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Prognostic Factors for Endometrial and Cervical Cancers of Uterus Treated With Immune-cell Therapy: A Retrospective Study

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Abstract. *Background/Aim: In this retrospective study, we aimed to investigate the efficacy of immune-cell therapy using T lymphocytes activated in vitro with or without dendritic cell vaccination in combination with standard therapies in terms of the survival of patients with advanced or recurrent endometrial and cervical cancers of the uterus. Patients and Methods: A total of 187 patients with advanced or recurrent uterine cancer were enrolled in this study. The correlation between overall survival and various clinical factors was examined by univariate and multivariate analyses. Results: Univariate analysis revealed that the prognosis was improved in uterine cancer patients who received immune-cell therapy without prior chemotherapy or without distant metastasis. Multivariate analysis demonstrated that the absence of prior chemotherapy for endometrial cancer and liver/lung metastasis of cervical cancer are indications for immune-cell therapy. Conclusion: Survival benefit in uterine cancer patients could be potentially obtained by a combination of immune-cell therapy with other therapies.*

Uterine cancers, such as endometrial and cervical cancers, are common pelvic gynecological malignancies. It has been reported that the morbidity of endometrial and cervical cancers in Japan was observed in 14,909 and 10,776 cases in 2018, respectively (1). Tumors of the female genital tract represent a huge health problem in Japan (2). Furthermore, the mortality is estimated to be more than 2,500 cases for each of these cancers in 2018 and is still increasing (1).

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For endometrial cancer, no standard screening test exists; it is often diagnosed at stage I/II owing to relatively frequent vaginal bleeding as the first symptom (3). More than 8% of the patients develop distant metastases at the time of diagnosis with limited response to treatments. In advanced or recurrent endometrial cancer, treatment options are very limited and include the administration of cytotoxic chemotherapy (primarily with taxanes, anthracyclines, and platinum drugs) (3, 4).

In the case of cervical cancer, important goals of prevention and treatment have been achieved: the worldwide spread of the Papanicolaou test has markedly increased the rate of diagnosis of precancerous conditions/early-stage tumors, and the extensive implementation of human papillomavirus (HPV) vaccination programs is expected to result in a massive decrease in the incidence of cervical cancer in the next few years (5-8).

Despite the differences in the clinical and molecular profiles between endometrial and cervical cancers, when these cancers progress to the advanced/metastatic stage, they both have poor prognosis and unsatisfactory outcomes with conventional chemotherapy. Thus, there is an urgent need to explore new treatment strategies, such as immunotherapy (9). The immune system can protect the host from tumorigenesis through immune surveillance mechanisms (10). One of the mechanisms attributed to the occurrence or development of cancer is the deficiency of the immune system. Various strategies, which include the use of cytokines, cancer vaccines, checkpoint inhibitors, and adoptive cell transfer (ACT), have been developed to improve the immune function of cancer patients. Strategies to block the programmed death 1 (PD1) pathway have been markedly developed over the last 2-3 years, with novel agents already approved for various cancers, including lung cancer, head and neck cancer, renal cancer, gastric cancer, esophageal cancer, and melanoma, and other agents at different steps of clinical development (11). There

are convincing data supporting the immunogenicity of these agents against gynecological malignancies, which may represent an ideal target for immunotherapy (9).

ACT is a form of passive immunotherapy using immune cells that are exogenously cultured or manipulated to promote an antitumor immune response (12). In ACT, cells from the blood or bone marrow are isolated from a patient, activated and expanded *in vitro*, and reinfused into the same patient (autologous) or a different patient (allogeneic). Several studies using ACT for advanced stage uterine cancers have shown some encouraging results in some patients, but the number of patients enrolled in such studies was small, and the efficacy of ACT for uterine cancer patients remains unclear (13-15).

In this study, we retrospectively analyzed patients with advanced and recurrent uterine cancer who had been administered immune-cell therapy with conventional therapy at the clinics of the Seta Clinic Group.

Patients and Methods

Patients. The database of patients administered immune-cell therapy at the clinics of the Seta Clinic Group was searched to identify patients with uterine cancer (endometrial and cervical cancers). As a result, 323 patients (148 with endometrial cancer and 175 with cervical cancer) were identified and enrolled in this study. We retrospectively reviewed the medical records of those administered αβT cell therapy, dendritic cell (DC) vaccine therapy, or both between 1999 and 2015. The study protocol was approved by the Research Ethics Committee of the Seta Clinic Group. Available data on age, sex, performance status (PS) score on the Eastern Cooperative Oncology Group (ECOG) scale, metastasis sites, clinical stage, treatments, and vital status were extracted from the medical records of the patients.

Treatment. For αβT cell therapy, activated lymphocytes were generated as previously described (16). In brief, peripheral blood mononuclear cells (PBMCs) were isolated from a patient's peripheral blood using Vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The PBMCs were activated in a culture flask with an immobilized monoclonal antibody to CD3 (Jansen-Kyowa, Tokyo, Japan) in Hymedium 930 (Kohjin Bio, Saitama, Japan) containing 1% autologous serum. The PBMCs were then cultured for 14 days with 700 IU/ml recombinant interleukin-2 (IL-2) (Proleukin®; Chiron, Amsterdam, the Netherlands), after which, 3-10×10^9 cells were harvested and suspended in 100 ml of normal saline for intravenous injection. To prepare a DC vaccine, PBMCs were collected from the patients by leukapheresis and allowed to adhere to a plastic culture flask. The adherent cell fraction was used for DC culture for 6 days using a medium supplemented with 50 ng/ml IL4 (Primmune Corp., Osaka, Japan) and 50 ng/ml granulocyte macrophage colony-stimulating factor (GM-CSF) (Primmune Corp.) to generate immature DCs. The DCs were pulsed with antigenic tumor-specific peptides or an autologous tumor lysate and allowed to mature for 24 h. After the culture, 1-10×10^6 mature DCs were harvested and suspended in 1 ml of normal saline for subcutaneous injection, and then cryopreserved until the day of administration. Immune-cell therapy consisted of αβT cell therapy, DC vaccine therapy, or both (hereafter, called combined immune-cell therapy) and was commonly administered 6 times, that was, every 2 weeks for 3 months, as one course.

Assessment. Overall survival (OS) was defined as the length of time from the initial administration of immune-cell therapy to death from any cause; it was calculated for every patient. The Kaplan–Meier analysis was used to calculate survival probabilities for all patients.

Statistical analyses. The OS of the patients was examined by the Kaplan–Meier analysis with the log-rank test, and the hazard ratio was obtained by Cox regression methods in univariate and multivariate analyses. All statistical analyses were two-sided and performed using JMP, version 11.2.0 for Microsoft Windows 7 (SAS, Cary, NC, USA). Differences were considered statistically significant when $p<0.05$.

Results

Patient selection. A total of 323 patients with uterine cancer were enrolled in this study (Figure 1). Among them, 148 patients were confirmed by biopsy to have endometrial cancer and 175 patients to have cervical cancer. Of the 148 patients with endometrial cancer, 80 had advanced or recurrent cancer, 34 patients were excluded because of insufficient data and 34 were excluded because immune-cell therapy had been administered as a prophylaxis against recurrence. Of the 175 patients with cervical cancer, 107 had advanced or recurrent cancer, 36 patients were excluded because of insufficient data and 32 were excluded because they had undergone prophylactic immune-cell therapy.

The patients' characteristics are summarized in Table I. In this study, the correlations between OS and various factors including age, PS score, clinical stage, histologic type, chemotherapy, radiotherapy, and immune-cell therapy were evaluated by univariate analysis and multivariate Cox regression analysis.

Overall survival. The median age of the patients with advanced or recurrent endometrial cancer was 62 (80 patients; range=18-86 years) and that with cervical cancer was 49 (107 patients; range=30-80 years), as shown in Table I. From the initiation of administration of immune-cell therapy up to the time of analysis, the median survival times (MSTs) of patients with advanced or recurrent endometrial and cervical cancers were 24.0 months and 15.5 months, respectively (Figures 2 and 3). The 3- and 5-year OS rates of patients with endometrial cancer were 29.7% and 27.2%, respectively (Figure 2). In cervical cancer patients, the 3- and 5-year OS rates were 30.0% and 20.5%, respectively (Figure 3). There were no significant differences in survival time in relation to age, PS score, clinical stage, and histologic type between endometrial and cervical cancer patients (Figures 4 and 5, Table II).

We then examined the effect of treatment strategy on the survival time of patients with endometrial and cervical cancers. In the case of endometrial cancer, there was no significant difference in survival time in relation to combined immune-cell therapy or prior therapy with surgical operation or radiotherapy (Figure 6 and Table III). The patients without chemotherapy

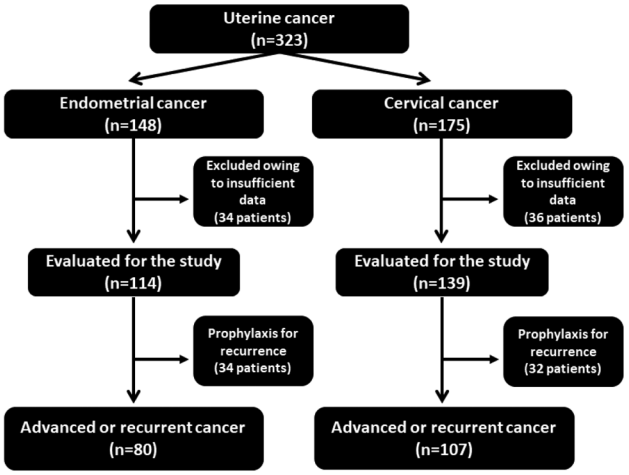


Figure 1. *Procedure for selection of patients enrolled in this study.*

Table I. *Patient characteristics.*

Characteristic	Endometrial cancer (%)	Cervical cancer (%)
Total, n	80	107
Median age (range), years	62 (18-86)	49 (30-80)
≥55	62 (77.5)	36 (33.6)
<55	18 (22.5)	71 (66.4)
Performance status		
0	60 (75.0)	76 (71.0)
1-4	20 (25.0)	31 (29.0)
Clinical stage		
II	18 (22.5)	32 (29.9)
III	4 (5.0)	31 (29.0)
IV	33 (41.3)	27 (25.2)
Unknown	25 (31.3)	17 (15.9)
Histology		
Squamous cell carcinoma	2 (2.5)	61 (57.0)
Adenocarcinoma	63 (78.8)	29 (27.1)
Adenosquamous cell carcinoma	1 (1.3)	4 (3.7)
Others	14 (17.5)	13 (12.1)
Treatment		
Operation		
Yes	75 (93.8)	63 (58.9)
No	5 (6.3)	44 (41.1)
Chemotherapy		
Yes	74 (92.5)	79 (73.8)
No	6 (7.5)	28 (26.2)
Radiation therapy		
Yes	24 (30.0)	57 (53.3)
No	56 (70.0)	50 (46.7)
Immunotherapy		
αβT	50 (62.5)	76 (71.0)
DC	1 (1.3)	2 (1.9)
αβT+DC	17 (21.3)	20 (18.7)
Others	12 (15.0)	9 (8.4)

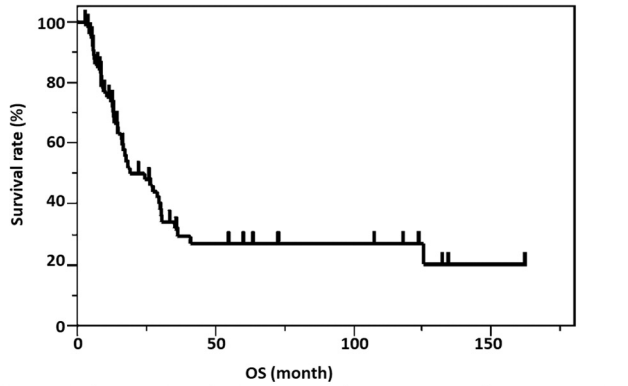
αβT: Activated lymphocyte therapy; DC: dendritic cell vaccine therapy.

before the administration of immune-cell therapy showed better prognosis than those with prior chemotherapy (HR=5.731; 95%CI=1.742-35.355; p=0.0018), but the combined immune-cell therapy with or without chemotherapy did not affect the patients' prognosis (Figures 6B and 6E, Table III). We did not find any significant difference in the survival time of patients with cervical cancer in relation to combined immune-cell therapy or prior therapy with surgical operation, radiotherapy, and CCRT (Figures 7 and 8, Table III). Similarly to endometrial cancer, chemotherapy before the administration of immune-cell therapy worsened the prognosis of cervical cancer patients (HR=1.800; 95%CI=1.098-2.991; p=0.0197; Figure 7, Table III). The combination of chemotherapy and immune-cell therapy did not affect the prognosis of cervical cancer patients (Figure 7, Table III).

Regarding survival analysis by the type of immune-cell therapy administered, there was no significant difference in MST between the endometrial and cervical cancer patients treated with DCs+αβT cells and those treated with only αβT cells (Figure 9, Table III).

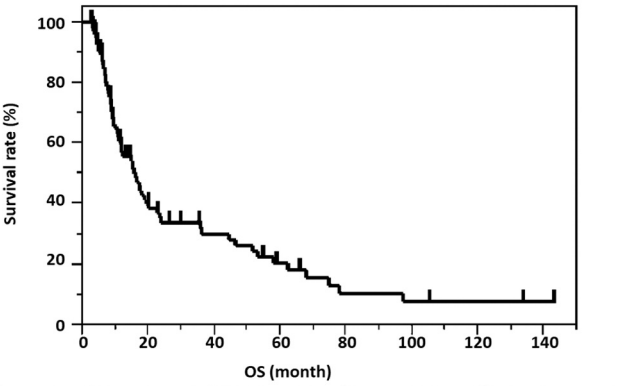
We then examined whether the metastasis sites affected OS in patients with endometrial and cervical cancers (Figures 10 and 11, Table IV). Kaplan–Meier analysis by the log-rank test showed that the MST of endometrial cancer patients with liver metastasis was shorter than that without metastasis (12.4 *vs.* 29.1 months; p=0.0081; Figure 10A). Furthermore, there was a significant difference in MST between cervical cancer patients with liver or lung metastasis and those without metastasis (liver: 5.8 *vs.* 15.9 months, p=0.0001; lung: 7.9 *vs.* 19.9 months, p=0.0005; Figures 11A and B). Univariate analysis also demonstrated that endometrial cancer patients without liver metastasis showed better prognosis than those with metastasis (HR=2.673; 95%CI=1.181-5.501; p=0.0202), and cervical cancer patients without lung or liver metastasis showed better prognosis than those with metastasis (HR=5.741, 95%CI=1.847-15.048, p=0.0044; HR=3.694, 95%CI=1.624-7.902, p=0.0026; Table IV).

Multivariate analyses. We performed multivariate analysis to identify the prognostic factors for endometrial and cervical cancer patients treated with immune-cell therapy. In the case of endometrial cancer, multivariate analysis demonstrated that the patients treated without prior chemotherapy showed better prognosis (HR=5.101, 95%CI=1.528-31.649, p=0.0049; Table V). Multivariate analysis revealed that the cervical cancer patients without either liver or lung metastasis showed better prognosis than those with metastasis (liver: HR=5.565, 95%CI=2.291-12.202, p=0.0004; lung: HR=2.399, 95%CI=1.267-4.450, p=0.0079; Table VI). These results indicate that the prognosis of endometrial cancer patients without prior chemotherapy and



N	MST (month)	95%CI	3-year Survival rate	5-year Survival rate
80	24.0	15.7 – 30.0	29.7%	27.2%

Figure 2. *Kaplan–Meier estimates of overall survival in the whole cohort of endometrial cancer patients. OS, overall survival (months); MST, median survival time. The number of patients (N) and MST are shown in the table below the graph showing the Kaplan–Meier curve.*



N	MST (month)	95%CI	3-year Survival rate	5-year Survival rate
107	15.5	10.8 – 19.9	30.0%	20.5%

Figure 3. *Kaplan–Meier estimates of overall survival in the whole cohort of cervical cancer patients. OS, overall survival (months); MST, median survival time. The number of patients (N) and MST are shown in the table below the graph showing the Kaplan–Meier curve.*

Table II. *Univariate analyses of overall survival in relation to clinical background of endometrial and cervical cancer patients.*

	Endometrial cancer				Cervical cancer			
Characteristics	Parameter	HR	95%CI	*p*-Value	Parameter	HR	95%CI	*p*-Value
Age, years	≥55	1.318	0.658-2.934	0.4526	≥55	1.140	0.668-1.890	0.6226
	<55	1			<55	1		
PS	≥1	1.386	0.680-2.644	0.3536	≥1	1.388	0.801-2.321	0.2346
	0	1			0	1		
Clinical stage	II-IV	1.305	0.665-2.800	0.4529	II-IV	1.360	0.795-2.420	0.2670
	I	1			I	1		
Histology	Adenocarcinoma	1.365	0.664-3.175	0.4149	SCC	1.422	0.864-2.339	0.1656
	Others	1			Others	1		

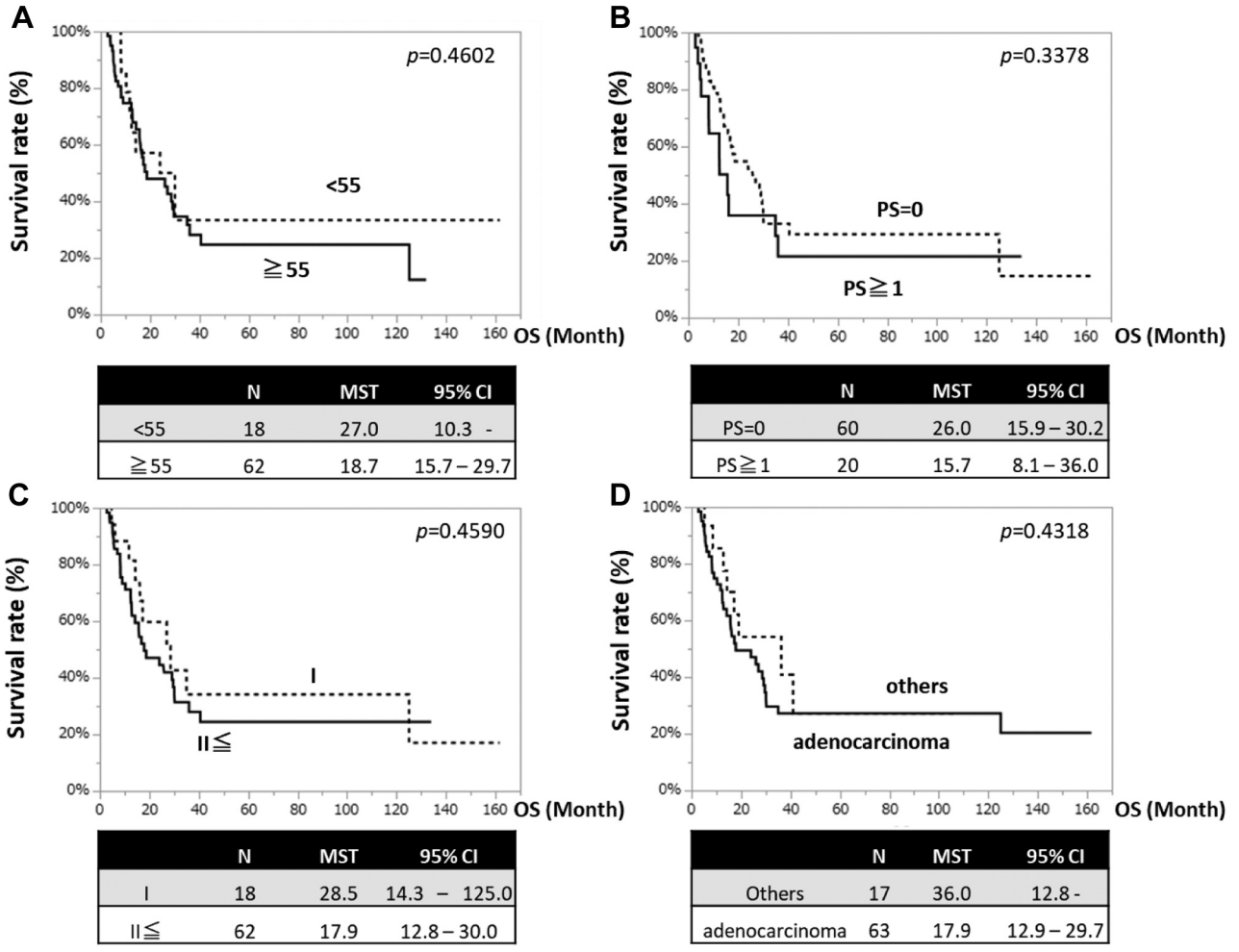
PS: Performance status; SCC: squamous cell carcinoma.

that of cervical cancer patients without liver or lung metastasis might be improved by immune-cell therapy.

Discussion

Many patients with endometrial and cervical cancers of the uterus have poor prognosis owing to relapse or metastasis, especially those in advanced stage, despite the development of combination chemotherapies and molecular targeting therapies that have prolonged the median survival time of patients with advanced endometrial and cervical cancers (3). Conventional treatments, including surgery, chemotherapy, and radiotherapy, may have various adverse effects that may impair the patients' antitumor immunity, resulting in residual tumor. In this retrospective study, we extracted data from 187 patients with endometrial and cervical cancers from 323 patients who had visited our clinic and were diagnosed as having these cancers, and analyzed the efficacy of immune-cell therapy combined with a standard therapy. As a result, we observed an increased efficacy of immune-cell therapy for patients with advanced and recurrent endometrial and cervical cancers.

The 3- and 5-year survival rates of endometrial and cervical cancer patients were almost similar or rather higher than those of the historical control reported in the "Cancer Registry and Statics" (1), because immune-cell therapy was administered in most of the patients several months after diagnosis (Figures 2 and 3). Although we observed no significant differences in survival time in relation to age, PS score, clinical stage, and histologic type between the endometrial and cervical cancer patients (Figures 4 and 5), the patients without prior chemotherapy before the administration of immune-cell therapy showed better prognosis than those with prior chemotherapy in both endometrial and cervical cancers (Figures 6 and 7, Table III). The combination of



	N	MST	95% CI
<55	18	27.0	10.3 -
≧55	62	18.7	15.7 – 29.7

	N	MST	95% CI
PS=0	60	26.0	15.9 – 30.2
PS≧1	20	15.7	8.1 – 36.0

	N	MST	95% CI
I	18	28.5	14.3 – 125.0
II≦	62	17.9	12.8 – 30.0

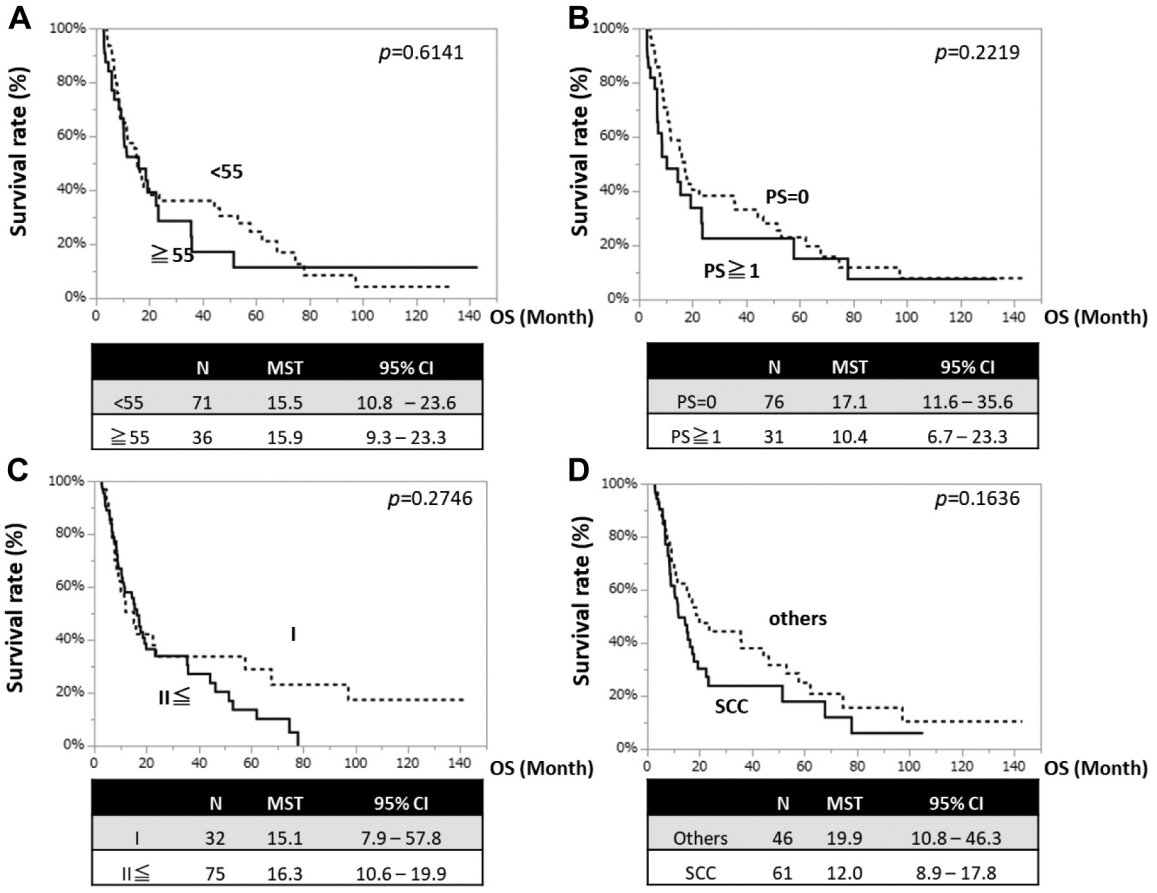
	N	MST	95% CI
Others	17	36.0	12.8 -
adenocarcinoma	63	17.9	12.9 – 29.7

Figure 4. *Correlation of Kaplan–Meier estimates of overall survival with age (A), performance status score (B), clinical stage (C), and histologic type (D) in patients with endometrial cancer. OS: Overall survival; MST: median survival time; PS: performance status. The number of patients (N) and MST are shown in the tables below the graphs showing the Kaplan–Meier curves.*

chemotherapeutic agents, such as cisplatin, with ACT has been reported to improve the survival time of patients with cervical cancer (17). In the comparison between immune-cell therapy alone and immune-cell therapy combined with other treatments, several studies have demonstrated that combination therapy shows better therapeutic effects than immune-cell therapy alone (16, 18-21). In our study, the combination of immune-cell therapy and chemotherapy did not provide any survival benefit for advanced or recurrent endometrial and cervical cancer patients, although the MST of these patients treated with a combination of immune-cell therapy and chemotherapy was longer than that of the historical control. The difference in immunological status or in the type of chemotherapeutic agent might affect the efficacy of immune-cell therapy. Note that most of the patients without prior chemotherapy had low-grade tumor or were at an early stage, suggesting that the suppression of immune system by chemotherapy before administration of immune-cell therapy affects patients' prognosis.

Advanced or recurrent endometrial and cervical cancer patients who developed distant metastasis to the lung and liver have been reported to have a poor prognosis (22). We have also found that a combination of immune-cell therapy and standard therapy could not improve the prognosis of these patients with lung/liver metastasis, although the MST of these patients was rather higher than that of the historical control. These findings indicate that it might be difficult to restore the impaired immunological status of advanced stage cancer patients by immune-cell therapy (Figures 10 and 11, Tables V and VI).

Adoptive immune-cell therapy is still under evaluation for use in advanced endometrial cancer, as in many other malignancies (16, 20, 21), but the more mature data available are about the checkpoint inhibitors. The PD-L1 expression levels in endometrial cancer have been estimated to be 67-100% (23).



	N	MST	95% CI
<55	71	15.5	10.8 – 23.6
≧55	36	15.9	9.3 – 23.3

	N	MST	95% CI
PS=0	76	17.1	11.6 – 35.6
PS≧1	31	10.4	6.7 – 23.3

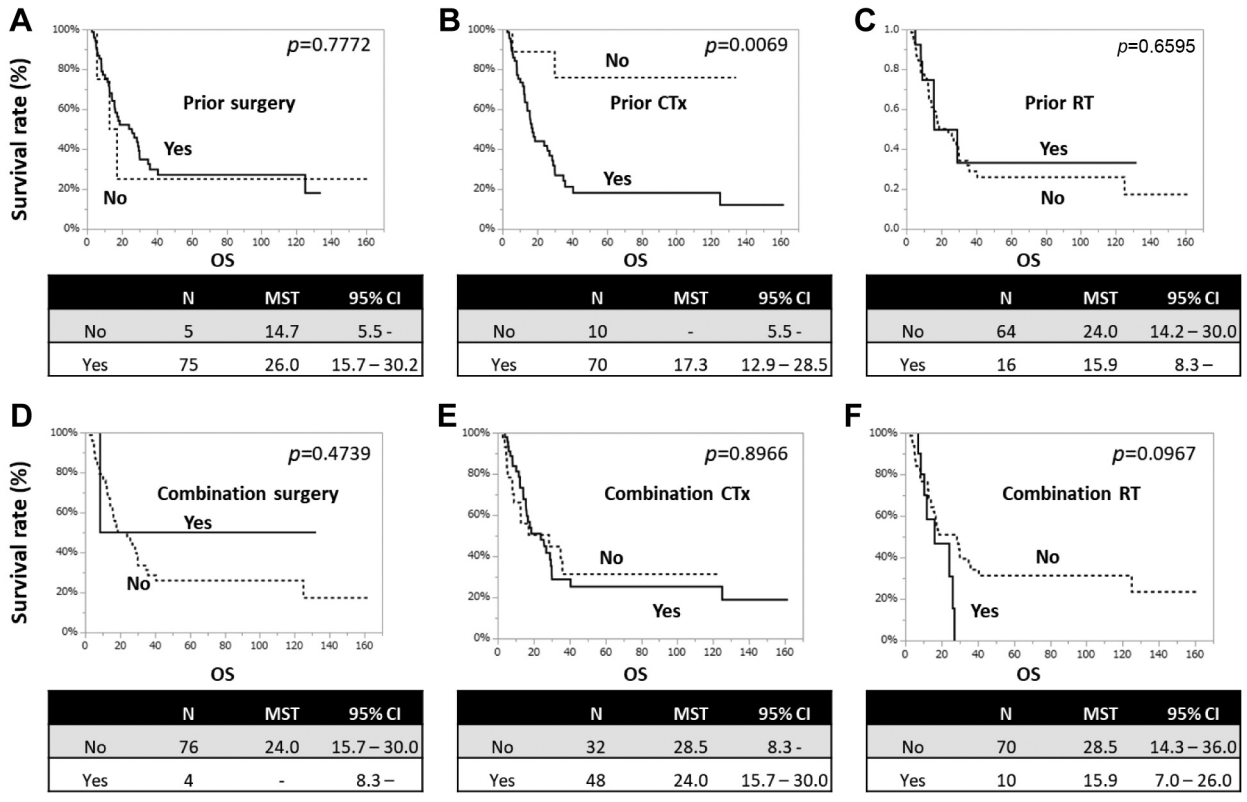
	N	MST	95% CI
I	32	15.1	7.9 – 57.8
II≦	75	16.3	10.6 – 19.9

	N	MST	95% CI
Others	46	19.9	10.8 – 46.3
SCC	61	12.0	8.9 – 17.8

Figure 5. *Correlation of Kaplan–Meier estimates of overall survival with age (A), performance status score (B), clinical stage (C), and histologic type (D) in patients with cervical cancer. OS: Overall survival; MST: median survival time; PS: performance status. The number of patients (N) and MST are shown in the tables below the graphs showing the Kaplan–Meier curves.*

Recently, endometrial cancer has been classified into four genomic types: (i) polymerase e (POLE)-ultramutated, (ii) MSI-hypermutated, (iii) low-copy-number, and (iv) high-copy-number types. The POLE-ultramutated and MSI-hypermutated types seem to be due to somatic mutations in the exonuclease domain of POLE and defective DNA mismatch repair (MMR), respectively (24). It has been reported that the POLE-ultramutated and MSI-hypermutated types are characterized by a high neoantigen load and a high number of tumor-infiltrating lymphocytes (TILs), which is counterbalanced by the overexpression of PD-1 and PD-L1 (25). Thus, targeting the PD1 pathway in these endometrial cancer types might be a reasonable strategy. All the monoclonal antibodies targeting the PD1 pathway are currently under evaluation for use in endometrial cancer, and they demonstrate both acceptable safety profiles and antitumor activity (11). Regarding the immunotherapy for cervical cancer, owing to the identification of HPV as an etiologic factor and the introduction of a specific vaccine into clinical practice, the incidence of cervical cancer is gradually decreasing (5-7). Although prevention of cervical cancer has been achieved, its prognosis is extremely poor in the advanced or relapsed stage. ADXS11-001, which is a live attenuated bioengineered bacterium, *Listeria monocytogenes* (Lm), that can secrete an HPV-16-E7 fusion protein targeting HPV-transformed cells, is now under clinical trial, which shows a significant clinical activity of this protein (26). Finally, adoptive immune-cell therapy using TIL is also under clinical trial for cervical cancer, and results show its promising efficacy, with two patients showing a complete regression of their cervical cancer (27). Similarly to endometrial cancer, cervical cancer has been associated with an amplification of the genes related to PD-L1 and PD-L2, providing a rational to target the PD-1 axis (28). Thus, the combination of immune-cell therapy and therapies targeting the PD-1 axis might be a promising strategy for patients with endometrial and cervical cancers.

In conclusion, a better prognosis could be obtained by the combination of immune-cell therapy with other therapies in patients with normal immune-cell function. However, to establish a comprehensive immunotherapy for endometrial and cervical cancers, it is necessary to conduct a randomized trial to



	N	MST	95% CI
No	5	14.7	5.5 -
Yes	75	26.0	15.7 – 30.2

	N	MST	95% CI
No	10	-	5.5 -
Yes	70	17.3	12.9 – 28.5

	N	MST	95% CI
No	64	24.0	14.2 – 30.0
Yes	16	15.9	8.3 –

	N	MST	95% CI
No	76	24.0	15.7 – 30.0
Yes	4	-	8.3 –

	N	MST	95% CI
No	32	28.5	8.3 -
Yes	48	24.0	15.7 – 30.0

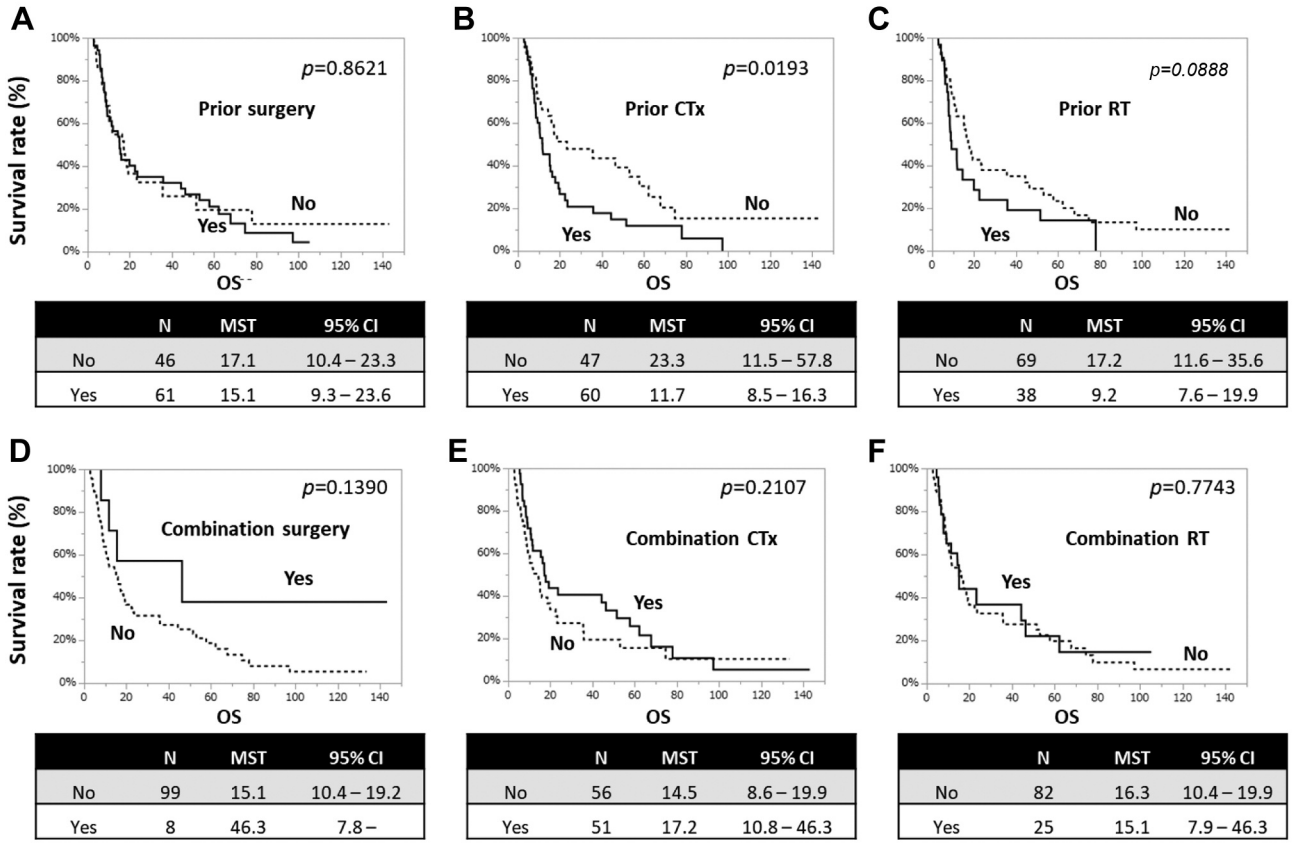
	N	MST	95% CI
No	70	28.5	14.3 – 36.0
Yes	10	15.9	7.0 – 26.0

Figure 6. *Correlation of Kaplan–Meier estimates of overall survival with or without prior surgery (A), CTx (B), RT (C) and with or without combination surgery (D), CTx (E), and RT (F) in patients with endometrial cancer. OS: Overall survival; MST: median survival time, CTx: chemotherapy; RT: radiotherapy.*

Table III. *Univariate analyses of overall survival in relation to therapy in endometrial and cervical cancer patients.*

		Endometrial cancer				Cervical cancer			
Characteristics	Parameter	N	HR	95%CI	*p*-Value	N	HR	95%CI	*p*-Value
Immune-cell therapy	αβT	50	1.106	0.548-2.417	0.7856	76	1.034	0.585-1.933	0.9111
	αβT+DC	17	1			20	1		
Prior therapy									
Surgical operation	Yes	75	0.842	0.302-3.510	0.7810	61	1.044	0.637-1.728	0.8655
	No	5	1			46	1		
Chemotherapy	Yes	70	5.731	1.742-35.355	0.0018	60	1.800	1.098-2.991	0.0197
	No	10	1			47	1		
Radiation therapy	Yes	16	0.818	0.309-1.803	0.6404	38	1.565	0.916-2.602	0.0994
	No	64	1			69	1		
CCRT	Yes	ND	–	–	–	49	1.065	0.652-1.741	0.8010
	No					58	1		
Combination therapy									
Surgical operation	Yes	4	0.489	0.027-2.297	0.4321	8	0.474	0.143-1.154	0.1073
	No	76	1			99	1		
Chemotherapy	Yes	48	0.962	0.518-1.859	0.9058	51	0.733	0.446-1.197	0.2144
	No	32	1			56	1		
Radiation therapy	Yes	10	1.943	0.820-4.118	0.1239	25	0.920	0.506-1.582	0.7701
	No	70	1			82	1		
CCRT	Yes	ND	–	–	–	2	0.352	0.020-1.607	0.2173
	No					105	1		

αβT: Activated lymphocyte therapy; DC: dendritic cell vaccine therapy; CCRT: concurrent chemoradiotherapy; N: number of patients.



	N	MST	95% CI
No	46	17.1	10.4 – 23.3
Yes	61	15.1	9.3 – 23.6

	N	MST	95% CI
No	47	23.3	11.5 – 57.8
Yes	60	11.7	8.5 – 16.3

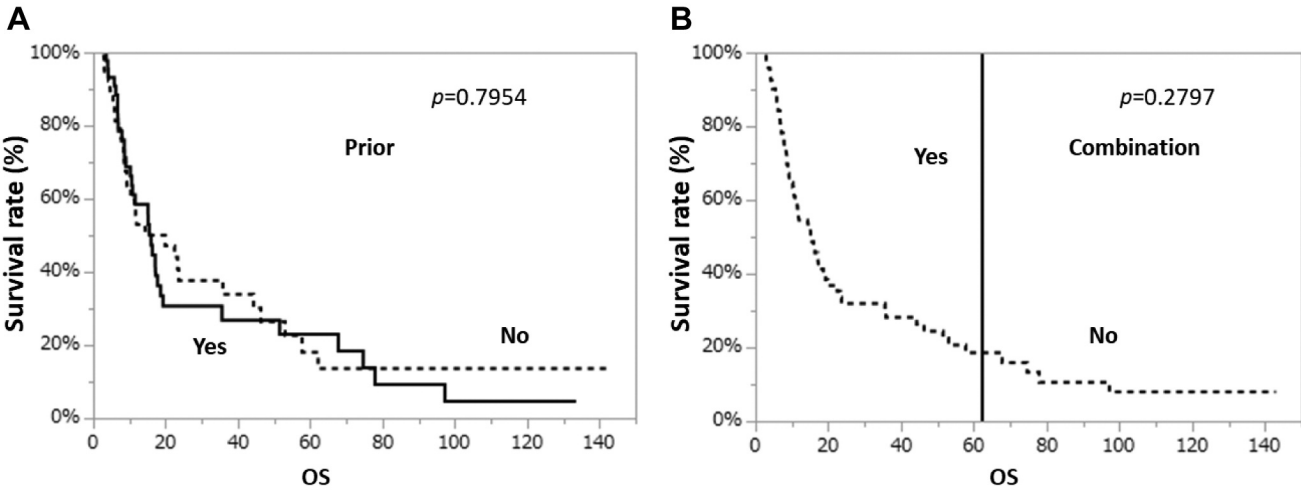
	N	MST	95% CI
No	69	17.2	11.6 – 35.6
Yes	38	9.2	7.6 – 19.9

	N	MST	95% CI
No	99	15.1	10.4 – 19.2
Yes	8	46.3	7.8 –

	N	MST	95% CI
No	56	14.5	8.6 – 19.9
Yes	51	17.2	10.8 – 46.3

	N	MST	95% CI
No	82	16.3	10.4 – 19.9
Yes	25	15.1	7.9 – 46.3

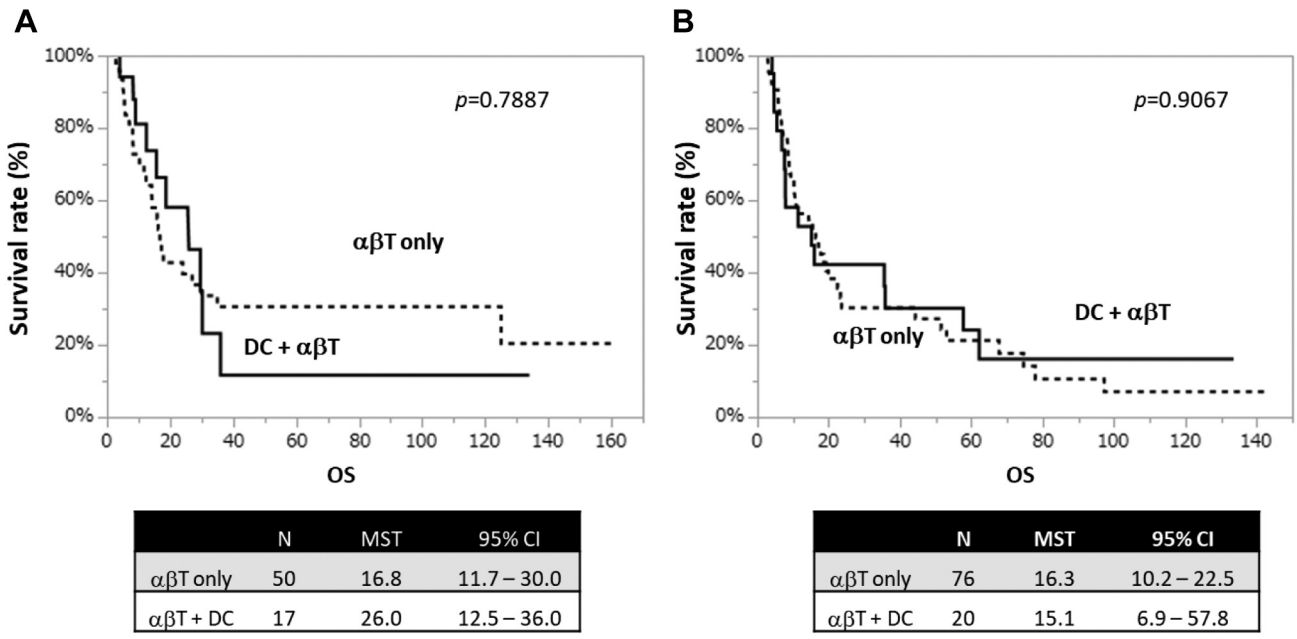
Figure 7. *Correlation of Kaplan–Meier estimates of overall survival with or without prior surgery (A), CTx (B), RT (C) and with or without combination surgery (D), CTx (E), and RT (F) in patients with cervical cancer. OS: Overall survival; MST: median survival time; CTx: chemotherapy; RT: radiotherapy.*



	N	MST	95% CI
No	58	19.9	9.2 – 35.9
Yes	49	15.9	10.2 – 18.6

	N	MST	95% CI
NO	105	15.5	10.6 – 19.2
Yes	2	62.2	-

Figure 8. *Correlation of Kaplan–Meier estimates of overall survival with or without prior CCRT (A) and combination CCRT (B) in patients with cervical cancer. OS: Overall survival; MST: median survival time; CCRT: concurrent chemoradiotherapy.*



	N	MST	95% CI
αβT only	50	16.8	11.7 – 30.0
αβT + DC	17	26.0	12.5 – 36.0

	N	MST	95% CI
αβT only	76	16.3	10.2 – 22.5
αβT + DC	20	15.1	6.9 – 57.8

Figure 9. *Correlation of Kaplan–Meier estimates of overall survival with immune-cell therapy in patients with endometrial (A) and cervical (B) cancers. OS: Overall survival; MST: median survival time; αβT: αβT immune-cell therapy; DC: dendritic immune-cell therapy.*

Table IV. *Univariate analyses of overall survival in relation to metastatic site in endometrial cancer patients.*

		Endometrial cancer				Cervical cancer			
Metastatic site		N	HR	95%CI	*p*-Value	N	HR	95%CI	*p*-Value
Liver	Yes	13	2.673	1.181-5.501	0.0202	5	5.741	1.847-15.048	0.0044
	No	62	1			56	1		
Lung	Yes	32	0.938	0.488-1.755	0.8439	14	3.694	1.624-7.902	0.0026
	No	43	1			47	1		
Lymph node	Yes	24	0.982	0.490-1.869	0.9580	30	0.926	0.473-1.798	0.8197
	No	51	1			31	1		
Bone	Yes	6	1.488	0.356-4.200	0.5355	7	1.341	0.396-3.428	0.5976
	No	69	1			54	1		
Brain	Yes	0				2	0.651	0.036-3.058	0.6524
	No	75	nd	nd	nd	59	1		
Pleura	Yes	0				0			
	No	75	nd	nd	nd	61	nd	nd	nd
Peritoneum	Yes	17	0.992	0.473-1.935	0.9828	6	1.074	0.318-2.732	0.8951
	No	58	1			55	1		

nd: Not determined; N: number of patients.

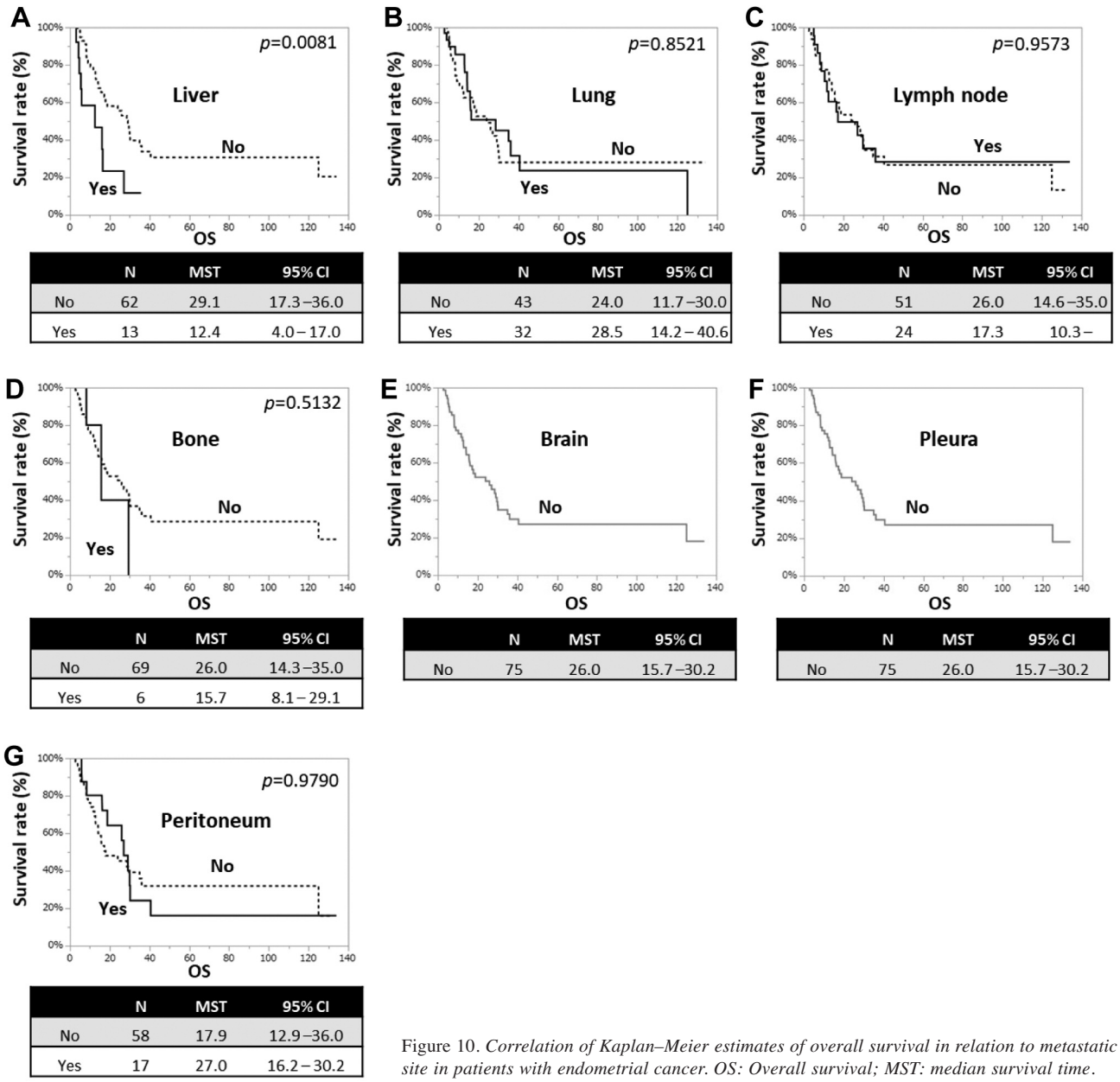
further elucidate the benefits of the combination of immune-cell therapy and various other treatments, such as chemotherapy, radiotherapy, and therapy with immune check-point inhibitors.

Conflicts of Interest

The Authors affirm that there are no potential conflicts of interest in relation to this study.

Authors' Contributions

Conception and design: R. Takimoto, T. Kamigaki, and S. Goto; Administrative support: S. Okada, H. Ibe, and E. Oguma; Collection and assembly of data: S. Okada, H. Ibe, E. Oguma, K. Naitoh, K. Yasumoto, and K. Makita; Data analysis and interpretation: R. Takimoto, S. Okada, T. Kamigaki, and S. Goto; Final approval of manuscript: All Authors.



	N	MST	95% CI
No	62	29.1	17.3–36.0
Yes	13	12.4	4.0–17.0

	N	MST	95% CI
No	43	24.0	11.7–30.0
Yes	32	28.5	14.2–40.6

	N	MST	95% CI
No	51	26.0	14.6–35.0
Yes	24	17.3	10.3–

	N	MST	95% CI
No	69	26.0	14.3–35.0
Yes	6	15.7	8.1–29.1

	N	MST	95% CI
No	75	26.0	15.7–30.2

	N	MST	95% CI
No	75	26.0	15.7–30.2

	N	MST	95% CI
No	58	17.9	12.9–36.0
Yes	17	27.0	16.2–30.2

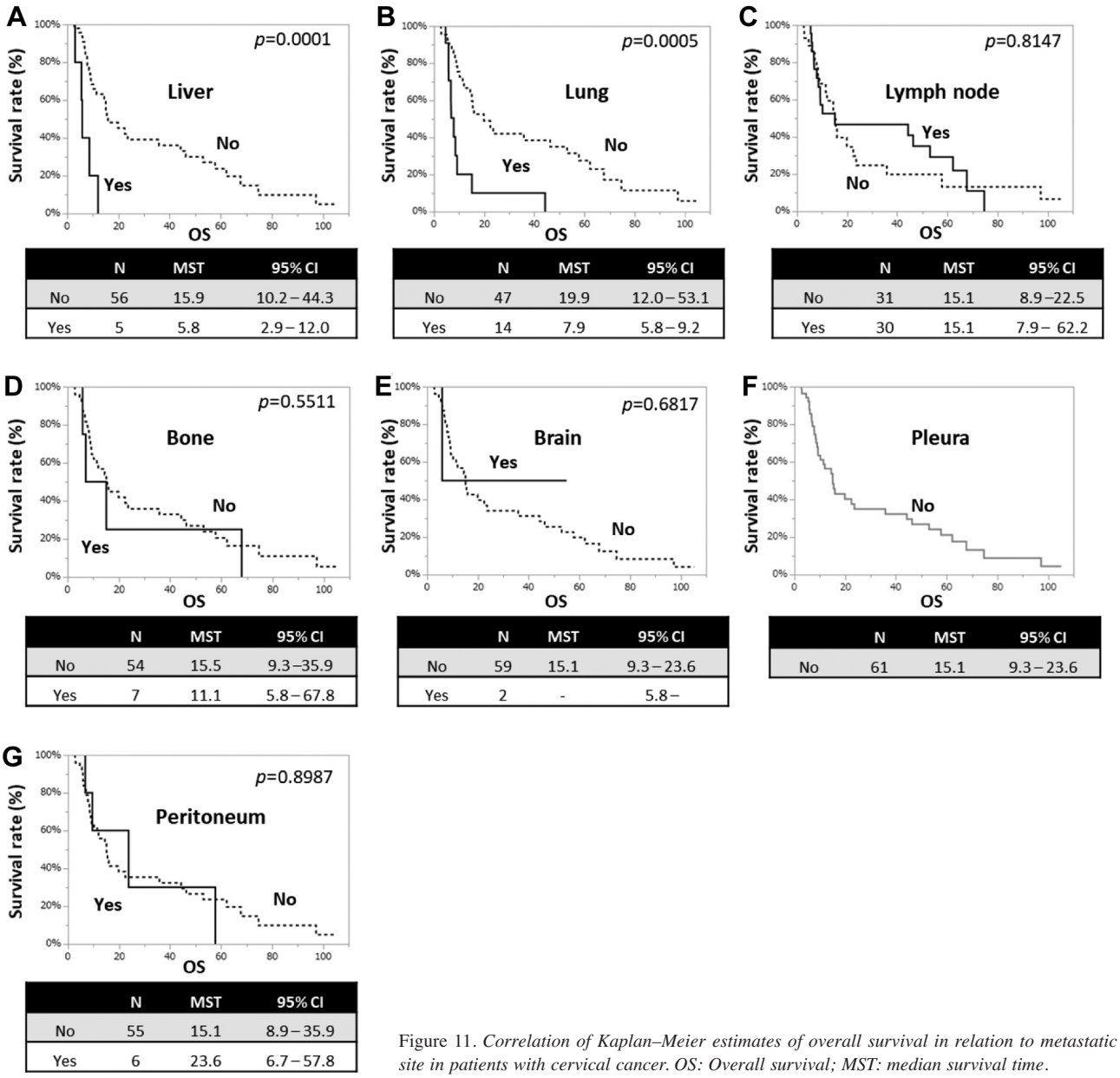
Figure 10. *Correlation of Kaplan–Meier estimates of overall survival in relation to metastatic site in patients with endometrial cancer. OS: Overall survival; MST: median survival time.*

Table V. *Multivariable analyses of overall survival in relation to therapy and clinical background of endometrial cancer patients.*

Characteristics	Parameter	HR	95%CI	*p*-Value
Prior chemotherapy	Yes (n=70)	5.101	1.528-31.649	0.0049
	No (n=10)	1		
Liver metastasis	Yes (n=15)	2.128	0.979-4.259	0.0562
	No (n=65)	1		

Table VI. *Multivariable analyses of overall survival in relation to therapy and clinical background of cervical cancer patients.*

Characteristics	Parameter	HR	95%CI	*p*-Value
Prior chemotherapy	Yes (n=60)	1.265	0.728-2.205	0.4043
	No (n=47)	1		
Liver metastasis	Yes (n=9)	5.565	2.291-12.202	0.0004
	No (n=98)	1		
Lung metastasis	Yes (n=25)	2.399	1.267-4.450	0.0079
	No (n=82)	1		



	N	MST	95% CI
No	56	15.9	10.2–44.3
Yes	5	5.8	2.9–12.0

	N	MST	95% CI
No	47	19.9	12.0–53.1
Yes	14	7.9	5.8–9.2

	N	MST	95% CI
No	31	15.1	8.9–22.5
Yes	30	15.1	7.9– 62.2

	N	MST	95% CI
No	54	15.5	9.3–35.9
Yes	7	11.1	5.8–67.8

	N	MST	95% CI
No	59	15.1	9.3–23.6
Yes	2	-	5.8–

	N	MST	95% CI
No	61	15.1	9.3–23.6

	N	MST	95% CI
No	55	15.1	8.9–35.9
Yes	6	23.6	6.7–57.8

Figure 11. *Correlation of Kaplan–Meier estimates of overall survival in relation to metastatic site in patients with cervical cancer. OS: Overall survival; MST: median survival time.*

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