

Leiomyosarcoma: investigation of prognostic factors for risk-stratification model

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Abstract

Background We performed this study to define distinctive clinical features of leiomyosarcoma by assessing prognostic factors.

Methods Between 1988 and 2011, 129 leiomyosarcoma patients who underwent surgical resection with curative intent were retrospectively reviewed.

Results Of the 129 leiomyosarcoma patients, the distribution of anatomic locations was: extremity ($n = 25$), pelvis ($n = 40$), thoracic cavity ($n = 11$), intra-abdomen ($n = 19$), retroperitoneum ($n = 23$), and head/neck ($n = 11$). We classified the anatomic locations into two categories as

abdominal (intra-abdomen and retroperitoneum, $n = 42$) and extra-abdominal (extremity, pelvis, thoracic cavity, and head/neck, $n = 87$). Prognosis was worse for the abdominal group than for the extra-abdominal group (median DFS 2.9 vs. 9.0 years, $P = 0.04$). Similarly, overall survival (OS) was also significantly worse for abdominal group ($P = 0.027$). Independent prognostic factors for survival were primary site ($P = 0.041$, hazard ratio (HR) 1.7; 95 % CI 1.2–2.8), tumor size ($P = 0.038$, HR 1.9; 95 % CI 1.13–3.38), margin status ($P = 0.019$, HR 2.1; 95 % CI 1.13–3.88), and histology grade ($P = 0.01$, HR 3.59; 95 % CI 1.64–7.87). We identified four different risk groups with different survival outcome: group 1 ($n = 8$), no adverse factors; groups 2 ($n = 37$) and 3 ($n = 61$) with one and two adverse factors, and group 4 ($n = 23$) with 3 or 4 adverse factors.

Conclusion Primary site, tumor size, resection margin, and histology subtype were independently associated with survival outcome. A prognostic model for leiomyosarcoma patients revealed four distinct groups of patients with good prognostic discrimination.

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Keywords Leiomyosarcoma · Prognostic factors · Risk stratification model

Introduction

Leiomyosarcoma is one of the most common soft-tissue sarcomas, accounting for 5–10 % of all soft tissue sarcomas [1–3]. It occurs in different sites in the body, approximately half being located in retroperitoneum or intra-abdominal sites. Leiomyosarcomas are excellent examples of the different biology of tumors on the basis of anatomic site. Depending on primary site there may be different prognosis and biological characteristics. Prognostic factors

described in many reports include age, tumor size, depth, necrosis, and vascular invasion. Most previous studies of leiomyosarcomas have used univariate analysis to focus on leiomyosarcoma of the extremities rather than on intra-abdomen leiomyosarcomas [4–7]. In addition, owing to the rarity and heterogeneity of this disease, clinical characteristics and optimum therapeutic strategies have not yet been extensively defined. Given the distinct genetic aberrations of leiomyosarcoma, there is an urgent need to redefine the clinical features and prognosis of subtypes of leiomyosarcoma.

In this study we analyzed clinicopathologic features and prognostic factors for histologically confirmed leiomyosarcoma patients. We also devised a prognostic model specific for the disease to facilitate decision making in leiomyosarcoma on the basis of initial clinical variables.

Patients and methods

Patients

Between June 1988 and Sep 2011 157 patients were newly diagnosed with leiomyosarcoma at the severance hospital in Korea. The criteria for case inclusion were:

1. pathologically confirmed diagnosis of leiomyosarcoma; and
2. complete set of clinical information which included patient demographics, primary tumor site, stage, treatment record, and vital status.

Of the 157 patients, a complete set of clinical data was available for 129 (82.2 %) with M0 stage. The primary site was divided into 6 groups: extremity, pelvis, thoracic cavity, intra-abdomen, retroperitoneum, and head/neck. The pelvis group included uterine, bladder, vagina, pre-pubic area, prostate, cervix, penile, testis, and pelvic mass. The intra-abdomen group included stomach, small bowel, liver, intra-abdominal soft tissue or mass, duodenum, colon, stomach. The retroperitoneum group included retroperitoneal mass, kidney, adrenal gland. The study design was approved by the ethics committee of Yonsei College of Medicine.

Statistics

The primary end point was assessment of survival outcome for resected leiomyosarcoma patients calculated by use of the Kaplan–Meier method. Disease-free survival (DFS) was measured from the time of surgery to initial tumor relapse or death. Overall survival (OS) was defined from the date of diagnosis to the date of death related to

the disease or complication. Survival data were compared for statistically significant differences by use of the log-rank test. OS was assessed with regard to: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, primary site, tumor size, resection margin, and LN stage. Multivariate analysis was performed by using stepwise Cox proportional hazards regression modeling. *P* values less than 0.05 were regarded as statistically significant and all *P* values corresponded to two-sided significance tests. The latter were performed by use of the Cox's proportional hazard regression model.

Results

Patient characteristics

One hundred and twenty-nine leiomyosarcoma patients who underwent surgical resection with curative intent were included in the analysis (Table 1). There were 42 males, and the median age was 56.4 years. Median tumor size was 7.95 cm (range 1–35). The distribution of anatomic locations was: extremity ($n = 25$, 19.4 %), pelvis ($n = 40$, 31.0 %), thoracic cavity (11, 8.5 %), intra-abdomen ($n = 19$, 14.7 %), retroperitoneum ($n = 23$, 17.8 %), and head/neck ($n = 11$, 8.5 %). On the basis of survival outcome we classified the anatomic locations into two categories: abdominal (intra-abdomen and retroperitoneum, $n = 42$) and extra-abdominal (extremity, pelvis, thoracic cavity, and head/neck, $n = 87$). One hundred and two (79.0 %) patients had negative resection margins, 14 (10.9 %) had microscopically positive margins, and 13 (10.1 %) had grossly positive margins.

Because of different characteristics of leiomyosarcoma, we performed analysis separately for those two distinct subsets of patients, as shown in Table 1. Median tumor size was significantly larger for the abdominal group (median 10.5 vs 6 cm, $P < 0.001$) than for the extra-abdominal group. There was no statistically significant difference for age, lymph node status, or histology grade between the two groups.

Treatment modalities and survival outcome

After median follow-up of 7.5 years, 66 patients remained alive without disease recurrence. The 5 and 10-year DFS probabilities were 50.7 and 40.6 %, respectively (Fig. 1a). The 5 and 10-year OS probabilities were 76.7 and 72.9 %, respectively (Fig. 1b). In terms of anatomic sites, 5-year DFS were 39.1, 35.3, 50.5, 63.6, 59.4, and 51.9 % for the abdominal cavity, retroperitoneum, extremity, thoracic cavity, pelvis, and head/neck (Fig. 2a). A similar tendency was also observed for OS (Fig. 2b). For the primary sites,

Table 1 Clinical characteristics of the 129 leiomyosarcoma patients

	Total	Abdomen	Extra-abdomen	<i>P</i> value
No. (%)	129	42 (32.6)	87 (67.4)	
Male (%)	42 (32.6)	19 (45.2)	23 (26.4)	0.064
Age (years)				
Median	56.4	59	54	0.686
Range	22–84	22–84	26–82	
ECOG				
0 (%)	55 (42.6)	16 (38.1)	39 (44.8)	0.099
1 (%)	72 (55.8)	24 (57.1)	48 (55.2)	
≥2 (%)	2 (1.6)	2 (4.8)	0 (0)	
Size (cm)				
Median	7.95	10.5	6	<0.001
Range	1–35	1–35	1–15	
Lymph node				
N0 (%)	123 (95.3)	39 (92.9)	84 (96.6)	0.359
N1 (%)	6 (4.7)	3 (7.1)	3 (3.4)	
Grade				
1	31 (24.0)	13 (31.0)	18 (20.7)	0.442
2	34 (26.4)	10 (23.8)	24 (27.6)	
3	64 (49.6)	19 (45.2)	45 (51.7)	
Resection margin				
R0	102 (79.0 %)	35 (83.3 %)	67 (77.0 %)	0.621
R1	14 (10.9 %)	3 (7.1 %)	11 (12.6 %)	
R2	13 (10.1 %)	4 (9.5 %)	9 (10.3 %)	

R0 resection: complete resection with no microscopic residual tumor (margins are microscopically negative according to the pathologist)

R1 resection: complete resection with no grossly visible tumor as defined by the surgeon, but microscopic cancer may be left behind (margins are microscopically positive according to the pathologist)

R2 resection: partial resection, with grossly visible tumor left behind
ECOG Eastern Cooperative Oncology Group

prognosis was worse for abdominal group than for the extra-abdominal group (median DFS 2.9 vs 9.0 years, $P = 0.04$, Fig. 2c). OS was also similar, with 10-year OS being significantly worse for the abdomen (63.4 vs 79.2 % $P = 0.027$) as shown in Fig. 2d.

Disease recurrence was observed for 66 patients (51.2 %), 13 with local recurrence and 53 with distant metastasis. Several metastatic sites were observed for 14 of these 53 patients, with recurrence in the lung being observed for 11. We compared patterns of recurrence on the basis of primary site, tumor size, lymph node status, and histology grade. Significantly more distant metastasis was observed for the abdominal group than for the extra-abdominal group ($n = 25$, 59.5 % vs $n = 28$, 32.2 %, $P = 0.013$). Higher histology grade also resulted in more frequent distant metastasis (46.9 vs 22.6 %, $P = 0.005$). The main organs were the liver ($n = 12$) for the abdomen group and the lung ($n = 15$) for the extra-abdominal group.

With regard to pattern of recurrence, no statistically significant difference was observed for tumor size or resection margin.

For all patients, administration of adjuvant treatment did not seem to confer survival benefit ($P = 0.8$). We further performed subgroup analysis to identify patients who may benefit most from postoperative radiotherapy or chemotherapy. However, there was no significant difference with regard to adjuvant treatment according to the primary site or resection margin status.

Survival and prognostic factors for survival

The clinical factors predicting poor DFS in univariate analyses were: primary site (abdomen, $P = 0.041$), tumor size (more than 15 cm, $P = 0.05$), resection margin (microscopically or grossly positive margin, $P = 0.02$), and histology grade (grade 2–3, $P = 0.001$). Forward Cox regression was used to establish independent prognostic factors. Independent prognostic factors for survival were primary site ($P = 0.041$, HR 1.7; 95 % CI 1.2–2.8), tumor size ($P = 0.038$, HR 1.9; 95 % CI 1.13–3.38), margin status ($P = 0.019$, HR 2.1; 95 % CI 1.13–3.88), and histology grade ($P = 0.01$, HR 3.59; 95 % CI 1.64–7.87), as shown in Table 2. On the basis of these prognostic factors we performed prognostic grouping according to following criteria: group 1 ($n = 8$), no adverse factor; group 2 ($n = 37$) and 3 ($n = 61$) with 1 and 2 factors; and group 4 ($n = 23$) with 3 or 4 factors. The prognostic model separated patients into 4 different risk groups as shown in Fig. 3. Five-year DFS was 72.9, 59.9, 45.9, and 43.5 %, respectively ($P = 0.048$, Table 3). Five-year OS was also significantly different according to the risk group.

Discussion

In this comprehensive study of the uncommon disease leiomyosarcoma we analyzed clinical features and prognosis. We categorized clinical features into two groups—abdomen and extra-abdomen. On the basis of these clinical features we then established a prognostic model which will, ultimately, facilitate risk-adapted therapeutic strategies.

Previous studies have reported the clinical characteristics and survival outcome of leiomyosarcoma [1, 8–11]. However, most of the studies were for one specific subtype, and current clinical practice is not optimized for different primary sites. Therefore, this comprehensive review of histology, anatomic site, and survival outcome was strongly warranted. We retrospectively analyzed all the primary sites of leiomyosarcoma patients. In this study, the most common primary sites were pelvis and extremity which account

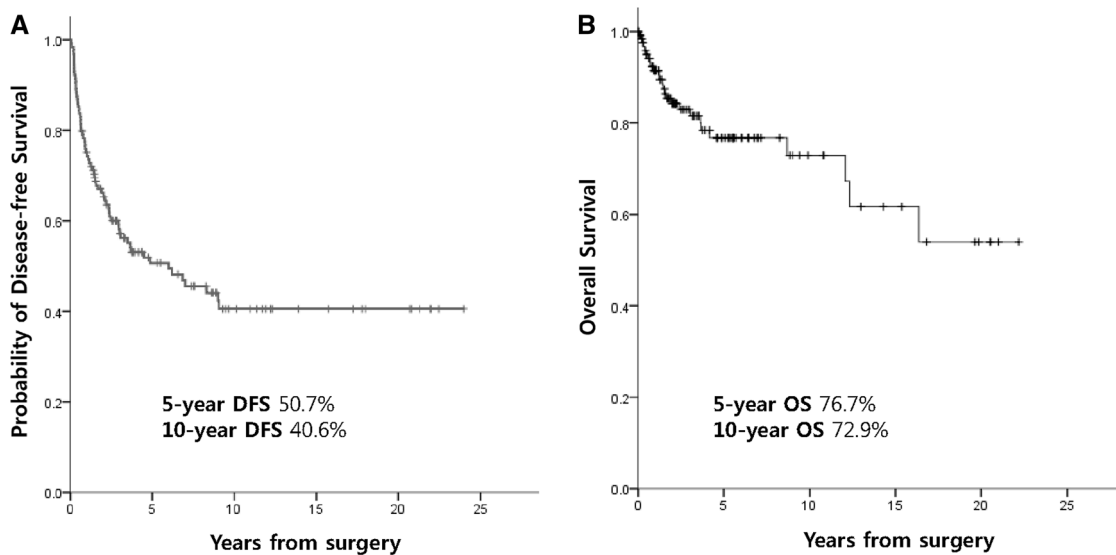


Fig. 1 Disease-free (a) and overall (b) survival for all patients. The 5 and 10-year DFS probabilities were 50.7 and 40.6 %, respectively (a). The 5 and 10-year OS probabilities were 76.7 and 72.9 %, respectively (b)

for half of all cases. Five-year DFS and OS were 50.7 and 76.7 %, respectively.

The prognosis of leiomyosarcoma has been reported after many previous studies [1, 2, 5, 6, 12, 13]. Age, tumor size/depth, mitotic rate, and vascular invasion were reported as important prognostic factors. However, most studies used univariate analysis and these findings have continued to be controversial. In this study we clarified prognostic factors by use of multivariate analysis, and survival outcome was statistically significantly different with those independent factors. In our series, primary site, tumor size, resection margin, and histology grade were found, by multivariate analysis, to be significantly correlated with survival.

Importantly, survival outcome differed significantly depending on the primary site of the leiomyosarcoma. Few studies have reported clinical outcome for the whole body. Oda et al. reported prognostic factors for 267 soft tissue sarcoma patients [14]. However, the prognostic factors were mainly based on histopathology status. From a clinical perspective, primary site is a more reliable factor because of the postoperative treatment option. In the primary analysis, survival outcome was worse for patients with leiomyosarcoma in the abdomen and retroperitoneum; twice as many patients with leiomyosarcoma in the abdomen experienced systemic relapse than those with the disease in other sites. Multivariate analysis demonstrated that anatomic site is an independent prognostic factor for survival. Abdominal area tumors were associated with an approximately two-fold greater risk of death compared with other primary sites. Relapse pattern and involved organ were also different for different primary sites. The abdominal primary site

resulted in more frequent distant metastasis, and mainly in liver, compared with lung recurrence for the extra-abdominal group. Therefore, our study strongly indicates that leiomyosarcomas are excellent examples of different tumor biology depending on anatomic site.

To improve risk-based stratification for therapy, we attempted to establish a prognostic model specifically devised for patients treated by surgical resection with curative intent. In multivariate analysis, primary site, tumor size, resection margin, and histology grade were statistically significant. Therefore, we established prognostic grouping on the basis of a scoring system for these adverse factors. This yielded 4 distinctive groups with different survival outcome. Nonetheless, prospective study is needed to validate this model for a larger population. Given the poor prognosis of patients with one or more risk factors, this subgroup of patients may potentially benefit from more aggressive pre and postoperative treatment; aggressive postoperative treatment in the context of clinical trials is therefore needed for this group.

The efficacy of adjuvant treatment to improve survival outcome has previously been reported for uterine leiomyosarcoma [15, 16]. The Gynecologic Oncologic Group conducted the first prospective randomized trial comparing adjuvant chemotherapy with surgery only for patients with stage I or II uterine sarcoma [16]. However, they could not demonstrate significant improvement in progression-free survival or overall survival as a result of chemotherapy. The study contained a variety of uterine sarcoma patients, and more than half had stage I disease. Considering the relatively good survival outcome of uterine leiomyosarcoma, prognosis was good for these patients and this may

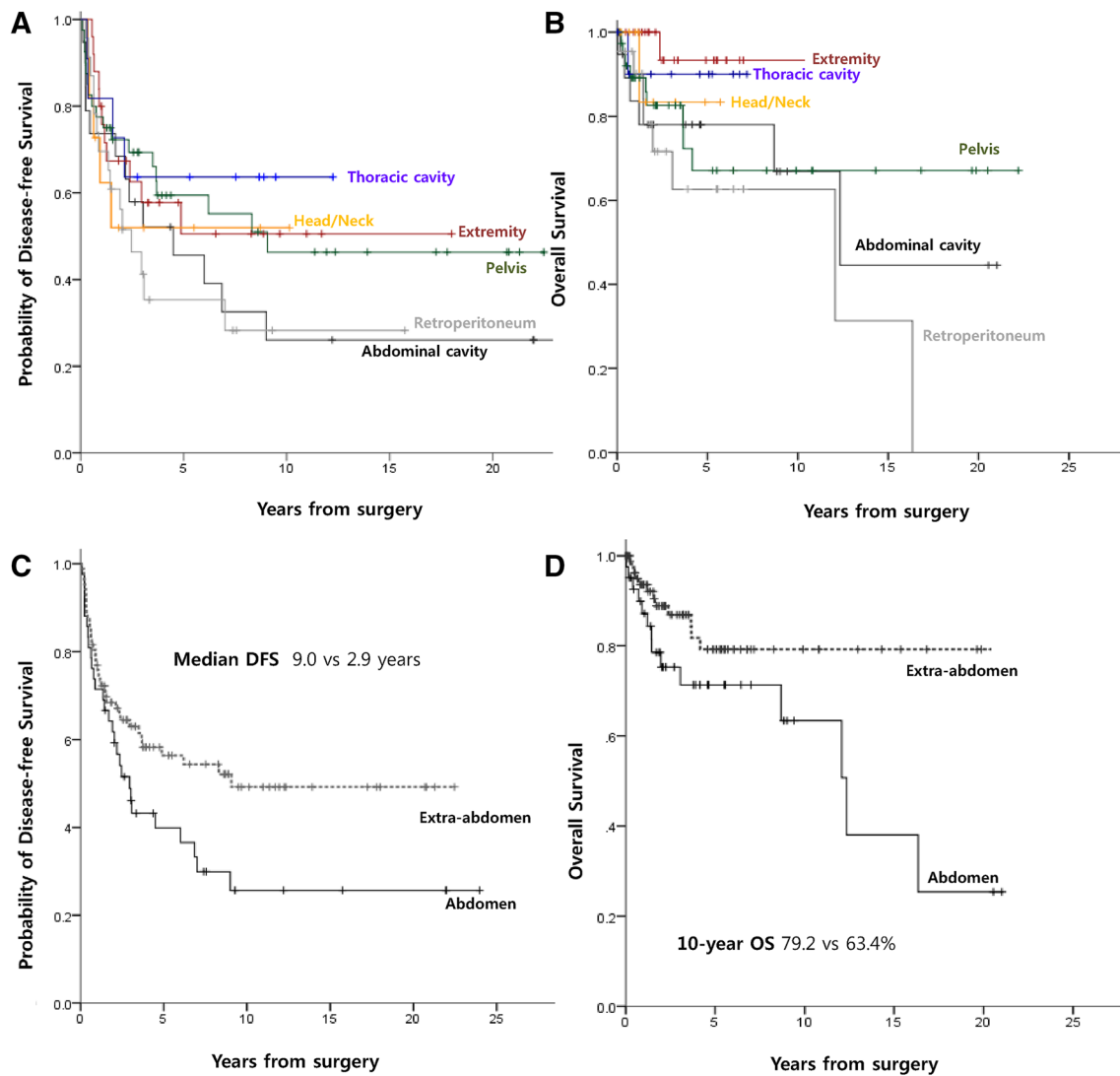


Fig. 2 Survival outcome according to primary site. **a** DFS and **b** OS for each primary site. **c** DFS and **d** OS for the abdominal and extra-abdominal groups. In terms of anatomic sites, 5-year DFS were 39.1, 35.3, 50.5, 63.6, 59.4 and 51.9 % for abdominal cavity, retroperitoneum, extremity, thoracic cavity, pelvis, and head/neck (**a**). The ten-

year OS was similar for OS (**b**). For the primary sites, prognosis was worse for the abdominal group than for the extra-abdominal group (median DFS 2.9 vs 9.0 years, $P = 0.04$, **c**). Similarly, 10-year OS was significantly worse for the abdomen group (63.4 % vs 79.2 % $P = 0.027$, **d**)

Table 2 Prognostic factors for survival for 129 leiomyosarcoma patients who had no distant metastasis (M0)

Factor	Univariate analysis	Multivariate analysis	
	<i>P</i> value	Hazard ratio (95 % CI)	<i>P</i> value
Primary site (extra-abdomen vs abdomen) ^a	0.041	1.7 (1.2–2.8)	0.041
Tumor size (≤ 15 vs >15 cm)	0.05	1.9 (1.13–3.38)	0.038
Resection margin (negative vs positive) ^b	0.02	2.1 (1.13–3.88)	0.019
LN (N0 vs N1–2)	0.57	–	0.25
Grade (1 vs 2–3)	0.001	3.59 (1.64–7.87)	0.01
Adjuvant treatment (no vs yes)	0.262		0.40

^a The anatomic locations were assigned to two groups, abdominal (abdomen and retroperitoneum) and extra-abdominal (extremity, pelvis, thoracic cavity, and head/neck)

^b Positive means microscopically or grossly positive margin

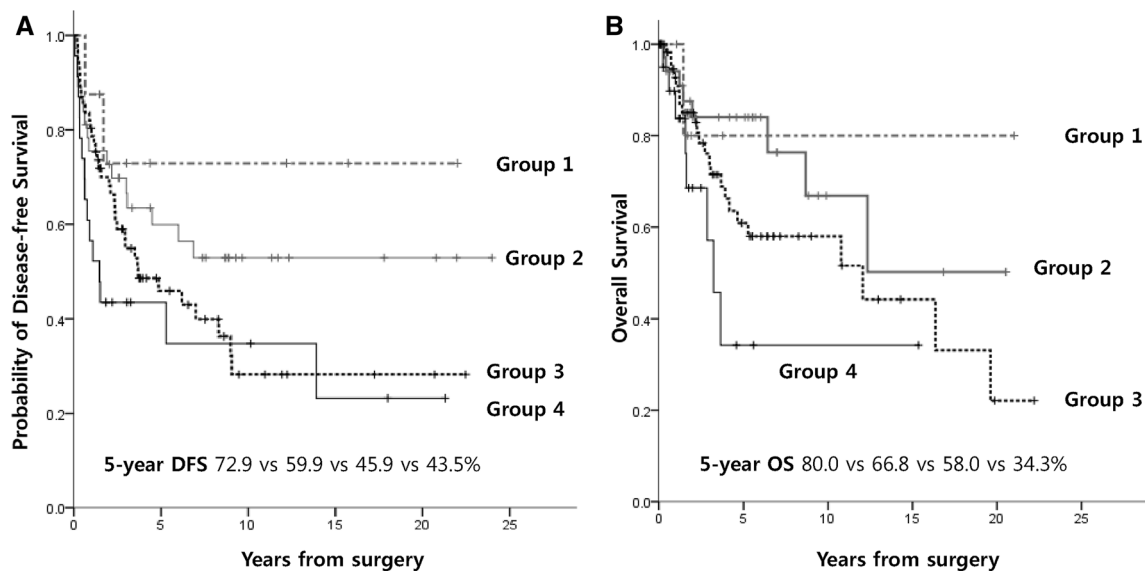


Fig. 3 DFS according to risk group as defined by the prognostic model. The prognostic model separated patients into 4 different risk groups as shown in figure. The 5-year DFS was 72.9, 59.9, 45.9, and

43.5 %, respectively ($P = 0.048$). Five-year OS was also significantly different according to risk group

Table 3 Survival and relative risk of death according to risk group as defined by the prognostic model

Risk group	No. of factors	No. of patients (%)	5-year DFS (%)	% of 5-year OS	HR (95 % CI) for death
Group 1	0	8 (6.2)	72.9	80.0	1
Group 2	1	37 (28.7)	59.9	66.8	1.27 (0.16–10.25)
Group 3	2	61 (47.3)	45.9	58.0	2.28 (0.31–17.0)
Group 4	3–4	23 (17.8)	43.5	34.3	4.06 (0.5–33.0)

DFS disease-free survival, OS overall survival, HR hazard ratio

diminish the benefit of adjuvant chemotherapy. In a follow-up study with sequential treatment with docetaxel/gemcitabine and doxorubicine, 78 % of patients remained progression-free at 2 years, a result which was favorable compared with historical estimates [15]. In a recently reported randomized trial comparing adjuvant chemotherapy followed by radiotherapy with radiotherapy alone, 3-year DFS was 55 % for chemoradiotherapy and 41 % for radiotherapy alone [17]. Three-year OS was also better for sequential adjuvant chemo and radiotherapy. Therefore, on the basis of our prognostic model, risk-based approach for adjuvant treatment is strongly warranted.

This is the first study to comprehensively review and describe the clinical features and prognosis of leiomyosarcoma patients. An aggressive clinical course and high rate of systemic relapse after curative resection was observed for the disease at an abdominal primary site. More aggressive pre and postoperative treatment should thus be considered for patients with high risk factors. Moreover, further validation and postoperative study of different strategies is warranted in the future.

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Conflict of interest The authors declare that they have no conflict of interest.

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