of reports of RPTs, and the clinical characteristics, including the methods of diagnosis, surgical approach, and surgical outcomes of RPT, are not well understood [10]. Furthermore, there are no reports that include data from multiple departments and the analysis for the RPT, including both benign and malignant tumors.

The aim of this study was to perform an interdepartmental and single institution data collection for RPTs, including both benign and malignant tumors, and to comprehensively clarify the clinical characteristics of this rare disease entity.

Patients and methods

This retrospective study was approved by the Nagoya University Hospital institutional review board (approved number 2019-0269).

Patients

All patients who were diagnosed with RPT from January 2005 to July 2018 at Nagoya University Hospital were included.

The gastrointestinal surgeons, urologists, orthopedic surgeons, pediatric surgeons, gynecologists, and physicians from other departments participated in this study. All histologic subtypes included in the data were diagnosed by pathologists using surgical and/or needle biopsy specimens. Patients with limbs and bone sarcomas and patients with incomplete medical information were excluded from the analytical cohort.

Data collection

The analyzed factors included demographics, clinical features, treatment methods, pathological diagnosis, and prognosis. The resection margin status using the surgical specimens was defined as follows: R0, no tumor at the surgical margin; R1, microscopic tumor at the surgical margin; and R2, macroscopic tumor at the surgical margin. Pathological diagnoses were made by pathologists in Nagoya University Hospital according to the 2013 World Health Organization (WHO) classification for tumors of soft tissue and bone [11]. Tumors were classified as mesodermal tumors, neurogenic tumors, extragonadal tumors, metastatic tumors, or other tumors according to the tissue origin [1]. Furthermore, the tumor was classified as benign, intermediate, and malignant tumors according to the World Health Organization (WHO) classification for tumors of soft tissue and bone [11]. Paraganglioma and gastrointestinal stromal tumor (GIST), which have malignant potential, were categorized as intermediate, whereas dedifferentiate liposarcoma and other soft tissue sarcomas (STSs) were categorized as malignant tumors.

Statistics

Continuous data were expressed as medians (ranges), and categorical data were expressed as numbers (percentages). The Kaplan–Meier method was used to calculate the disease-free survival (DFS) and overall survival (OS) curves. SPSS statistical software (version 26; IBM Institute Inchiro1208, Chicago) was used to conduct all analyses.

Results

Demographics

A total of 422 patients (215 males and 207 females) with primary RPTs were identified. The median (range) age at first diagnosis of RPT was 52 years old (0–88 years old). The distribution chart of age showed two peaks at ages under 10 years old and 60–69 years old (Fig. 1a).

Several departments in Nagoya University Hospital treated RPTs. The departments of gastrointestinal surgery ($n = 113$, 27%), orthopedics ($n = 86$, 20%), and urology ($n = 74$, 18%) treated the largest number of patients (Fig. 1b). Many patients with RPTs ($n = 186$, 44%) had no subjective symptoms, and the tumors were incidentally found by screening imaging examination (Suppl Fig. 1a).

There was no predominant laterality for the original site of the tumor (right, $n = 163$; middle/bilateral, $n = 66$; left, $n = 180$) (Suppl Fig. 1b). In terms of the imaging

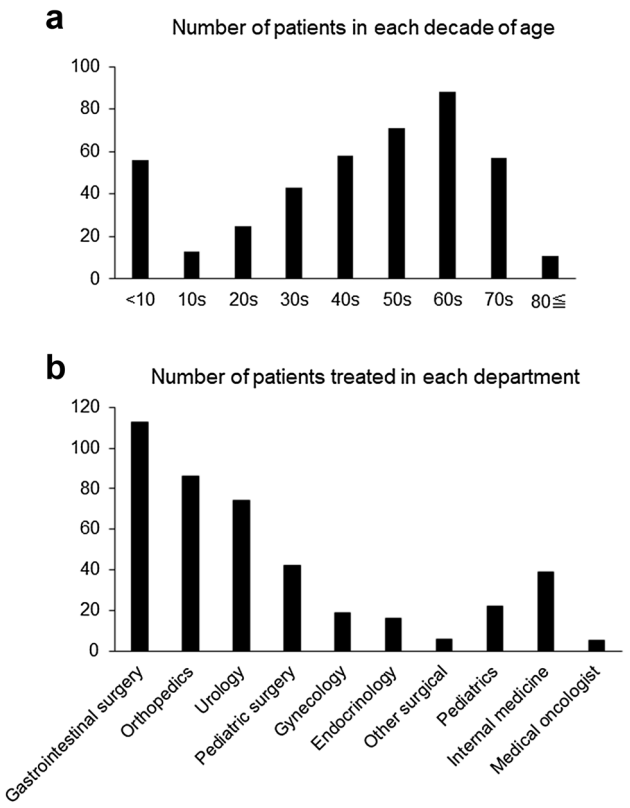

Fig. 1 Incidence of retroperitoneal tumors according to age (**a**) and treatment department (**b**)

modalities used for the diagnosis, 393 patients (93%) underwent computed tomography (CT), magnetic resonance imaging (MRI), or ^{18}F-FDG-positron emission tomography (FDG-PET). A CT scan was used in 360 patients (85%), MRI was used in 267 patients (63%), and FDG-PET was used in 75 patients (18%) (Suppl Fig. 2a). Two modalities were used in 213 patients (50%), and three modalities were used in 48 patients (11%).

The median (range) maximum tumor size of the RPT was 72 mm (10–352 mm). The most frequent size was 50–99 mm ($n=148$, 35%), and some patients ($n=23$, 5%) had a tumor size greater than 200 mm (Suppl Fig. 2b).

Methods of pathologic diagnosis

Biopsy for RPT was performed in 180 patients (43%). Among them, 123 patients (68%) underwent a needle biopsy mostly from the retroperitoneal side using CT or ultrasound-guided method. Another 57 patients (32%) underwent incisional biopsy either by open laparotomy or by laparoscopic procedure.

Treatment strategy

Among 422 patients, 239 patients (57%) underwent surgery (Fig. 2). Eighty-nine patients did not undergo surgery because of an inoperable malignant lesion, and these patients received either chemotherapy, radiotherapy, chemoradiotherapy, or best supportive care. Ninety-four patients did not undergo surgery and were periodically followed up in the outpatient clinic. Neoadjuvant therapy for far advanced RPT was performed in 16 patients (7%). Two hundred and thirty-nine patients finally underwent surgery. Among them, 175 patients (73%) underwent surgery without undergoing preoperative biopsy.

Wide resection with a tumor margin greater than 1 cm was possible in only 17 patients (7%), and most of the resection resulted in marginal resection with a minimum tumor margin, at least in some part of the tumor (Fig. 2). Combined organ or tissue resection was performed in 80 patients (33%). The most commonly resected retroperitoneal organ was the kidney, followed by the intestine, adrenal gland, pancreas, spleen, and genitalia. Some patients underwent a combined resection of the retroperitoneal tissue or vasculature, such as the inferior vena cava, common iliac artery, common iliac vein, iliac bone, psoas muscle, and femoral nerve.

Pathological findings

Among 239 resected tumors, the most common tissue origin was mesodermal ($n=99$, 41%), followed by neurogenic ($n=54$, 23%), extragonadal ($n=27$, 11%), and metastatic tumors ($n=13$, 5%) (Fig. 3a). Among the 99 resected mesodermal tumors, the most common pathological subtypes were liposarcoma ($n=55$, 56%), followed by leiomyosarcoma ($n=16$, 16%), undifferentiated pleomorphic sarcoma (UPS) ($n=5$, 5%) and malignant peripheral nerve sheath tumor (MPNST) ($n=4$, 4%) (Fig. 3b). In addition, there was extensive variability in the pathological type of mesodermal RPTs.

Pathological malignancy was defined in 389 patients. Among them, 161 (41%) were benign, 55 (14%) were intermediate, and 173 (45%) were malignant tumors. The most common pathological subtypes in benign tumors were schwannoma ($n=49$, 30%), teratoma ($n=24$, 15%), lymphangioma ($n=14$, 9%), and ganglioneuroma ($n=12$, 7%) (Fig. 3c). Except for these, there was extensive variability in the pathological type of benign RPTs.

The most common pathological subtypes in intermediate tumors were well-differentiated liposarcoma ($n=31$, 56%), followed by paraganglioma ($n=16$, 29%) and GIST ($n=4$, 7%). The most common pathological subtypes in malignant tumors were dedifferentiated liposarcoma ($n=35$, 20%), followed by metastatic tumors ($n=34$, 20%), STSs other than dedifferentiated liposarcoma and leiomyosarcoma ($n=28$,

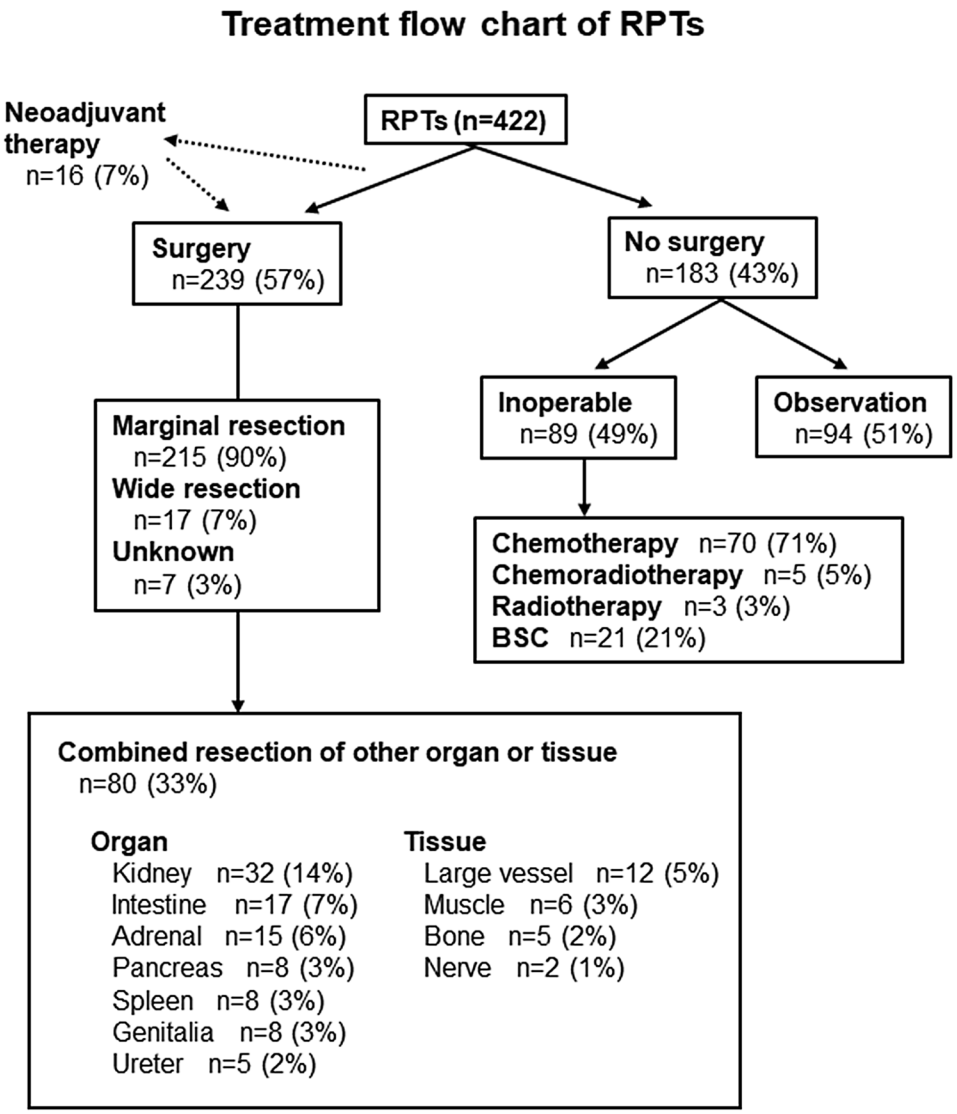

Fig. 2 Treatment flow chart of retroperitoneal tumors (RPTs) ($n = 422$)

16%), malignant lymphoma ($n = 23$, 13%), leiomyosarcoma ($n = 19$, 11%), and neuroblastoma ($n = 17$, 10%). In patients under 10 years of age, 60% of RPTs were benign tumors, and the proportion of intermediate/malignant lesions increased according to age (Fig. 4a). The proportion of intermediate/malignant lesions also increased as the size of the tumor increased (Fig. 4b).

Prognosis

The long-term outcomes after surgery were analyzed in 71 patients with intermediate and malignant tumors (29 intermediate and 42 malignant). Among 71 patients, resection margin status was R0 (no tumor at the resection margin) in 24 patients (34%), R1 (presence of microscopic tumor at the resection margin) in 41 patients (58%), and R2 (presence of macroscopic tumor at the resection margin) in 6 patients (8%). Forty-two patients (59%) had recurrent tumors after surgery, and most of them had local recurrences (Suppl Fig. 3). The recurrence rates were not significantly different between intermediate and malignant tumors (52% vs. 64%). Resection for the recurrent tumor was performed in 62% of patients. Nevertheless, re-recurrence occurred in 65% of patients, and resection for the second recurrence was performed in 76%. After the resection, the first tumor recurrence occurred at a median (range) of 410 days (41–5610 days), and the second tumor recurrence occurred at a median (range) of 447 days (120–1450 days) after the second resection. Only a few patients could undergo a third or more repeated resection.

The median follow-up period was 35.8 months. The 3- and 5-year DFS in the intermediate tumors were 68.2% and 54.2%, respectively, whereas those in the malignant tumors were 48.6% and 28.9%, respectively (Fig. 5a). The 3- and 5-year OS rates in the intermediate tumors

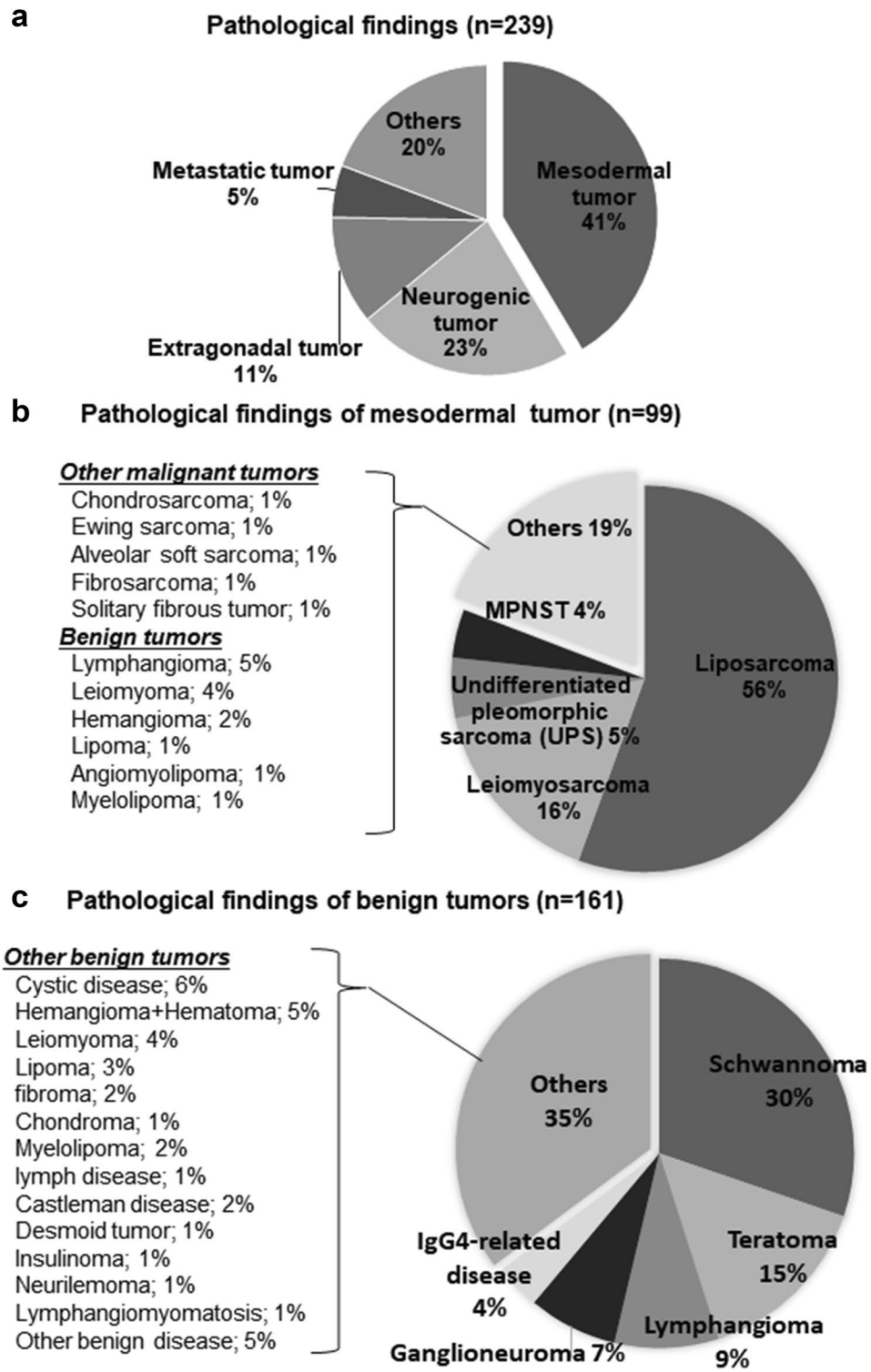

Fig. 3 Pathological findings of retroperitoneal tumors. **a** Pathological findings of 239 resected tumors according to the tissue origin. **b** Pathological findings of 99 resected tumors classified as mesodermal tumors, including both benign and malignant tumors. **c** Pathological findings of 162 benign retroperitoneal tumors, including those resected by surgery or those that were biopsied for pathological diagnosis

were 100% and 94.1%, respectively, whereas those in the malignant tumors were 78.4% and 72.8%, respectively ($p = 0.009$) (Fig. 5a).

Discussion

RPT is a rare disease that originates from the retroperitoneal compartment. The retroperitoneum is bounded anteriorly by the posterior parietal peritoneum and posteriorly by the transversalis fascia [1]. RPT frequently abuts or involves

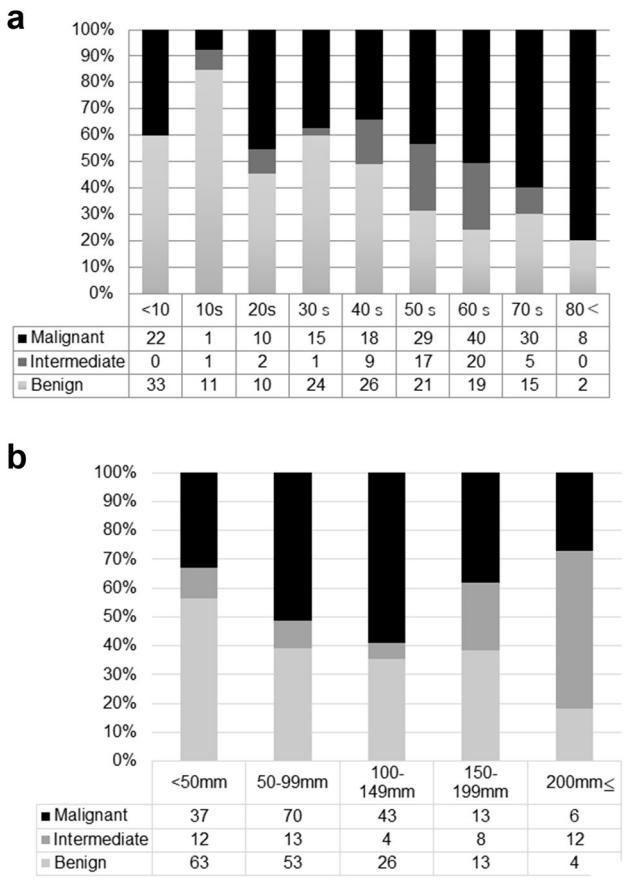

Fig. 4 Percentage of benign, intermediate, and malignant tumors according to age (**a**) and tumor size (**b**)

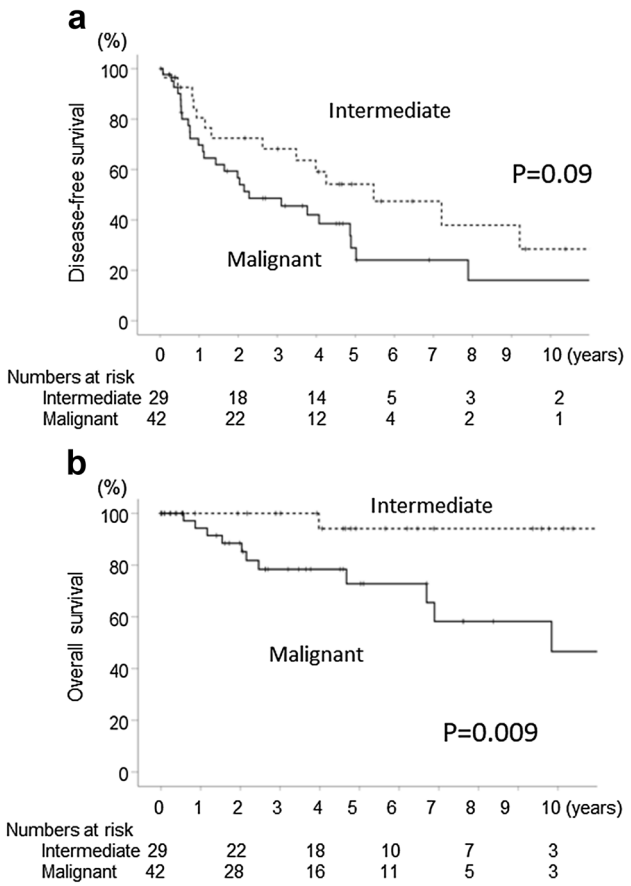

Fig. 5 Kaplan–Meier curves of disease-free survival (**a**) and overall survival (**b**) after surgery for patients with intermediate (dotted line) and malignant (solid line) retroperitoneal tumors

retroperitoneal organs such as the kidney, adrenal gland, pancreas, and intrapelvic organs. Because of its original location, many RPTs are found incidentally by imaging examination without any symptoms. In our hospital, 44% of RPTs were found by screening imaging examination. Some patients were diagnosed with a large tumor greater than 200 mm in diameter. These patients mostly had symptoms such as abdominal pain, abdominal fullness, and mass palpitation for more than 6 months. Therefore, physicians should always be aware of the possibility of retroperitoneal tumors when they meet with a patient with abdominal pain and abdominal fullness.

RPTs comprise only 0.1–0.2% of all malignant tumors [1]. However, most surgeons who treat intraabdominal tumors (irrespective of their department specialty) may have experience treating RPTs. In fact, in our hospital, RPTs have been treated not only by gastrointestinal surgeons but also by orthopedic surgeons, urologists, pediatric surgeons, and gynecologists. However, some departments have treated only a small number of patients. A previous report showed that the prognosis of RPTs is worse in low-volume centers compared to high-volume centers [6]. Because RPTs are diagnosed in various departments, it may be important to have the opportunity to discuss the treatment strategy for RPTs among multiple departments. Through this process, all departments may unanimously agree with the treatment strategy, and the quality of patients' management for RPT may improve. It is also recommended to unify the style of database in each department, in the hospital, among the hospitals, or among nations.

It has been reported that the frequency of STS, including extremities, is approximately 1% of all adult malignant tumors and 15% of pediatric malignant tumors [12]. STS originating from the retroperitoneum comprises approximately 15% of all STSs [12]. In this study, the most common STS from the retroperitoneum were mesodermal tumors such as liposarcoma and leiomyosarcoma [13]. These tumors, especially liposarcoma, sometimes have been found as large tumors by CT or MRI. The larger the tumor diameter, the greater is the possibility of malignancy [2, 13, 14]. In fact, in this study, the proportion of mesodermal malignant lesions (including intermediate malignancy) was 45% when

the tumor diameter was less than 50 mm, whereas it was more than 80% when the tumor diameter exceeded 200 mm.

Ideally, it is preferable to know the tumor pathology before surgery when surgical treatment is planned for RPT [15]. However, in this study, only 64 out of 239 patients (27%) who underwent surgery underwent preoperative biopsy. In these patients, the results of preoperative biopsy were consistent with the final diagnosis in 50 patients (78%). One of the reasons for omitting biopsy for RPTs was to avoid dissemination along the biopsy route. However, according to previous reports, the local recurrence rate with the needle biopsy route was 0.37–2% [16, 17]. Another report showed that the local recurrence with the biopsy route did not have an impact on the overall survival [18]. In this series, no recurrence alongside the biopsy route was observed. Therefore, we recommend performing biopsy when necessary. Our policy for performing the biopsy for RPTs is as follows: (1) to diagnose the malignant potential of the tumor before surgery to determine whether wide resection, including combined organ resection, is necessary to obtain a secure surgical margin; (2) to diagnose specific types of sarcomas that should be subjected to preoperative chemotherapy (i.e., Ewing's sarcoma, alveolar type rhabdomyosarcoma, and others); and (3) to differentiate retroperitoneal desmoid tumor, which is not an indication of surgery. The real benefit of performing biopsy for RPT before surgery should be discussed in future studies.

In contrast to reports regarding malignant RPT, reports regarding benign RPT are very rare. Therefore, the demographics, frequency, and type of pathology of benign RPT are largely unknown. This study indicated that there is great variety in the pathological findings of benign RPTs. The most common benign RPT was lipoma in mesodermal tumors, schwannoma in neurogenic tumors, and teratoma in extragonadal tumors. However, there are so many other types of benign tumors, and the differentiation of these tumors by imaging modalities such as CT, MRI, and PET without surgery is extremely difficult. Furthermore, biopsy for the tumor was not always possible because of the size and location of the tumor. Further data accumulation using a nationwide database may be necessary to clarify the clinical characteristics of benign RPTs.

The fundamental treatment strategy for intermediate and malignant RPT is surgical resection [19–23]. Although a wide resection margin is theoretically ideal when treating STSs, it is sometimes difficult to have a wide resection margin in STSs originating from the retroperitoneum. In this study, 90% of patients underwent marginal resection of the tumor irrespective of the combined organ resection. Furthermore, with respect to the surgery for representative sarcomas (i.e., liposarcoma and leiomyosarcoma), R0 resection was achieved in only 34% of patients. Consequently, 59% of patients developed recurrence, and 62% of patients underwent re-resection for recurrent disease. In our hospital, recurrent lesions are aggressively resected as much as possible. In fact, some patients underwent repeating resection for repeating recurrence. In patients with intermediate-type tumors, approximately half of the patients experience recurrence within 5 years of the intermediate tumor, and most of the patients survive more than 10 years. These results indicate a clinical benefit of repeating resection for the recurrent lesion in the intermediate-type tumor. In contrast, the benefit of repeating resection for malignant tumors may be limited. The clinical benefit of re-resection for recurrent RPTs should be further clarified by accumulating more data.

There are several limitations in this study. This is a retrospective data analysis in a single institution. RPTs were treated in multiple departments, and there were some differences in the treatment policy and strategy among departments. There were several patients who were diagnosed and treated in our hospital but were followed up in other hospitals. Further multiple institutional data collection (including multiple departments) is necessary to clarify the clinical characteristics and to establish a better treatment algorithm for RPTs.

In conclusion, the clinical manifestations of RPTs were extremely variable. There was a survival benefit in repeating resection for recurrent intermediate malignancy tumors. In a hospital without a specific department that mainly treats RPTs, it may be important to discuss the treatment strategy for RPTs among multiple departments.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest in the subject matter in this manuscript.

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