의학석사 학위논문

초기 자궁육종 환자의 원격 전이 예측 모델

Prediction of distant metastasis in patients with early ~ locally advanced uterine sarcoma

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이 논문을 석사학위 논문으로 제출함

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국문요약

배경

자궁육종은 자궁의 중배엽에서 기원하는 매우 드문 악성 종양으로 수술 전 발병을 예측하기 매우 어려운 질환 중 하나이다. 따라서 상당수의 자궁 육종은 수술 전 자궁 근종으로 예측되어 자궁근종절제술을 시행하는 경우도 있으며 자궁근종이라는 가정 하에 자궁근종절단술(morcellation)을 시행하기도 한다. 이는 병기가 낮은 자궁 육종 환자에서도 이후 높은 재발율과 낮은 전체 생존율을 보이는 이유이기도 하다. 같은 자궁육종 1기라도 어떤 환자들은 재발이나 질병의 진행이 빠른 경우가 있는데 현재 병기 결정 방법에서는 그 환자군을 걸러내지 못하고 있다. 따라서 이 연구에서는 자궁 육종 환자들을 대상으로 진단 당시 추후 생존율을 예측하는 모델 및 초기 자궁육종 환자의 원격 전이의 재발 예측 모델을 개발함으로써 수술 후 추가로 치료가 필요한 군을 선별하여 향후 예후에 기여하고자 한다.

연구 방법

2007년 1월 1일부터 2017년 12월 31까지 서울아산병원에서 적어도 한 번 이상의 자궁육종 수술을 받은 환자들을 대상으로 후향적 연구를 진행하였다. 자궁육종은 평활근육종(leiomyosarcoma), 저등급 및 고등급 자궁내막간질육종(low grade endometrial stromal sarcoma, high grade endometrial stromal sarcoma), 악성 뮬러관 종양(malignant mixed Mullerian tumor)을 포함하였다. 대상 환자들의 임상적인 특징을 분석하고 5년 생존율 및 원격 전이를 예측하는 두가지 모델을 개발하였다. 예측모델(nomogram)을 구성하는 변수들은 통계적으로 의미 있는 항목과 임상적으로 질병의 경과에 연관이 있다고 입증된 항목들로 구성하였다. 최종적으로 나이, 조직학적 분류, 종양의 크기, 전이 발생 장소가

포함되었다. 붓스트랩 기술로 예측모델에 대하여 내적 검증을 시행하여 신뢰도를 분석하였다.

결과

189명의 환자들 중 169명의 환자들이 연구에 포함되었으며 분석결과를 바탕으로 예측모델 제작하였다. 5년 생존율을 예측하는 모델에는 169명의 환자들이 모두 포함되었으며 원격전이를 예측하는 모델 개발에는 초기 치료 시 잔여 병변이 있어 재발의 여부를 판단하기 어려운 환자 8명이 제외되어 161명이 포함되었다. 추적관찰의 중앙값은 28.9개월이었으며 질병의 무진행기간의 중앙값은 19개월이었다. 80명(51.5%)의 환자들에게서 재발이나 질병의 진행이 관찰되었으며 60명(35.5%)의 환자들이 사망하였다. 예측된 생존기간은 99개월(95% 신뢰구간 66.7-131.3개월)이었으며 5년 생존율은 61% 였다. 5년 생존율 예측모델의 신뢰도(concordance probability)는 0.838 였으며 붓스트랩으로 교정한 신뢰도는 0.839로 나타났으며 원격전이를 예측하는 모델의 신뢰도는 0.801, 붓스트랩으로 교정한 신뢰도는 0.808이었다.

결론

이 논문을 통해 제시하고 있는 예측모델은 여러가지 종류의 자궁육종 환자들을 대상으로 기존의 병기 설정 방법보다 더 우수하게 5년 생존율을 예측할 수 있다. 또한 초기 자궁육종 환자를 대상으로 기존의 병기 설정 방법으로는 예측하기 어려운 원격 전이의 재발을 예측 할 수 있다. 따라서 초기의 자궁육종 환자들 중에서도 추가 치료가 필요한 자궁육종 환자군을 설정함으로써 자궁육종 치료 및 예후 향상에 도움을 줄 것으로 사료된다.

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1. Introduction

Uterine sarcoma is rare tumor arising from mesodermal origin and is challenging to diagnose before the surgery. Magnetic resonance imaging is helpful in some aspect to differentiate uterine sarcomas from leiomyoma, but any of imaging technique cannot suggest pathognomonic features.(1, 2) Therefore, considerable patients with uterine sarcoma have operations such as myomectomy with uterine mass morcellation in the presumed benign setting. (3) This continues to high recurrence rate and low overall survival rate, even in localized uterine sarcoma. And according to the current guideline provided by National Comprehensive Cancer Network, no adjuvant treatment or systemic chemotherapy is recommended for stage I high-grade endometrial stromal sarcoma, leiomyosarcoma, undifferentiated uterine sarcoma. (4) However, some patients shows fast disease progression or short progression free survival although they did not have advanced stage uterine sarcoma. Thus, I suggest 2 nomograms for uterine sarcoma to predict overall survival and distant recurrence at the time of diagnosis for distinguishing the patients group who require further adjuvant treatment, and which is expected to attributed to improve prognosis.

2. Materials and method

1) Study population

From January 1, 2007 to December 31, 2017, patients who had at least one operation for uterine sarcoma(leiomyosarcoma, low grade endometrial stromal sarcoma, high grade endometrial stromal sarcoma, malignant mixed Mullerian tumor) at out institution were identified. Patients who had initial incidental mass excision or hysterectomy at other hospitals are included, if her staging or debulking operation was done at our hospital and her initial tissue specimen was reviewed at our pathologic department. To meet the criteria for the study population, patients had to have at least one image modality to evaluate tumor size or metastasis before the hysterectomy. In case of unexpected uterine sarcoma after the surgery, metastasis was evaluated by image modality within a month from the final pathologic report. Clinical data collected for the analysis included age at diagnosis, body mass index, preoperative mass size, number and site of metastasis, date of surgery(date of first incidental mass excision and followed secondary staging surgery for those who were not expected to have uterine sarcoma), surgical procedures(laparoscopy or laparotomy, myomectomy or hysterectomy) pathologic analysis(histologic grade, mass size, lymphovascular space invasion, mitotic index, stage, involvement of uterine cervix, regional metastases, distant metastases, lymph node metastases), date and site of first recurrence or progression of disease, date and disease status of last visit and date of death. Preoperative and postoperative tumor size was measured by longest dimension of the tumor described in image modality report and from the pathologic report respectively.

Patients who decided to save their uterus at the time of first diagnosis were not included and cases that could not provide enough information were excluded. Totally, 169 patients are eligible for study.

2) Statistical methods

The first predicted end point of our study was 5-year overall survival, which is the time interval the last visit date or date of death from the first diagnosis. Overall survival was calculated by Kaplan-Meier method. Clinical characteristics including survival rate and recurrence rate were also statistically analyzed.

The second end point was to develop nomograms to predict 5-year overall survival and distant metastasis. For statistical analysis, some continuous variables were transformed to categorical variables. Cox proportional hazards regression analysis and multivariable analysis were used to discriminate factors associated with overall survival and recurrence. Finally, 6 variables were selected to develop nomograms. Calibration curve was gained and bootstrap technic was used for internal validation.

3. Results

1) Demographics of study population

From 2007 to 2017, 189 patients had operation for uterine sarcoma. However, 13 patients did not have enough information, 6 patients saved the uterus and 1 patient did not revisit the hospital after total hysterectomy. Finally 169 patients were included for the analysis. The clinical characteristics of patients are on the Table 1-1 and 1-2. The median follow-up was 28.9 months (range, 0.6-166.3 months). The median progression free duration was 19 months (range, 0-129 months). Of the 169 patients, 80(51.5%) patients experienced recurrence or disease progression and 60(35.5%) patients were died for the disease. Estimated median OS was 99 months (95% confidence interval, 66.7-131.3 months, Fig 1.) and 5-year overall survival rate was 61%. Frequency of recurrence or progression of disease by stage is on the table 2. Uterine sarcoma was usually detected in stage 1. Rate of recurrence or progression of disease was higher in more advanced stage. 5-year overall survival by stage were on the table 3 and Kaplan-Meier graph is on the figure 2.

Characteristic		Number of patients (N=169)	%
Age			
	Median	50	29.6
	Range	20-73	
Incidental mass excision			
	No	99	58.6
	Yes	70	41.4
Morcellation			
	No	114	67.5
	Yes	54	32.0
Histology			
	LMS	67	39.6
	LG ESS	46	27.2
	HG ESS	7	4.1
	MMMT	49	29.0
Stage			
	I	97	57.4
	II	16	9.5
	III	28	16.6
	IV	28	16.6
Cx invasion			
	No	144	85.2
	Yes	25	14.8
Size(mm)			
	Median	80	47.3
	Range	10-300	
LVSI			
	No	106	62.7
	Yes	63	37.3
Metastasis			
	No	103	60.9
	Yes	66	39.1
	pelvic metastasis	24	14.2
	abdominal metastasis	26	15.4
	distant metastasis	16	9.5
PLN metastasis		29	17.2
PALN metastasis		17	10.1

Table 2-1. Characteristics of study population LMS, leiomyosarcoma; LG-ESS, low-grade endometrial stromal sarcoma; HG-ESS, high-grade endometrial stromal sarcoma; MMMT, malignant mixed Mullerian tumor

Follow up(month)		
Median	28.9	
Range	0.6-166.3	
Progression free duration(month)		
Median	19	
Range	0-129	
Survival(month)		
No. of patients	109	64.5 %
Estimated mean OS	99	
95% CI	66.7-131.3	

Table 1-2. Characteristics of study population Follow up duration and estimated mean overall survival

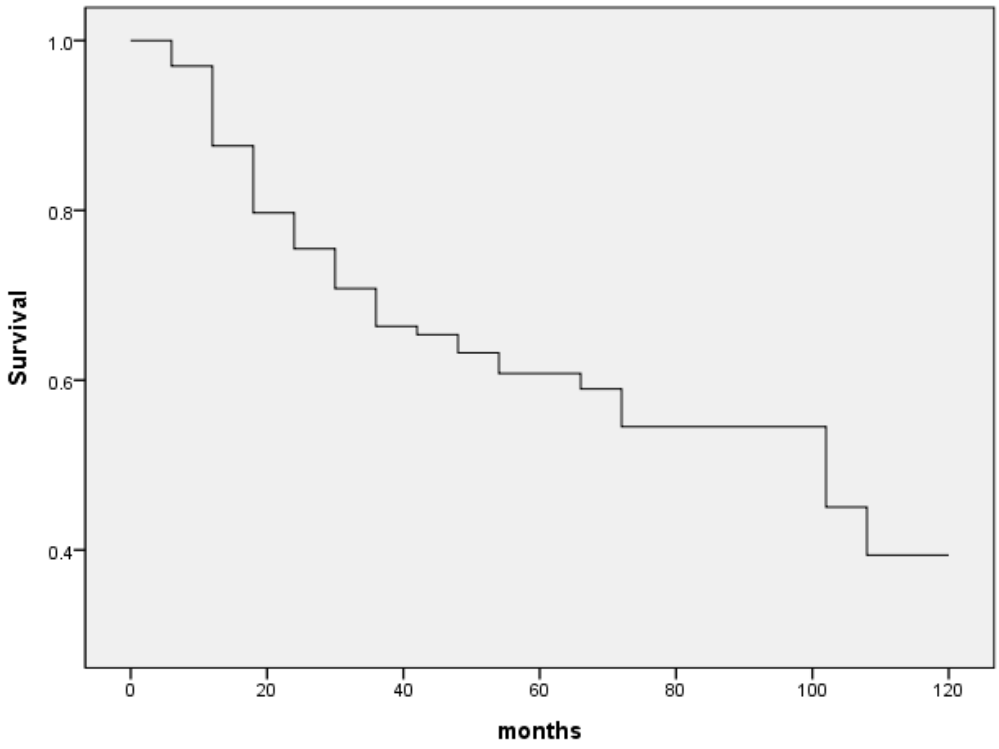

Figure 4. Overall survival of uterine sarcoma patients This graph shows the median overall survival of study population. The estimated median overall survival was 99 months, with 95% confidence interval 66.7-131.3 months.

		Stage				Total
		1.00	2.00	3.00	4.00	
No recurrence	Number of patients	63	7	7	4	81
	%	64.9%	43.8%	25.0%	14.3%	48.5%
Recurrence or PD	Number of patients	34	9	21	24	83
	%	35.1%	56.3%	75.0%	85.7%	51.5%
	Sum	97	16	28	28	169

Table 2. Frequency of recurrence or disease progression by stage Recurrence or progression of disease rate is higher in more advanced stage.

Stage	Total	Death	Mortality	5Y OS,%
1.00	97	17	17.5%	78.9%
2.00	16	4	25.0%	73.8%
3.00	28	18	64.3%	29.4%
4.00	28	21	75.0%	15.6%
Total	169	60	35.5%	61%

Table 3. Mortality rate and 5 year overall survival by stage The results shows higher mortality rate and lower 5Y OS in the more advanced stage

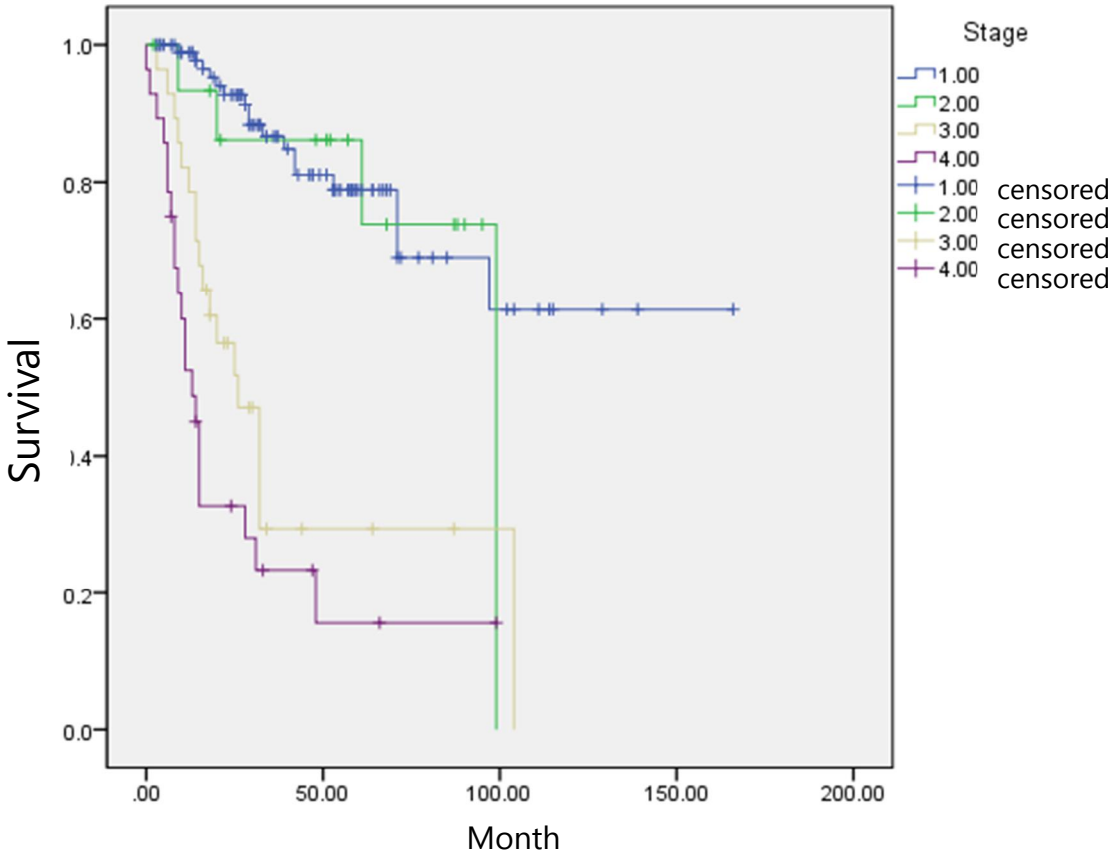

Figure 5. Kaplan-Meier graph for uterine sarcoma by stage Survival is significantly different between early stage(1,2) and advanced stage(3,4)

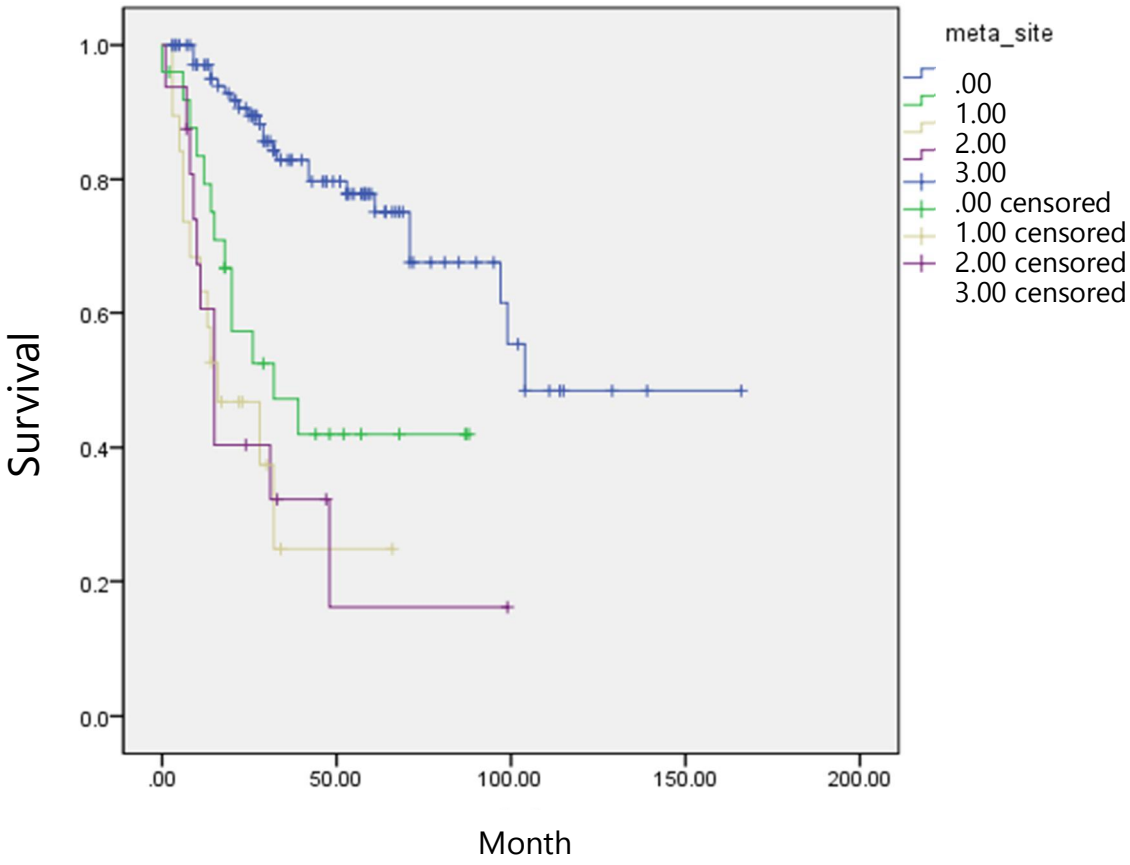

Figure 6 Kaplan-Meier graph for uterine sarcoma by metastatic site Survival curves by metastatic site are slightly different with the curves by stage. Blue, confined to uterus; green, pelvic metastasis including pelvic lymph node metastasis; yellow, abdominal metastasis including paraaortic lymph node metastasis; purple, distant metastasis

2) Nomogram to predict 5-year survival

All of 169 patients were included to analysis for 5-year overall survival. By univariate cox regression analysis, almost every variables were related to survival(table 4-1.). However by multivariable cox regression analysis, histology, size, distant metastasis were significantly associated to survival(table 4-2).

Developed nomogram is provided in Fig 4. Totally, 6 variables(age, histology, tumor size, 3 types of metastatic site) were included in the nomogram. Variables that shows significant hazard ratio were assigned to larger point and histology was the strongest factor. Concordance probability (CP) of this nomogram was 0.838(95% CI, 0.761-0.915) and the bootstrap-validated CP was 0.839. Internal validation was done by bootstrap technique. (Fig 5.)

Clinically, a patients can gain points according to the nomogram. Patient of serial number 47 was 47 years old(49 points) and her tumor was leiomyosarcoma(98 points) on the final pathologic report. Size was 100mm(42 points), there was no metastasis. She totally gained 189 points and predicted 5-year survival was less than 0.6.

	Univariate	
	HR (95% CI)	p-value
Age		
<50	Reference	
≥50	2.375(1.367-4.127)	0.002
Incidental mass excision	0.523(0.301-0.910)	0.022
Morcellation		
No	Reference	
Mass excision(+)	0.334(0.046-2.427)	0.278
Morcellation(+)	0.595(0.321-1.102)	0.099
Histology		
LMS	Reference	
LGESS	0.201 (0.070-0.577)	0.003
HGESS	1.264 (0.298-5.349)	0.751
MMMT	1.840 (1.073-3.157)	0.027
Stage I	Reference	
Stage II	1.300 (0.436-3.880)	0.638
Stage III	5.441 (2.784-10.636)	<0.001
Stage IV	9.435 (4.915-18.113)	<0.001
Cervix invasion	2.657 (1.510-4.677)	0.001
Size		
<5cm	Reference	
≥5cm	2.788(1.267-6.139)	0.011
LVSI	3.339 (1.973-5.648)	<0.001
Metastasis	5.296 (3.053-9.186)	<0.001
PALN(+)	4.197 (2.276-7.737)	<0.001
PLN(+)	3.606 (2.087-6.230)	<0.001

Table 4-1. Survival associated factors and univariable analysis CI, confidence interval; HR, hazard ratio; LMS, leiomyosarcoma; LG-ESS, low-grade endometrial stromal sarcoma; HG-ESS, high-grade endometrial stromal sarcoma; MMMT, malignant mixed Mullerian tumor; LVSI, lymphvascular space invasion; PALN, paraaortic lymph node; PLN, pelvic lymph node

	Multivariate	
	HR (95% CI)	p-value
Age	1.029(0.996-1.063)	0.083
Histology		0.007(overall)
LMS	Reference	
LGESS	0.173(0.051-0.592)	0.005
HGESS	0.831(0.182-3.801)	0.812
MMMT	1.030(0.505-2.102)	0.935
Size		
<10cm	Reference	
≥10cm	2.132(1.192-3.814)	0.011
Metastasis		
Pelvic metastasis	2.000(0.989-4.042)	0.054
Abdominal metastasis	2.085(1.015-4.285)	0.450
Distant metastasis	2.589(1.247-5.374)	0.011

Table 4-2. Survival associated factors and multivariate analysis CI, confidence interval; HR, hazard ratio; LMS, leiomyosarcoma; LG-ESS, low-grade endometrial stromal sarcoma; HG-ESS, high-grade endometrial stromal sarcoma; MMMT, malignant mixed Mullerian tumor

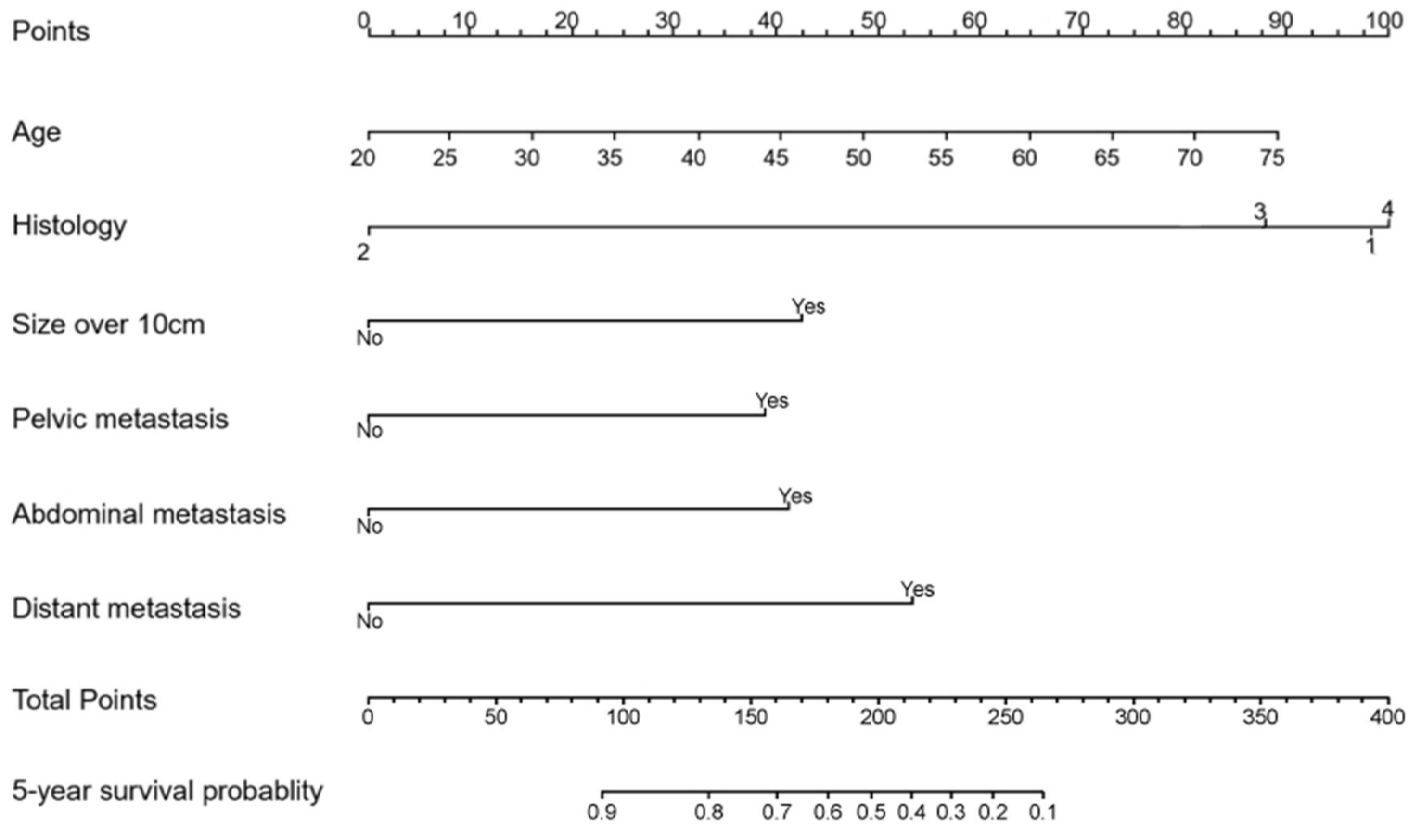

Figure 4. Nomogram for 5-year overall survival The numbers represent subtypes of uterine sarcoma; 1 for leiomyosarcoma, 2 for low-grade endometrial stromal sarcoma, 3 for high-grade endometrial stromal sarcoma and 4 for malignant mixed Mullerian tumor.

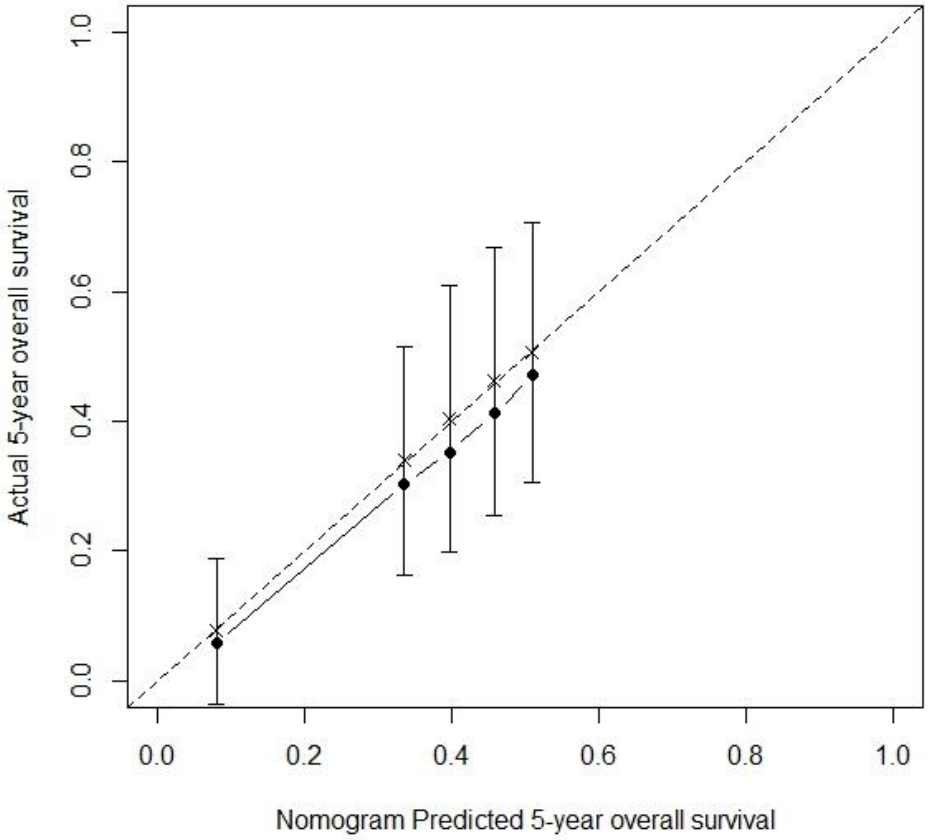

Figure 5. Calibration curve for nomogram to predict 5-year overall survival The actual 5-year overall survival were estimated by Kaplan-Meier method. After prediction by the nomogram, patients were grouped by the scale. 95% confidence interval of each group was expressed as vertical bars. Dashed line is the ideal line for the nomogram and solid line is the result of scoring and prediction by the nomogram. Dots represent predictive accuracy, and crosses indicate the bootstrap-correction. The curve's maximum error was 0.046, average error was 0.036, intercept was -0.018 and slope was 0.949.

3) Nomogram to predict distant metastasis as a recurrence

For the nomogram to predict distant recurrence, 8 patients were excluded because of the residual tumor after the first-line treatment. 161 patients was analyzed by multivariable cox regression analysis, age, size, pelvic metastasis were significantly associated to distant recurrence(table 5).

Developed nomogram is provided in Fig 6. Totally, 6 variables(age, histology, tumor size, 3 types of metastatic site) were included in the nomogram. Concordance probability (CP) of this nomogram was 0.801(95% CI, 0.706-0.895) and the bootstrap-validated CP was 0.808. Calibration curve was on the Fig 7.

Similar to the nomogram for 5-year overall survival, patient of serial number 47 gained 94 points (45 points for age, 28 point for leiomyosarcoma type, 21point for tumor size). Her predicted distant recurrence was near 0.3.

	Multivariate	
	HR (95% CI)	p-value
Age	1.057(1.018-1.098)	0.004
Histology		0.081(overall)
LMS	Reference	
LGESS	0.422(0.150-1.186)	0.102
HGESS	2.609(0.707-9.620)	0.150
MMMT	0.962(0.439-2.106)	0.927
Size		
<10cm	Reference	
≥10cm	1.912(1.034-3.535)	0.039
Metastasis		
Pelvic metastasis	2.168(1.054-4.463)	0.036
Abdominal metastasis	1.961(0.908-4.234)	0.087
Distant metastasis	2.289(0.984-5.322)	0.054

Table 5. Recurrence associated factors and multivariate analysis CI, confidence interval; HR, hazard ratio; LMS, leiomyosarcoma; LG-ESS, low-grade endometrial stromal sarcoma; HG-ESS, high-grade endometrial stromal sarcoma; MMMT, malignant mixed Mullerian tumor

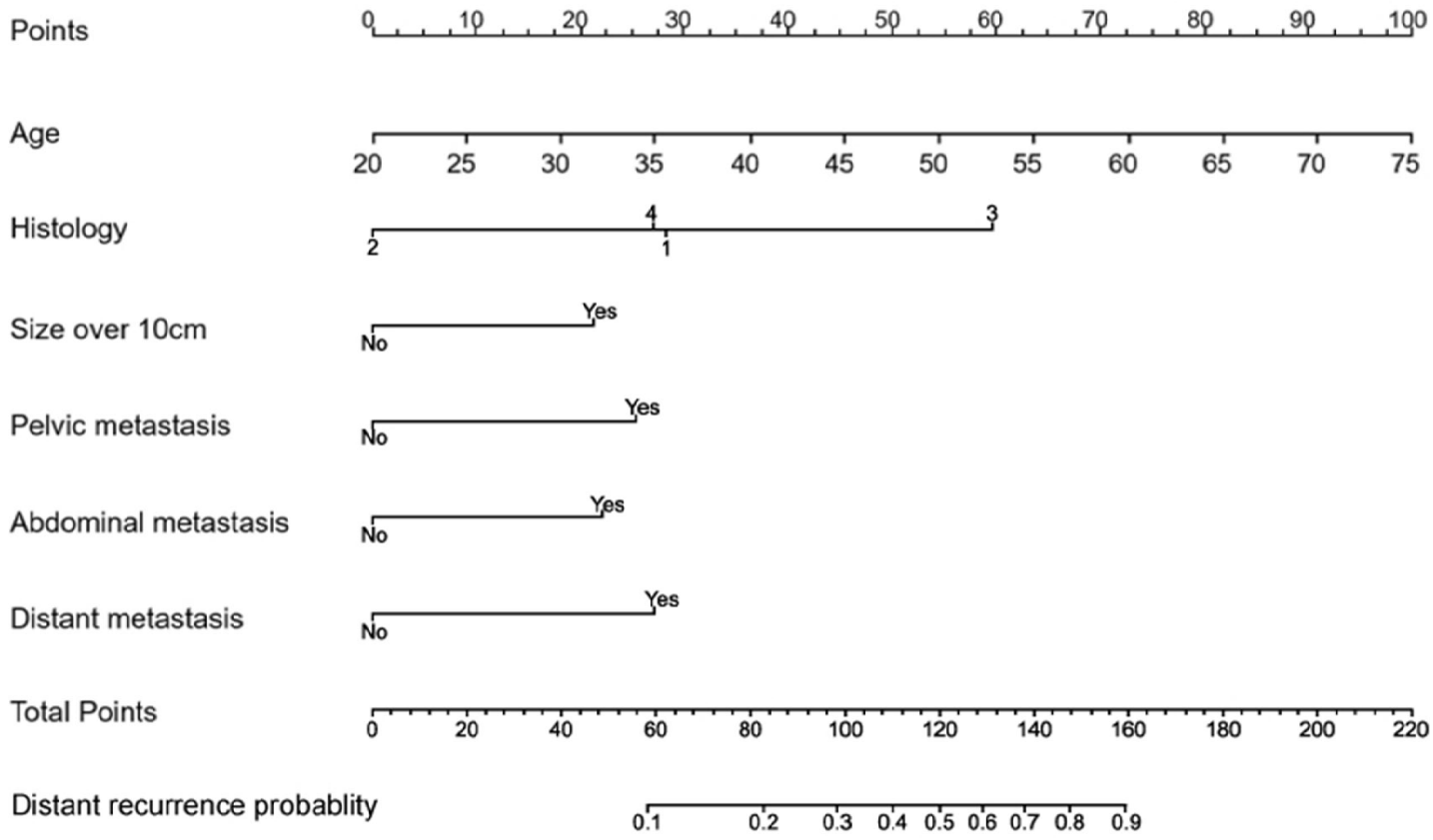

Figure 6. Nomogram for distant recurrence The numbers represent subtypes of uterine sarcoma; 1 for leiomyosarcoma, 2 for low-grade endometrial stromal sarcoma, 3 for high-grade endometrial stromal sarcoma and 4 for malignant mixed Mullerian tumor.

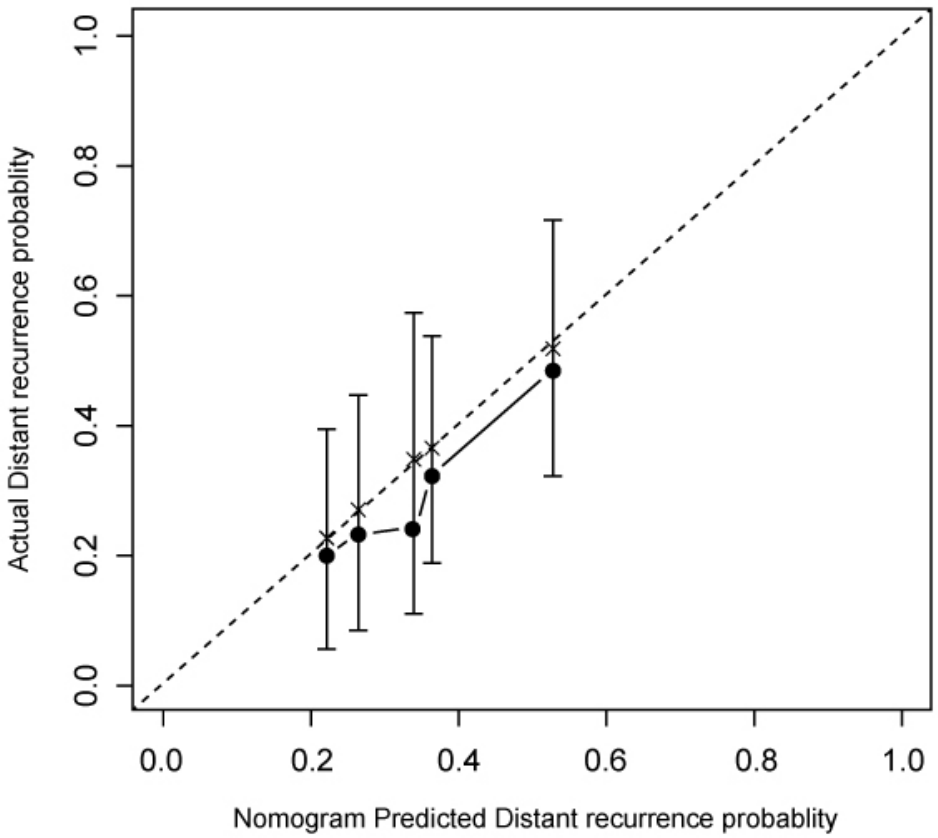

Figure 7. Calibration curve for nomogram to predict distant recurrence The actual distant recurrence and estimated recurrence by nomogram were compared. After prediction by the nomogram, patients were grouped by the scale. 95% confidence interval of each group was expressed as vertical bars. Dashed line is the ideal line for the nomogram and solid line is the result of scoring and prediction by the nomogram. Dots represent predictive accuracy, and crosses indicate the bootstrap-correction. The curve's maximum error was 0.102, average error was 0.045, intercept was -0.022 and slope was 0.933.

4. Discussion

Treatment for uterine sarcoma is still challenging. Because distant spread of disease is a main limitation in the treatment of uterine sarcoma and mortality is very high in patients who show local recurrences or distant metastases, a need for effective adjuvant treatment is arising.(5, 6) Currently, the effect of adjuvant treatment for uterine sarcoma is controversial but various clinical trials are ongoing. One of the most recent agent for sarcoma, Olaratumab, shows significant improvement of 11.8 months in median overall survival.(7) On the strength of several clinical trials, it is getting more important to discriminate the proper patients group for adjuvant treatment.

Nomogram is useful tool for various types of cancer to predict specific event such as nodal metastasis, overall survival or treatment response based on the clinical information that the patients had at the time of diagnosis.(8-10) Because current staging system for uterine sarcoma shows poor performance to predict prognosis, a novel nomogram to predict survival for uterine leiomyosarcoma was developed.(11, 12) Also, a few nomograms to predict metastasis and survival retroperitoneal sarcoma or soft tissue sarcoma were reported.(13, 14)

However, there was no nomogram for uterine sarcoma that embrace several histology. Besides, nomogram which compares subtypes' prognosis together is not reported yet, although it is well known that low grade endometrial stromal sarcoma shows relatively better prognosis but leiomyosarcoma, high grade endometrial stromal sarcoma and malignant mixed mullerian tumor are very aggressive.(5) Also, some types of uterine sarcoma are extremely rare, a useful tool that covers those rare types is strongly necessary to understand the patients.

When developing these nomograms, statistically significant variables were selected by the results of multivariable analysis and some other variables that were previously reported to be strongly associated with the survival or recurrence(15, 16). In the current staging system, the furthest metastasis decide the stage. However, in this nomogram, all of the metastatic site is considered as

a risk factor, so points are raising in the situation of multiple site metastases. Cervical invasion, lymphovascular invasion, lymph node metastasis had been proved as a risk factors though various studies(15, 16) but were not significantly associated with prognosis in this study. Those factors were not included as variables.

Among the 6 variables of this nomogram, morcellation and pathologic stage were not included. Morcellation has been thought to be associated to worse outcome in multiple studies. (3, 17) But when analyzing the associated variables, morcellation was mostly performed on the mass that was expected to benign uterine mass. Almost of those cases were confirmed to stage 1 or 2 on the final pathologic report, I discard morcellation as a variable with apprehension of bias.

Stage is one of the strongest factor to be associated with 5-year survival. However, nomogram is developed to overcome the shortness of current staging system and staging is kind of categorization of various factors that overlapped with the variables already included in the nomogram. I decided to deselect stage to avoid duplicate error.

5. Conclusions

There are some limitations in this study. The study population is small(161-169 patients) so external validation was not included. And patients' medical data was collected retrospectively that the distribution of study population was not even.

However, these nomograms cover 4 types of histology of uterine sarcoma and demonstrate relative risk of death and distant metastasis by histology. Metastases were separated to pelvis, abdomen, distant site and lymph nodes to weigh the importance by the range. Therefore we could line the patients by measuring the score which were in the same stage group before.

These nomograms can suggest a new patients group that who need adjuvant treatment even in early stage of uterine sarcoma. With modification though the further study and external validation, these nomograms could be an option to improve prognosis of uterine sarcoma.

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Abstract

Introduction

Uterine sarcoma is difficult to diagnose before the surgery and sometimes it presumed as a benign mass. And uterine sarcoma shows high recurrence rate and low overall survival rate even in the early stage. It means that the current system cannot discriminate the patients who has worse prognosis and recurrent possibility. There is a need of a novel uterine sarcoma nomograms to predict overall survival and distant metastasis at the time of diagnosis for distinguishing the patients group who require further adjuvant treatment, and which is expected to attributed to improve prognosis.

Methods

From January 1, 2007 to December 31, 2017, patients who had at least one operation for uterine sarcoma(leiomyosarcoma, low grade endometrial stromal sarcoma, high grade endometrial stromal sarcoma, malignant mixed Mullerian tumor) at out institution were identified. The patients' medical record were analysis to predict 5-year overall survival and distant metastasis. Variables for nomogram were selected based on the statistical significance and clinical evidence. Final model included age, histology, mass size, metastatic site. Calibration curve was gained and bootstrap technic was used for internal validation

Results

169 patients were included in the study among the 189 patients. The median follow-up was 28.9 months (range, 0.6-166.3 months). The median progression free duration was 19 months (range, 0-129 months). Of the 169 patients, 80(51.5%) patients experienced recurrence or disease progression and 60(35.5%) patients were died for the disease. The estimated median overall survival was 99

months, with 95% confidence interval 66.7-131.3 months and estimated 5-year overall survival rate was 61%. For nomogram to predict 5-year survival, all of 169 patients were included and for the model to predict distant metastasis, 161 patients were analyzed except 8 patients who had residual lesion after the first-line treatment. After statistical analysis, nomograms were developed with 6 variables. Concordance probability of nomogram for 5-year overall survival was 0.838 and 0.839 by the bootstrap-corrected estimates and CP of nomogram for distant metastasis was 0.801 and 0.808 respectively.

Conclusions

There nomograms can predict 5-year overall survival and distant metastasis more accurate than the current staging system. With these nomograms, a new patients group that who need adjuvant treatment could be discriminated. With modification though the further study and external validation, these nomograms could be an option to improve prognosis of uterine sarcoma

Keyword: Uterine sarcoma, nomogram, overall survival, distant metastasis