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Adoptive Immune-Cell Therapy for the Treatment of Neuroendocrine Carcinoma of the Uterine Cervix

SHIGENORI GOTO[1,2], YASUHISA TERAO[3], TAKASHI KAMIGAKI[1,2], RISHU TAKIMOTO[1,2], KEIKO NAITOH[1], KAORI MAKITA[1], KOSEI YASUMOTO[1], SACHIKO OKADA[1,2], KEN TAKIZAWA[1], NORIYUKI YOKOMICHI[4], NAO SUZUKI[4] and SATORU TAKEDA[3]

[1]*Seta Clinic, Tokyo, Japan;*
[2]*Department of Next-Generation Cell and Immune Therapy, Juntendo University School of Medicine, Tokyo, Japan;*
[3]*Department of Obstetrics and Gynecology, Juntendo University School of Medicine, Tokyo, Japan;*
[4]*Department of Obstetrics and Gynecology, St. Marianna University School of Medicine, Kawasaki, Japan*

Abstract. *Background/Aim: We aimed to investigate the efficacy of immune-cell therapy in terms of the survival of patients with neuroendocrine carcinoma of the uterine cervix (NECC), which lacks standardized therapeutic approaches. Patients and Methods: We identified 17 patients who were diagnosed as having NECC and treated with immune-cell therapy. The clinical characteristics of these patients were extracted from their records and their overall survival was measured. Results: Of the 17 patients, two patients with early-stage NECC without recurrence and three patients with less than four treatments were excluded. The median survival times from the time of diagnosis and from the initial administration of immune-cell therapy were 49.7 and 24.4 months, respectively. The overall survival rates at 1, 2, and 5 years were 63.6%, 38.2%, and 25.5%, respectively. Long-term survival was observed in the patients with distant metastases. Conclusion: The preliminary results of this retrospective study suggested the potential efficacy of immune-cell therapy for NECC.*

Neuroendocrine carcinoma of the uterine cervix (NECC) is a rare malignant disease that accounts for less than 5% of all cervical cancer. NECC can be classified into small-cell, large-cell, or mixed-cell type, all of which are aggressive, with early nodal and distant metastases, often resulting in a poor prognosis. In a study of 130 patients with small-cell NECC, the 5-year cancer-specific survival was reported to be 63% at Federation of Gynecology and Obstetrics (FIGO) stage I, 54% at IIa, 26% at IIb, and 0% at stages III and IV (1), indicating a very poor prognosis for patients with advanced-stage NECC. Viswanathan *et al*. investigated the cases of 21 patients with small-cell NECC without distant metastases at the time of diagnosis and observed that 14 of them had a relapse, showing an unfavorable prognosis even in those with a surgically resectable tumor. They reported that the long-term survival of NECC patients is limited to those without lymph node metastasis at FIGO stage IB1 (2). A study of patients with large-cell NECC at stage I or IIa showed that seven out of 10 patients died 6 to 24 months after hysterectomy (3). Although there are few reports of the survival rate among patients with recurrent NECC, it seems to be even worse than that among patients with advanced-stage disease (4). The treatment of NECC is often a failure with unmet clinical needs; therefore, an effective treatment is clearly expected for patients with NECC, especially for those in the advanced stage (5).

In immunotherapy, the anticancer immunoresponse of the patient is augmented. There are several immunotherapy options and immune-cell therapy is one of them, which uses immune cells such as T-lymphocytes and dendritic cells obtained from patients and processed *ex vivo*. Recently, randomized controlled trials and their meta-analyses have demonstrated the efficacy of immune-cell therapy in terms of overall survival (OS) against several types of cancer (6-9). Dammeijer *et al*. searched the literature for randomized controlled trials investigating immune-cell therapy in non-small-cell lung cancer, and identified eight, which included a total of 1,568 patients. They concluded that immune-cell therapy improved OS (6). The efficacy of adoptive T-cell immunotherapy or dendritic cell (DC) therapy was also revealed by meta-analyses of renal cancer and hepatocellular carcinoma. In a double-blind, placebo-controlled, multicenter trial, the use of sipuleucel-T for immune-cell therapy prolonged OS among men with metastatic castration-resistant prostate cancer (8).

Correspondence to: Dr. Shigenori Goto, Seta Clinic, New Surugadai Bldg. 2-1-45, Kandasurugadai, Chiyoda-ku, Tokyo 101-0062, Japan. Tel: +81 352800086, Fax: +81 352800890, e-mail: goto@j-immunother.com

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Immune-cell therapy has also been suggested for gynecological cancer (10). However, NECC is a rare disease as mentioned earlier, so it will take much effort and time to collect a sufficient number of cases for prospective analysis.

The Seta Clinic Group, which includes four private clinics in Japan providing specialized types of immune-cell therapy in cooperation with cell-processing facilities, has treated a large number of patients with cancer over the past 10 years (11) and has investigated the effects of immune-cell therapy. It has reported some favorable results in some principal tumor types, including prolongation of survival time (12-19). In our practice of immune-cell therapy for patients with gynecological malignancies, we have experience treating several patients with NECC who responded to immune-cell therapy markedly well. In the present study, we retrospectively analyzed the OS of patients with NECC who received immune-cell therapy.

Patients and Methods

Study design. A database of patients who received immune-cell therapy at Seta Clinic between January 2004 and December 2015 was searched to identify patients who were diagnosed as having NECC. We identified 17 patients and retrospectively reviewed their cases. They received adoptive T-cell therapy with or without DC therapy between 2004 and 2015 at Seta Clinic. The study protocol was approved by the Research Ethics Committees of Juntendo Hospital (no. 13-106) and Seta Clinic (no. SCG13080). Available data on age, time of diagnosis, histological type, FIGO stage, sites of metastatic disease, treatment, and vital status were extracted from the medical records of the patients. OS was measured in two ways: Firstly, as the time from diagnosis to death from any cause, and secondly, as the time from the initial administration of immune-cell therapy to death from any cause.

Immune-cell therapy. Two types of immune-cell therapy were used in this study: Adoptive T-cell therapy and DC therapy. Immune-cell therapy consists of adoptive T-cell therapy, DC vaccination, or their combination and is commonly administered six times at 2-week intervals for 3 months as one course. For adoptive T-cell therapy, activated lymphocytes were generated as previously described (14, 15). In brief, peripheral blood mononuclear cells (PBMCs) were isolated from the patient's peripheral blood using a Vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The PBMCs were then activated in a culture flask with an immobilized monoclonal antibody to CD3 (Janssen-Kyowa, Tokyo, Japan) in Hymedium 930 (Kohjin Bio, Saitama, Japan) containing 1% autologous serum, and then cultured for 14 days with 700 IU/ml recombinant interleukin-2 (Proleukin®; Chiron, Amsterdam, the Netherlands). After the culture, 3-10×10^9 cells were harvested and suspended in 100 ml of normal saline for intravenous injection. For 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 using a medium supplemented with 50 ng/ml IL4 (Primmune Corp., Osaka, Japan) and 50 ng/ml granulocyte–macrophage colony-stimulating factor (Primmune Corp.) for 6 days to generate immature DCs. The DCs were pulsed with antigens such as 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.

Statistical analysis. Median survival time (MST) and survival rates were calculated by the Kaplan–Meier method using JMP, version 11.2.0 for Microsoft Windows 7 (SAS, Cary, NC, USA).

Results

Patient characteristics. Seventeen patients with histopathologically diagnosed NECC who underwent immune-cell therapy at Seta Clinic between January 2004 and December 2015 were enrolled in this study, and their medical data were available for analysis. The median age at the time of the first visit was 40 years (range=27-57 years). Eleven patients were categorized as having the small-cell type, three the large-cell type, and three the mixed type. At the time of diagnosis, the FIGO stage was Ib in eight patients, II in three, III in one, and IV in five. Of the 17 patients, two whose FIGO stage at the time of diagnosis was Ib or IIb showed no tumor recurrence at the start of immune-cell therapy (cases 11 and 13). Therefore, 15 out of the 17 patients had refractory or recurrent tumor at the start of immune-cell therapy. Prior to receiving immune-cell therapy, 13 patients had undergone surgery, 12 received radiation therapy, and 14 received chemotherapy. The clinical characteristics of the patients are summarized in Table I.

Immune-cell therapy. Of the 17 patients, the combination of adoptive T-cell therapy and DC vaccination was administered to five, and adoptive T-cell therapy alone was administered to 12 patients. However, three of the patients received only few infusions owing to difficulty in visiting the clinic to receive immune-cell therapy (cases 7, 9, and 14 with one, two, and three infusions, respectively); thus, they withdrew from the study. The type of immune-cell therapy and number of infusions given to each patient are summarized in Table II.

Survival. Two sets of analysis were performed for MST and survival rates calculated by the Kaplan–Meier method. The first was the full analysis set for all 17 patients. The second set was for the 12 patients extracted from the 17 patients, which excluded two patients with early-stage NECC without recurrence and three patients with fewer than four treatments.

The MSTs from the time of diagnosis and MSTs from the initial administration of immune-cell therapy were 38.8 and 13.5 months for all the 17 patients (Figure 1A) and 49.7 and 24.4 months for the 12 patients (Figure 1B), respectively. The OS rates at 1, 2, and 5 years were 56.7%, 40.5%, and 32.4% for the group of 17 patients and 63.65, 38.25, and 25.5% for the group of 12 patients, respectively.

Table I. *Patient clinical characteristics at the start of immune-cell therapy.*

Case	Age, years	Previous treatment	Histology	Stage at diagnosis	Status at start of immune-cell therapy	Site of cancer lesion
1	42	S, R, C	Large cell	Ib1	Recurrence	Parametrium, inguinal LN
2	32	C	Small cell	IV	IV	Liver, brain
3	45	S	Small cell	IV	IV	Pancreas, LN
4	47	R, C	Small cell	IV	IV	Lung, bone
5	37	S	Large cell	III	Recurrence	LN
6	52	S, R	Large cell	II	Recurrence	Lung, Bone
7	35	S, R, C	Small cell	Ib2	Recurrence	Bone, LN
8	41	S, R, C	Small cell	Ib2	Recurrence	Lung, Bone
9	27	S, R, C	Small cell	IIa	Recurrence	Lung, LN
10	40	R, C	Small cell	IV	IV	Neck and para-aortic LN
11	33	S, R, C	Mixed	IIb	IIb	None
12	37	R, C	Small cell	Ib	Recurrence	Lung, liver
13	40	S, C	Small cell	Ib1	Ib1	None
14	42	S, R, C	Small cell	IV	IV	Bone, Skin, Pancreas, LN
15	39	S, C	Small cell	Ib	Recurrence	Liver, LN
16	31	S, R, C	Mixed	Ib	Recurrence	Bone, liver
17	57	S, R, C	Mixed	Ib1	Recurrence	Lung, kidney, LN

S: Surgery; R: radiotherapy; C: chemotherapy; LN: lymph nodes.

The two patients with early-stage NECC have, at the time of writing, survived more than 51.2 and 87.3 months without recurrence from the time of the initial administration of immune-cell therapy. Two patients who had distant metastases have survived for 101.2 and 54.7 months from the start of immune-cell therapy and remain free of the disease (Table II, cases 1and 2). Case 1 had lymph node and liver metastases. Her disease course is described in detail in the case report in the results section. In case 2, liver and brain metastases occurred before the start of immune-cell therapy. She had undergone partial resection of the liver. Brain metastases had been treated with gamma knife radiosurgery twice. She was treated with immune-cell therapy and showed no recurrence thereafter. One patient with refractory tumor survived for 46.3 months and died of their disease (Table II, case 5).

Table II. *Patient treatments and outcomes.*

Case	No. of infusions		Outcome	Survival, months	
	T-Cell	DC		From start of immune-cell therapy	From diagnosis
1	14	6	Survived	101.2	153.2
2	6	-	Survived	54.7	79.6
3	8	-	Survived	13.3	14.9
4	6	1	Died	7.6	18.0
5	21	29	Died	46.3	49.7
6	26	-	Died	9.2	27.9
7	3	-	Died	2.0	10.8
8	8	-	Died	24.4	58.5
9	2	-	Died	1.0	15.8
10	9	-	Died	13.5	38.1
11	11	-	Survived	51.2	54.6
12	2	4	Died	4.7	31.5
13	6	-	Survived	87.3	94.1
14	1	-	Died	2.8	38.8
15	6	3	Died	5.4	14.2
16	6	-	Survived	2.4	24.4
17	6	-	Survived	10.2	47.5

T-Cell: Adoptive T-cell therapy; DC: dendritic-cell therapy; -: not applied.

Case report. A 38-year-old Japanese woman who was diagnosed as having large-cell NECC at FIGO stage Ib underwent radical hysterectomy without postoperative adjuvant therapy (case 1). She was subsequently found to have a 40-mm recurrent tumor in the left parametrium with infiltration of tumor cells beneath the rectal mucosa and into the inguinal lymph node 5 years later during a follow-up examination (Figure 2A). She received concurrent chemoradiotherapy (CCRT) consisting of cisplatin and paclitaxel, and extracorporeal irradiation (60 Gray) of the whole pelvis and inguinal lymph node for 4 months. After CCRT, the tumor in the parametrium was partially responsive to the treatment; however, that in the inguinal lymph node progressively increased in size (Figure 2B). Following CCRT, she received six infusions of adoptive T-cells at 2-week intervals at Seta Clinic. Two months after the completion of adoptive T-cell therapies, a markedly elevated neuron-specific enolase level (10 to 90 ng/ml) was observed,

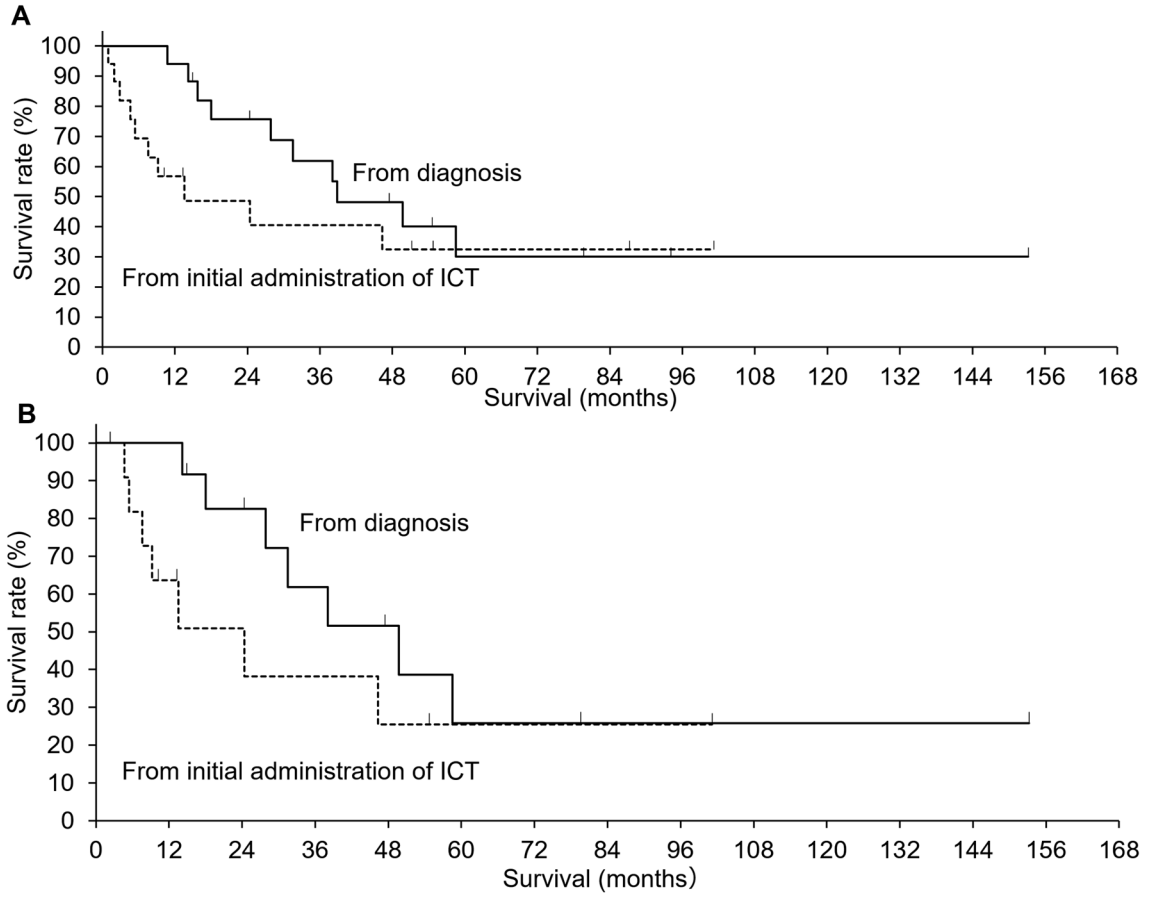

Figure 1. *Kaplan–Meier estimates of overall survival in the full analysis set of patients (A) and the subset of 12 patients (B) treated with immune-cell therapy (ICT).*

and a 90-mm liver metastatic tumor appeared on follow-up computed tomographic 3 months later. She received chemotherapy consisting of cisplatin and irinotecan, and then underwent hepatectomy at Juntendo Hospital (Figure 3A). The histopathological findings of the resected tumor indicated large-cell type neuroendocrine carcinoma (Figure 3B, C). Tumor lysate was prepared from a specimen from a resected liver tumor. DCs were cultured and pulsed with the tumor lysate. After the administration of the DC vaccine six times at Seta Clinic, the immune-cell therapy was completed. Despite pelvic evisceration due to a recurrence 4 years after completion of immune-cell therapy, she remains free of the disease 6 years after the recurrence was resolved.

Discussion

Only 17 patients with NECC who underwent immune-cell therapy were included in this study. As NECC is a very rare gynecological malignancy, the results are considered to be worth reporting, even though the number of patients studied was small.

In this study, the MSTs of the patients with recurrent or metastatic NECC were 49.7 months from the time of diagnosis and 24.4 months from the first administration of immune-cell therapy. Both MSTs were quite long compared with those in other studies of NECC. A previous retrospective study on the survival of 34 patients with recurrent small-cell NECC treated with chemotherapy revealed that the median OS was about 9 months (4). The prognosis of patients with the large-cell and mixed types of NECC was also poor in previous investigations (3, 20).

In fact, the duration of survival in this study of NECC should be compared with that of NECC reported from other Japanese institutes because the OS recorded in Japan is considered to be longer than those in other countries for cervical cancer. Clinical trials in Japan showed that the median OS of patients with recurrent cervical cancer was 18 months, which is longer than that observed in other countries (21). There have been neither a clear explanation nor discussion of this but it was speculated that the greater use of postprogression treatment might have prolonged the OS observed in clinical trials in Japan.

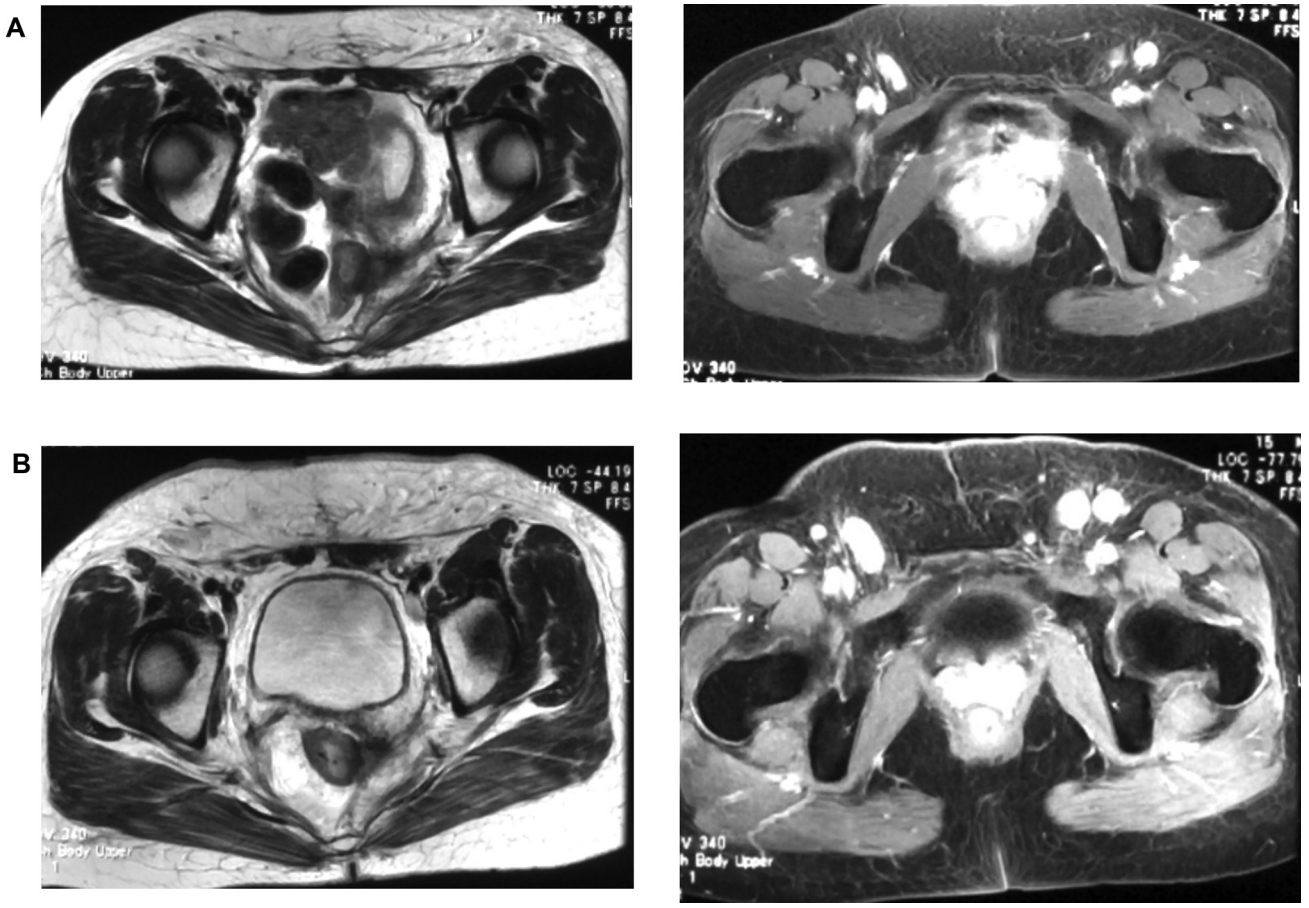

Figure 2. *Magnetic resonance images of the pelvis of case 1. A: 40-mm Recurrent tumor in left parametrium and metastatic tumor in the inguinal lymph node were found in January 2008. B: The tumor in the parametrium decreased in size; however, that in the inguinal lymph node was found in May 2008 to have progressively increased in size.*

Nagao *et al*. reported the clinical features of NECC in 23 patients in Japan. They showed that five patients had stage III/IV disease, and they died within 36 months after diagnosis (22). However, a large-scale study of advanced-stage NECC has not been carried out in Japan to date. Instead, we used the statistics from the report of the survival time for patients with squamous or adenocarcinoma of the uterine cervix from the Japan Clinical Oncology Group trial reported in 2015 (23) for comparison. In that report, the median OS time defined as the interval between the random assignment of the study and death was 18 months in metastatic or recurrent cases. The survival outcome of NECC is considered to be markedly poorer than that of squamous or adenocarcinoma of the uterine cervix (24). Therefore, the MST of 24.4 months in the present study of NECC was assumed to be longer than that generally obtained for NECC, even in Japan. This finding indicates the beneficial effect of immune-cell therapy on the survival of patients with advanced-stage NECC.

Immune-cell therapy may have the beneficial effect of preventing recurrence in those with early-stage as well as those with advanced-stage disease. In this study, two patients at stages IIb and Ib without metastatic or recurrent tumor were administered immune-cell therapy; they showed no recurrence, surviving for 51.2 and 87.3 months thereafter. A previous study of 10 patients with NECC who were surgically treated in Japan showed that seven had stage Ib1 and one each stages Ib2, IIa, and IIb. Only three out of the seven patients with Ib1 disease had no relapse; however, seven out of the 10 had a relapse, and six of them died of their disease (25). Our results indicate that immune-cell therapy might be effective for preventing recurrence in early-stage as well as those with advanced-stage disease.

In this study, three patients who underwent fewer than four infusions were excluded from some of the analyses. Generally speaking, some of the patients were not in a sufficiently good condition to undergo chemotherapy. However, they were able to receive immune-cell therapy

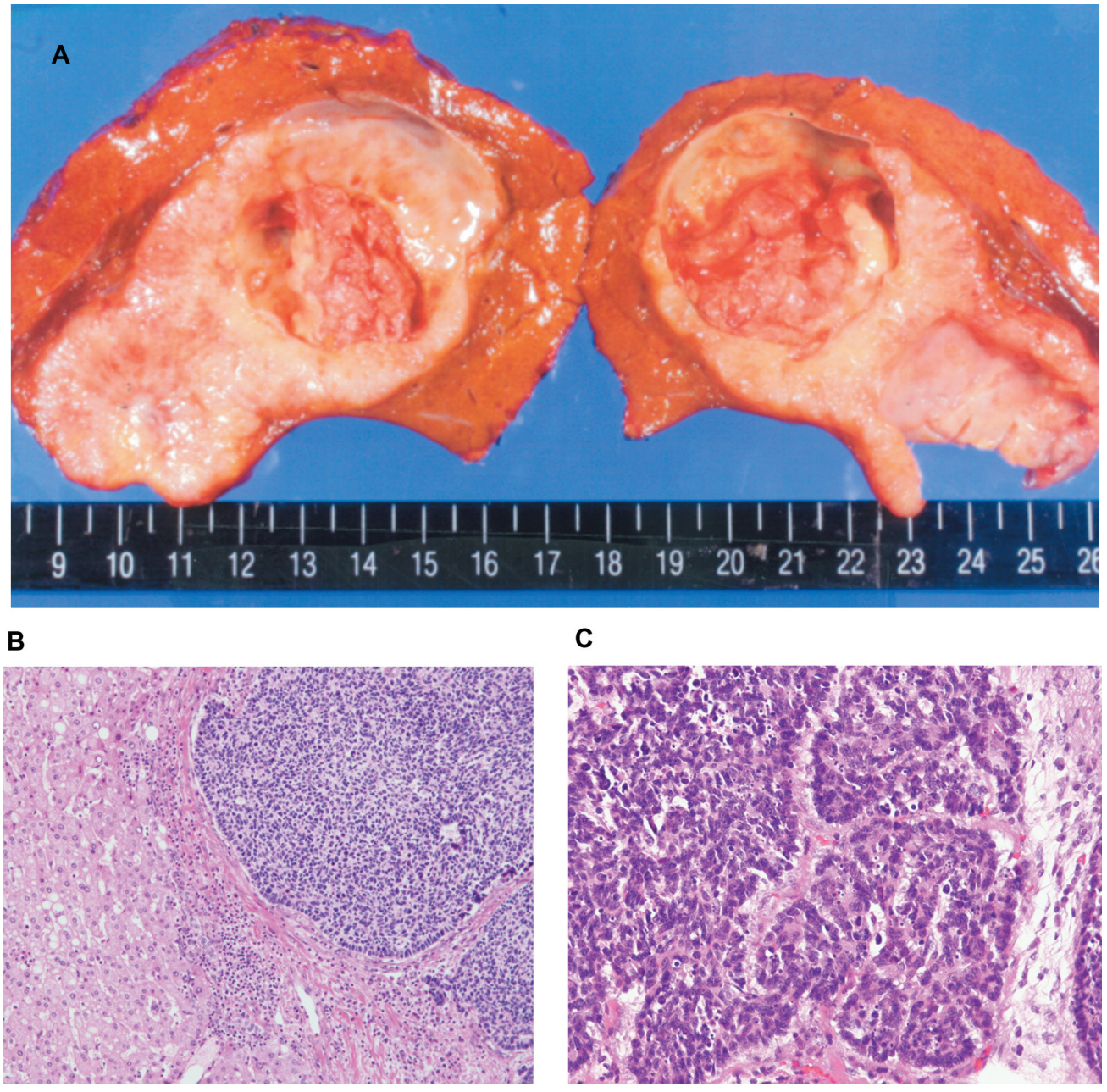

Figure 3. *Neuroendocrine carcinoma, large-cell type of case 1. A: A metastatic tumor in the liver was 90 mm in diameter. B: The tumor grew in nests (hematoxylin and eosin stain; magnification ×100). C: Large cells had scant cytoplasm resembling stripped nuclei with rosette formations (hematoxylin and eosin stain; magnification ×200).*

because it is tolerable and causes no severe adverse events.

Three patients withdrew from immune-cell therapy after fewer than four infusions because of disease progression, with one infusion in one patient, two in another patient, and three in the remaining patient. They died 0.9, 1.9, and 2.8 months, respectively, after the initial administration of immune-cell therapy. It is considered that immune-cell therapy had no effect on them; therefore, these patients were excluded from some of the analyses.

The representative case of one patient is presented in this report. The disease-free survival of the patient of 9 years after recurrent liver tumor resectomy with NECC, whose prognosis is generally poor, was quite long compared with those in previous reports. In this case, the patient had

recurrence of liver tumor 1 month after the immune-cell therapy ended, which was treated by chemotherapy and then surgically resected. As observed for immune-checkpoint inhibitors, the effect of immunotherapy is sometimes delayed (26, 27), which might result in this recurrence. However, this long disease-free survival can hardly be expected with only chemotherapy and hepatectomy. Therefore, it is assumed that immune-cell therapy exerted its effect synergistically with chemotherapy and hepatectomy. The efficacy of immunotherapy including the use of immune checkpoint inhibitors is considered to be sustainable and to contribute to long-term survival (26, 27). Therefore, immune-cell therapy might lead to disease-free long-term survival in this case owing to its sustainable efficacy over a period of 9 years after the treatment ended.

Although the precise mechanism underlying the efficacy of immune-cell therapy against NECC is not yet clearly understood, it might be related to human papillomavirus (HPV). HPV infection has frequently been detected in cases of NECC (20, 28, 29). Stevanovic *et al*. treated nine patients with metastatic cervical cancer by infusion of tumor-infiltrating T-cells selected for their HPV reactivity, and observed a durable complete response longer than 15 months in two cases and a partial response in one case (30). They mentioned that the HPV reactivity of tumor-infiltrating T-cells correlated positively with clinical response. Other previous reports also suggest the efficacy of immunotherapy with various options such as the use of therapeutic vaccines, immune checkpoint inhibitors, and adoptive T-cells for cervical cancer (29). Exceptional responses to nivolumab and stereotactic body radiation therapy for NECC were also reported (31). These observations suggest the efficacy of immunotherapy for NECC.

Conclusion

The preliminary findings of this retrospective study suggest some potential of immune-cell therapy for treating NECC, and prospective clinical trials should be carried out in the near future.

Conflicts of Interest

The Authors have no conflicts of interest directly relevant to the contents of this article.

Authors' Contributions

SG and YT designed the study, took charge of data collection and interpretation, and wrote the initial draft of the article. TK, RT, KN, KM, KT, NY, and NS contributed to the data collection, interpretation, and articlepreparation. KY and ST contributed to data analysis and interpretation, and assisted in the preparation of the article. SO assisted in the preparation of the article.

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