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BRIEF ARTICLE

Recurrent abdominal liposarcoma: Analysis of 19 cases and prognostic factors

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Abstract

AIM: To evaluate the clinical outcome of re-operation for recurrent abdominal liposarcoma following multidisciplinary team cooperation.

METHODS: Nineteen consecutive patients who had recurrent abdominal liposarcoma underwent re-operation by the retroperitoneal sarcoma team at our institution from May 2009 to January 2012. Patient demographic and clinical data were reviewed retrospectively. Multidisciplinary team discussions were held prior to treatment, and re-operation was deemed the best treatment. The categories of the extent of resection were as follows: gross total resection (GTR), palliative resection and partial resection. Surgical techniques were divided into discrete lesion resection and combined contiguous multivisceral resection (CMR). Tumor size was determined as the largest diameter of the specimen. Patients were followed up at approximately 3-monthly intervals. For survival analysis, a univariate analysis was performed using the Kaplan-Meier method, and a multivariate analysis was performed using the Cox proportional hazards model.

RESULTS: Nineteen patients with recurrent abdominal liposarcoma (RAL) underwent 32 re-operations at our institute. A total of 51 operations were reviewed with a total follow-up time ranging from 4 to 120 (47.4 ± 34.2) mo. The GTR rate in the CMR group was higher than that in the non-CMR group (P = 0.034). CMR was positively correlated with intra-operative bleeding (correlation coefficient = 0.514, P = 0.010). Six cases with severe postoperative complications were recorded. Patients with tumor sizes greater than 20 cm carried a significant risk of profuse intra-operative bleeding (P = 0.009). The ratio of a highly malignant subtype (de-differentiated or pleomorphic) in recurrent cases was higher compared to primary cases (P = 0.027). Both single-factor survival using the Kaplan-Meier model and multivariate analysis using the Cox proportional hazards model showed that overall survival was correlated with resection extent and pathological subtype (P < 0.001 and P = 0.02), however, relapse-free interval (RFI) was only correlated with resection extent (P = 0.002).

CONCLUSION: Close follow-up should be conducted in patients with RAL. Early re-operation for relapse is preferred and gross resection most likely prolongs the RFI.

Key words: Overall survival; Recurrent abdominal liposarcoma; Relapse-free interval

Core tip: Recurrent abdominal liposarcoma (RAL) is an intractable disease encountered by both general surgeons and surgical oncologists. RAL commonly affects multiple organs, and re-operation for RAL is often difficult and is associated with significant risk, even when debulking is imminent. The high likelihood of postoperative complications and a lower survival outcome are

detractors for repeat operations. A multidisciplinary team approach, realistic risk stratification, and careful management may help increase the success rate of gross total resection, lower these complication rates, improve survival, and increase the quality of life of these patients. Overall survival, relapse-free interval and other clinical follow-up data are also presented in detail in this study.

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INTRODUCTION

Liposarcoma is the most common retroperitoneal sarcoma[1,2]. It accounts for more than 20% of all sarcomas in adults and up to 41% of all retroperitoneal sarcomas[3,4]. Liposarcomas also originate from the mesentery, gastrointestinal wall, and even from solitary organs, which has been reported sporadically[4-11]. Complete surgical resection is the only effective treatment method for retroperitoneal liposarcomas[3,12,13].

However, liposarcomas are associated with a high local recurrence rate[14-16]. Re-operation is the only effective treatment for recurrent abdominal liposarcoma (RAL)[17]. For those who are not amenable to complete radical resection, debulking resection should be performed to relieve symptoms, reduce complications, and increase the life span[18]. However, there is no consensus concerning the utility of repeat debulking resections. RAL commonly affects multiple organs, and re-operation for RAL is often difficult and is associated with significant risk, even when debulking is imminent. The high likelihood of post-operative complications and a lower survival outcome are detractors for repeat operations.

A multidisciplinary team approach, realistic risk stratification, and careful management may help lower these complication rates, improve survival, and increase the quality of life of these patients. We have treated 19 RAL patients over the past 3 years using a multidisciplinary team approach. The clinical and follow-up data of these patients were retrospectively analyzed and summarized.

MATERIALS AND METHODS

Patient enrollment and operation selection

Between May 2009 and Jan 2012, 19 consecutive patients with RAL were treated by the retroperitoneal sarcoma team at our institution. Patients were identified by reviewing a database that accrued data prospectively. Histology was reviewed and classified according to the World Health Organization classification[19,20]. The multidisciplinary team were involved in case discussions which were held prior to treatment, and repeat resection was deemed the best treatment. The multidisciplinary team members included general surgeons, a pathologist, radiologist, oncologist, radiologist, urologist and gynecologist. Multivisceral resection was recommended only in cases of expected gross tumor resection. The operative plan was explained to the patient in detail, and informed consent was obtained before surgery.

Extent of resection

The categories of the extent of resection were as follows: gross total resection (GTR), whether the margin was histologically free or not; palliative resection; and partial resection. Palliative resections were performed when the gross disease could not be completely removed and less than a 1 cm rim of tumor remained. Partial resections were defined as visually more than a 1 cm rim of remaining tumor. Surgical techniques were divided into discrete lesion resection (DLR) and combined contiguous multivisceral resection (CMR). Tumor size was determined as the largest diameter of the specimen.

Clinical data

Patients' demographic and clinical data were reviewed retrospectively and included age, gender, disease onset date, combined resected organ, pathology subtype, tumor size, intra-operative bleeding, post-operative complications, disease relapse date and survival time in order to analyze prognostic factors.

Follow up

Patients were followed-up at approximately 3-mo intervals. The relapse-free interval (RFI) was defined as the time between initial surgery and confirmation of clinical recurrence.

Statistical analysis

The median and standard error were used to present continuous variables. Fisher's test or a crosstab analysis was performed to compare variables between groups. For survival analysis, a univariate analysis was performed using the Kaplan-Meier method, and a multivariate analysis was performed using the Cox proportional hazards model. $P < 0.05$ was considered statistically significant.

RESULTS

Patient clinical characteristics

Nineteen patients with RAL underwent 32 re-operations at our institute. The patient demographic, surgical, and pathological data are summarized in Table 1. A total of 51 operations were reviewed. The recurrences were tracked from Mar 2002 to Aug 2011, with a total follow-up time ranging from 4 to 120 (47.4 ± 34.2) mo.

Surgical treatment

The surgical methods and resection extent are summarized in Table 2. Five of the nineteen patients underwent the primary operation at our institute. The resected or-

Table 1 Patient demographics and clinical data *n* (%)

Variables	Mean/median
Age (yr)	
mean ± SD	55 ± 10.8
Median (range)	58 (34-84)
Gender	
Male	12 (63.2)
Female	7 (36.8)
No. of operations	
Two	11 (57.9)
Three	4 (21.1)
Four	3 (15.9)
Five	1 (5.3)
Follow-up time (mo)	
mean ± SD	48.9 ± 34.8
Range	4-120
Primary tumor location	
Retroperitoneum	13 (68.4)
Mesentery	3 (15.8)
Omentum	1 (5.3)
Small intestine	1 (5.3)

Table 2 Surgical methods and resection extent of primary and recurrent liposarcomas *n* (%)

Variables	DLR	CMR	Total
Primary tumor			
GTR	11 (57.89)	4 (21.05)	15 (78.94)
Palliative resection	3 (15.79)	0 (0.00)	3 (15.79)
Partial resection	1 (5.26)	0 (0.00)	1 (5.26)
Total	15 (78.95)	4 (21.05)	19 (100.00)
Recurrent tumor			
GTR	5 (15.63)	15 (46.88)	20 (62.50)
Palliative resection	2 (6.25)	6 (18.75)	8 (25.00)
Partial resection	3 (9.38)	1 (3.13)	4 (12.50)
Total	10 (31.25)	22 (68.75)	32 (100.00)

DLR: Discrete lesion resection; CMR: Contiguous multivisceral resection; GTR: Gross total resection.

gans included the small intestine (n = 14), colon (n = 11), kidney (n = 8), spleen (n = 7), pancreas (n = 5), stomach, appendix, ovary (n = 3 each), and liver, bladder, testicle, and abdominal wall (n = 1 each). The GTR rate in the CMR group was higher than that in the non-CMR group (P = 0.034). Only one CMR case underwent partial resection. This patient had a spontaneous enterobrosis and therefore required an emergency operation. He lived for 3 mo after this salvage treatment. The median intra-operative blood loss was 500 mL. Thirteen cases had bleeding ranging from 500-4000 (1300 ± 1100) mL; bleeding in 12 of these 13 cases occurred during CMR. CMR was positively correlated with intra-operative bleeding (correlation coefficient = 0.514, P = 0.010). Six cases with severe postoperative complications were recorded. Two cases experienced anastomotic leakage, and the other four experienced either pleural effusion, subdiaphragmatic effusion, abdominal abscess, or an abdominal wall wound infection.

Pathology data

The primary tumor size was recorded in nine patients, including one patient with multiple lesions; the other eight tumors ranged in size from 13-38 (22.6 ± 9.9) cm. A total of 24 relapse cases were observed who had measurable specimens with tumor sizes ranging from 4-46 (27.2 ± 14.5) cm, and 8 cases had multiple lesions. The median size was 20 cm for all specimens. The resection extent, surgical approach, and operative blood loss were compared according to tumor size. The relapse cases were subgrouped by median tumor size when comparing the clinical data with the number of cases. Patients with tumor sizes greater than 20 cm carried a significant risk of profuse intra-operative bleeding (P = 0.009), as detailed in Table 3.

Table 3 Comparison of clinical data according to recurrent tumor size

Tumor size	< 20 cm	> 20 cm	Total
GTR	4	10	14
Palliative resection	3	5	8
Partial resection	2	0	2
DLR	4	2	6
CMR	6	12	18
Bleeding (< 500 mL)	4	6	10
Profuse bleeding (≥ 500 mL)[1]	1	13	14

[1]P = 0.009 between different recurrent tumor size group. DLR: Discrete lesion resection; CMR: Contiguous multivisceral resection; GTR: Gross total resection.

The pathological subtypes were significantly different between recurrent and primary tumors. The subtype frequently changed with each recurrence within the same patient. In this series, well-differentiated and myxoid liposarcomas were more commonly found within the primary tumor; however, dedifferentiated liposarcomas were more common in recurrent tumors. The ratio of a highly malignant subtype (dedifferentiated or pleomorphic) in the recurrent cases was higher compared to the primary cases (5/9 *vs* 23/9, P = 0.027).

Follow-up and survival analysis

Survival was tracked during the follow-up period. Six patients died of their disease after an overall survival (OS) of 8-90 (33.7 ± 29.7) mo. Single-factor survival was analyzed according to surgical method, resection extent, tumor location, tumor size, and pathological subtype of the primary disease. Patients with a GTR of the primary tumor had a longer survival than those with a palliative or partial resection (P = 0.001, Figure 1A). Patients who underwent a CMR at first operation had a slightly longer survival (P = 0.081, Figure 1B). Patients with a primary retroperitoneal liposarcoma had a worse survival than liposarcoma at any other site (mesentery, omentum and small intestine, P = 0.054, Figure 1C). Patients with a less malignant subtype of primary liposarcoma (well differentiated and myxoid cell type) tended to live longer than those with a more highly malignant subtype (dedifferentiated and pleomorphic cell type, P = 0.002, Figure 1D). Multivariate analysis using the Cox proportional hazards model showed that OS correlated with resection extent and pathological subtype (P < 0.001 and P = 0.02).

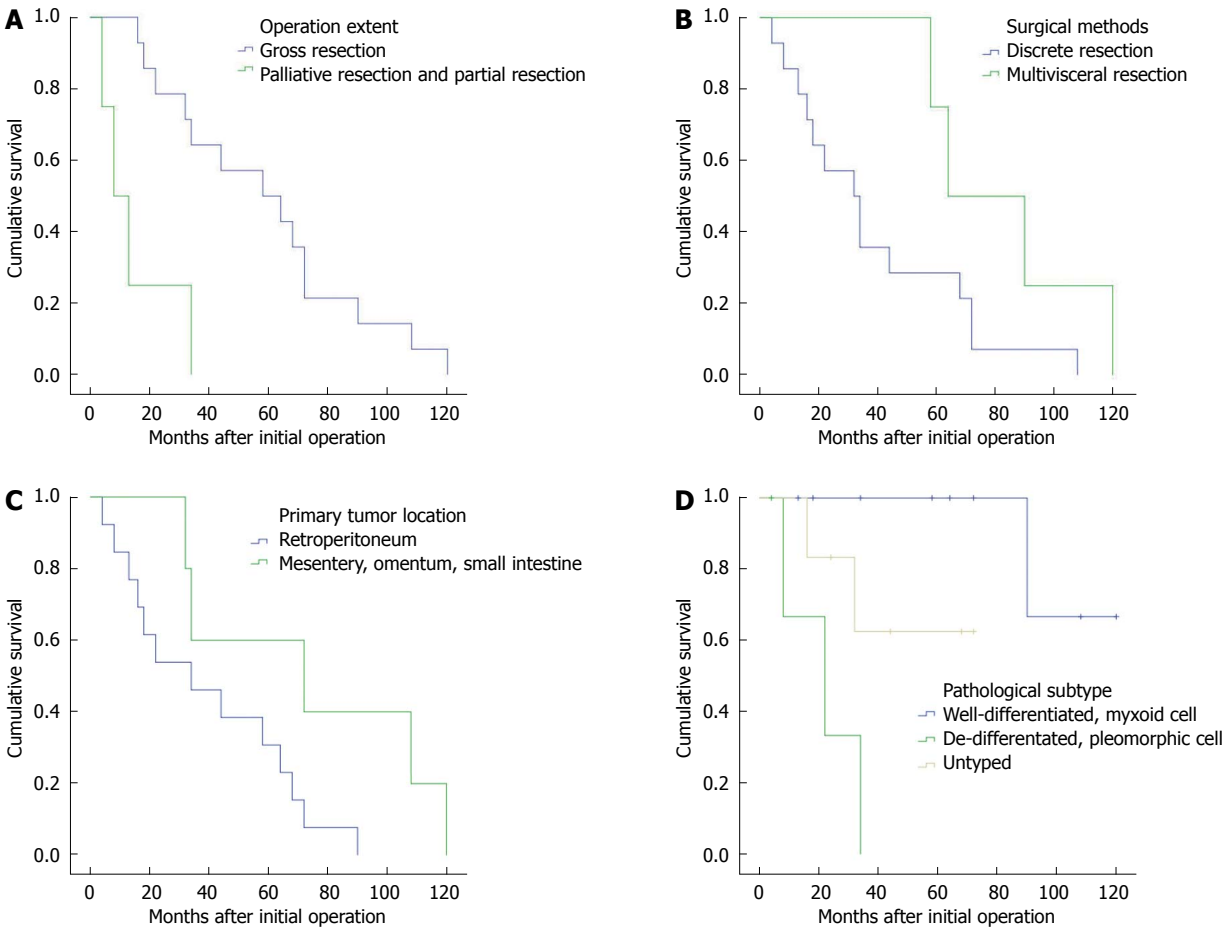

Figure 1 Relationship between overall survival and operation extent (A), surgical methods (B), tumor origin (C), and pathological subtype (D) in patients who underwent resection of a primary abdominal liposarcoma.

The RFI of the primary surgical treatment ranged from 2-84 (22.0 ± 21.2) mo. The RFI differed between GTR patients (6-84/27.0 ± 21.2 mo) and patients who underwent partial or palliative resections (2-4/3.3 ± 1.0 mo, $P = 0.001$). Eighteen recurrences were observed after a gross or palliative resection for recurrent tumor, and the RFI was 1-28 (8.3 ± 7.4) mo. Of these, 11 were post-GTR (RFI = 4-28/12.5 ± 7.4 mo) and seven were post-palliative resection (RFI = 3-6/4 ± 1.3 mo). Eight post-GTR cases had a follow-up of 3-30 (10.3 ± 10.1) mo with no relapse. Patients who underwent GTR had a longer RFI than those who underwent palliative resection ($P = 0.01$).

The RFI was compared according to the revision operation time, surgical method, resection extent, primary tumor location, tumor size, simultaneous tumor number, and pathological subtype. The RFI was shorter in patients who underwent more than 2 operations ($P = 0.035$, Figure 2A). No significant differences in RFI were found between CMR and DLR ($P = 0.599$, Figure 2B). However, there was a significant difference between GTR cases and non-GTR cases ($P < 0.001$, Figure 2C). Patients with well-differentiated liposarcomas had a longer RFI compared to those with other liposarcoma subtypes ($P = 0.007$, Figure 2D). When grouped by median tumor size (20 cm) or simultaneous tumor number (solitary or multiple), no significant difference was observed ($P = 0.54$, Figure 2E and $P = 0.33$, Figure 2F). A multivariate analysis using a Cox proportional hazards model showed that the RFI only correlated with resection extent ($P = 0.002$).

DISCUSSION

Liposarcoma is the most common mesenchymal tumor in the abdomen. To date, surgical resection is the only effective treatment for liposarcoma. Unfortunately, these tumors are almost always very large at the time of diagnosis due to their slow growth and often vague symptoms[11], which make GTR difficult. These tumors are known for their frequent local recurrence and expansive growth with contiguous organ infiltration, which are the main causes of death from this disease. There is no strong evidence that chemotherapy or radiotherapy is curative[21,22]. Re-operation is still the mainstay of treatment, but is associated with significant risk. Using a multidisciplinary team approach, the surgical management of RAL has been improved at our institute. Very few studies have focused on the re-operative treatment of RAL.

In this series, we reviewed 19 patients with RAL who

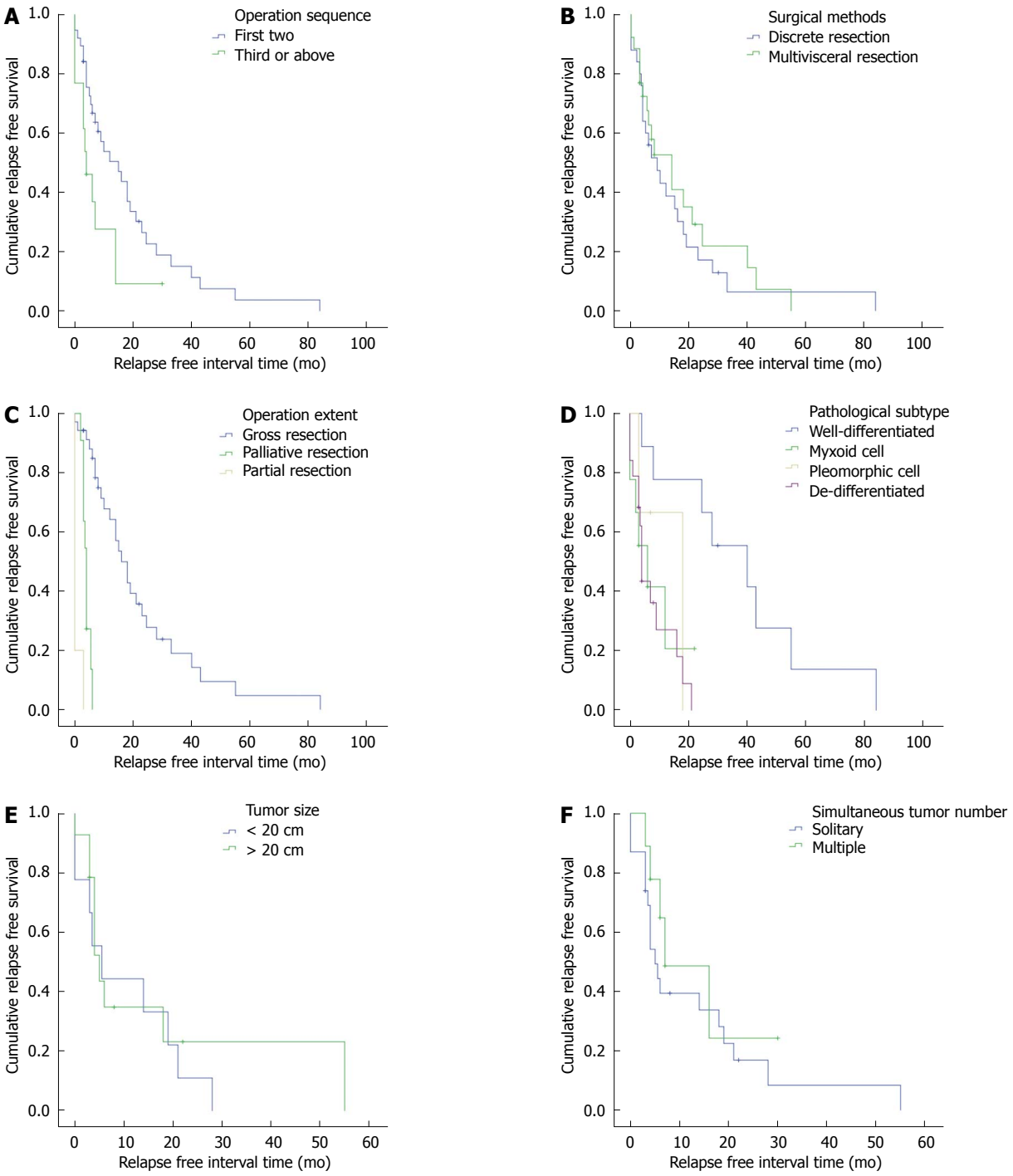

Figure 2 Relationship between the relapse-free interval and operation sequence (A), surgical method (B), operation extent (C), pathological subtype (D), tumor size (E), and simultaneous tumor number (F) in patients who underwent resection of an abdominal liposarcoma.

underwent 32 re-operations. All 19 patients had a successful re-operation with no intra-operative mortalities. However, the surgical treatment of RAL was associated with intra-operative bleeding and postoperative complications. These were most notable in cases where CMR was anticipated. The most common postoperative complications were anastomotic leak and effusion/infection.

There is no consensus in the literature regarding the guiding principles of surgical treatment for RAL. A large series of 177 primary retroperitoneal liposarcoma patients demonstrated that the pathological subtype on gross resection was the most significant prognostic factor[16]. In our multi-disciplinary team, the benefits and risks of re-operation were evaluated, and plans were formulated for all the RALs we encountered. GTR is the preferred approach for patients with RAL when CMR is necessary. If there was no possibility of gross resection, palliative resection was performed without multivisceral resection. Partial resections for RAL should only be performed in patients with intolerable symptoms (*e.g.*, extreme increas-

ing intra-abdominal pressure, grave complications, and in some emergency conditions). CMR should be avoided in patients who have undergone partial resection because this does not result in cure and incurs greater morbidity. One partial resection included an enterectomy due to spontaneous perforation caused by the RAL.

In this study, 75% (15/20) of patients who underwent GTR involved CMR. There is no similar study from our institute or similar data in the literature. It is unknown whether CMRs increase the GTR rate for RAL. However, the GTR rate was higher in CMR cases than in non-CMR cases for RALs. In operations for the primary tumor, there were more non-combined resections in GTR patients (57.9% *vs* 21.1%). The tumor size was 4-46 (median 20) cm, which is similar to that in another retrospective study of 21 cases of primary retroperitoneal liposarcoma[25]. The most frequently combined resected organ was the small intestine, which is in contrast to another study reporting the kidney[24]. In our study, the small intestine was associated with a risk of anastomotic leak. Tumor size was also correlated with intra-operative profuse bleeding (> 20 cm, $P = 0.009$). Additionally, a pathologic subtype change was observed in the RALs compared to the primary tumors or previous relapsed tumors. A pathologic subtype change predicted deterioration in repeat relapse cases[25]. Dedifferentiated liposarcomas were more commonly found as recurrent tumors[14,26-28].

There have been no studies that have focused on recurrent abdominal liposarcomas or retroperitoneal liposarcomas. Most reported studies are single cases or include less than 3 cases in a report. However, several studies have described primary and recurrent retroperitoneal liposarcoma, with more than 10 cases reported since 1991[23,25,29-32], but no primary mesentery or omental liposarcomas have been described. In our study, patients with primary retroperitoneal liposarcoma had a poorer survival, however, this was not statistically significant ($P = 0.054$). It is generally recognized that complete or gross total resection at the initial operation is very important, resulting in a more favorable prognosis[33]. In our study, patients who underwent gross resection of the primary tumor had a longer survival than those who underwent a palliative or partial resection. CMR for retroperitoneal sarcoma was recommended for the initial operation in a study of 77 patients due to an infiltrative tumor pattern[34]. Dedifferentiated tumors tend to present more often as a recurrence[35,36], frequently require multi-organ resection, and carry a shorter disease-free interval when compared to well-differentiated subtypes[25]; a similar result was observed for well-differentiated tumors in this study. OS was correlated with the resection extent and pathological subtype ($P < 0.001$ and $P = 0.02$). CMRs may increase the chance of complete resection.

Macroscopic complete resection for recurrent retroperitoneal liposarcoma has been recommended[37]. It is believed that palliative resection is worthwhile for treating the troublesome symptoms of recurrence in patients who have little chance of gross resection[32]. Repeat operations were performed in our study, and the RFI was shorter in patients who underwent more than two operations. GTR was a significant prognostic factor for the RFI ($P < 0.001$). Tumor subtype in a well-differentiated liposarcoma resulted in a significantly longer RFI compared to other types, according to the Kaplan-Meier analysis. The surgical extent was the only significant prognostic factor, as demonstrated by the Cox regression model. This showed that GTR was the major factor affecting the relapse time regardless of whether the tumor was a primary or recurrent tumor. Our results show that surgical management is the key factor in the successful treatment of abdominal liposarcoma. Multidisciplinary team cooperation has the advantage of a well-designed surgical management plan. Whether tumor size affects OS in addition to the relapse-free interval is controversial. Some authors have reported that large tumor size is negatively associated with prognosis[23,29] as large tumors require more difficult operations. However, other reports have shown no obvious difference in OS or relapse-free interval according to tumor size[25,37]. Tumor size did not affect the RFI in our study. However, it was one of the factors associated with the GTR rate, which indirectly affected OS. Multidisciplinary team approaches and multivisceral resections used in the surgical management of these cases reduced the risk of tumor residue when operating on larger abdominal liposarcomas.

Most abdominal liposarcomas are asymptomatic in the early stages. As the tumor grows patients may experience abdominal distention or other symptoms related to the tumor compressing contiguous organs, vessels, or even the ureter. Some tumors were large when the patients presented to the hospital, and it was difficult to completely resect these tumors at the time of surgery. The abdominal liposarcomas were often recurrent, particularly those with a highly malignant subtype. It is important that such patients have appropriate follow-up. However, to date, follow-up has not been standardized. The relapse time after the initial operation has been reported to vary due to the surgical extent and pathologic subtype. Postoperative adjuvant chemotherapy or radiotherapy was also not recommended as there is little evidence of benefit[38,39]. Proactive re-operation for RAL is strongly recommended. In such cases, close follow-up is necessary to identify relapse early.

RAL is a difficult disease to treat. The surgical treatment of RALs can be particularly challenging for surgical oncologists. GTR is the most important positive prognostic factor for these patients, and proactive surgical treatment is recommended. A multidisciplinary team approach most likely increases the chance of GTR, and CMR is frequently required to achieve gross tumor clearance. Palliative or partial resections are indicated in patients with recurrent disease and insufferable symptoms.

COMMENTS

Background

Abdominal liposarcomas are associated with a high local recurrence rate. Re-operation is the only effective treatment for recurrent abdominal liposarcoma

(RAL). For those who are not amenable to complete radical resection, debulking resection may relieve symptoms, reduce complications, and increase the life span. However, RAL commonly affects multiple organs, and re-operation for RAL is often difficult and is associated with significant risk, even when debulking is imminent, There is no consensus concerning the utility of repeat debulking resections. The high likelihood of post-operative complications and a lower survival outcome are detractors for repeat surgery.

Research frontiers

Re-operation is widely accepted as the treatment for recurrent abdominal liposarcoma. However, repeat re-operation for RAL is associated with high risk and a high complication rate. There are no recommended general criteria regarding when or how the re-operation should be performed. A multidisciplinary team approach, realistic risk stratification, and careful management may help lower the complication rate and improve survival.

Innovations and breakthroughs

Recurrent abdominal liposarcoma is an intractable disease encountered by general surgeons or surgical oncologists. It is generally believed that chemotherapy or radiotherapy provide minor help for patients with abdominal liposarcoma. Macroscopic complete resection or gross total resection is still the only treatment that correlates with overall survival or disease-free survival. However, recurrent lesions involve several adjacent organs in most cases. Multiple contiguous organ resections should be carried out under such conditions, however, this is associated with significant risks of failing to resect the lesion completely, multiple complications and even intra- or post-operative death. With the advantage of a multidisciplinary approach, the surgical oncologist can prepare for the treatment of this difficult disease, enhance the successful rate of gross resection and lower the morbidity and mortality related to the operation. This preliminary study summarized the outcome of multidisciplinary team cooperation in the treatment of abdominal liposarcoma which can be subsequently improved.

Applications

The study results suggest that repeat re-operation for recurrent abdominal liposarcoma with multidisciplinary team cooperation may help lower the complication rates, improve survival, and increase the quality of life of these patients.

Terminology

Recurrent abdominal liposarcoma: Recurrent abdominal liposarcoma is a disease where the liposarcoma relapses mainly in the peritoneal cavity, whether the liposarcoma originated from the retroperitoneal area or another region. Gross total resection: is the same as macroscopic complete resection, and means that the tumor is totally resected whether the pathological margin is negative or positive.

Peer review

This is a good retrospective study in which authors analyze the clinical outcome of repeated re-operation on recurrent abdominal liposarcoma. The results are interesting and suggest that repeated re-operation on recurrent abdominal liposarcoma under multidisciplinary team cooperation gain satisfactory clinical outcome.

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