Survival of patients with metastatic malignant pheochromocytoma and efficacy of combined cyclophosphamide, vincristine, and dacarbazine chmotheraphy

Survival of Patients with Metastatic Malignant Pheochromocytoma and Efficacy of Combined Cyclophosphamide, Vincristine, and Dacarbazine Chemotherapy

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Context: About 10% of pheochromocytomas are malignant. Exact survival has not been reported, nor has an analysis of the efficacy of chemotherapy on survival time.

Objective: The aim of this study was to analyze the survival curves and survival times of patients with malignant pheochromocytoma and to determine the efficacy of chemotherapy on prolongation of life.

Design: An inception cohort and Kaplan-Meier survival analysis was conducted.

Patients and Outcome Measured: Thirty-two patients with metastasized malignant pheochromocytoma were analyzed for survival. Twenty-five patients had undergone excision of their primary tumors. Survival curves were compared among the 16 patients in this group treated with combined chemotherapy using cyclophosphamide, vincristine and dacarbazine (CVD) and the nine patients not treated with chemotherapy.

Results: The survival curve of the 32 patients declined continuously and linearly to at least 20 yr after the diagnosis of pheochromocytoma. The 50% survival rate was estimated to be 14.7 yr. In the 25 patients whose primary tumor was excised, patients who already had metastases at the time of pheochromocytoma diagnosis had better survival than those whose metastases were found later. The survival rate after diagnosis of metastasis was worse in the CVD group than in controls. When the effects of CVD were examined after stratifying several factors, female gender and adrenal origin of tumor were found to be negative prognostic factors for CVD chemotherapy.

Conclusion: The present study revealed a long survival time. CVD chemotherapy was not shown to extend survival, especially for women and patients with adrenal gland-derived primary tumors. (*J Clin Endocrinol Metab* **94: 2850–2856, 2009**)

Pheochromocytomas produce and secrete catecholamines. They mostly occur in the adrenal medulla, but may also present in the extraadrenal sympathetic nervous system as paraganglioma. About 10% of pheochromocytomas are malignant in nature. However, even pathological examination of surgically excised tumors cannot be used to discriminate malignant tumors from benign ones. The gold standard for diagnosing malignant pheochromocytoma, at present, is evidence of a metastatic tumor in the non-chromaffin tissues. The period from disease onset to recurrence is highly variable (1, 2). Some metastatic tumors may become prominent after more than 20 yr. This tumor's variable growth rate and rare incidence have made it difficult for studies to determine the exact prognosis of patients and therefore to determine the efficacy of the present therapeutic strategy. Sur-

Abbreviations: CI, Confidence interval; CVD, cyclophosphamide, vincristine, and dacarbazine; ^{131}I-MIBG, ^{131}I-metaiodobenzylguanidine; TAE, transcatheter arterial embolization.

vival rates that have been reported previously were based on a small number of patients and were so fragmented and descriptive that they could not reveal a pattern in the survival curve, *i.e.* continuous or intermittent; or linear, convex, or concave. We have used an inception cohort study with a significant number of patients with malignant pheochromocytomas using Kaplan-Meier survival analysis to reveal the survival curves and times for these patients.

The main therapeutic strategy for this tumor is surgical excision or debulking of accessible tumors (3). Internal radiation using ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) (4) and/or chemotherapy has also been used. Combination chemotherapy using cyclophosphamide, vincristine, and dacarbazine (CVD) may be the most popular regimen for malignant pheochromocytoma. Its antineoplastic effect has been recently reviewed as being limited, and relapse occurred within 2 yr in most patients (5). Reports on the efficacy of CVD chemotherapy were based on results using surrogate endpoints such as changes in tumor volume or hormone levels. The effect on survival time remains to be determined. A randomized controlled trial with an endpoint of mortality or survival rate is generally considered to be the most valid to clarify the efficacy of treatment but is difficult in practice in the case of malignant pheochromocytoma. As the next best thing, patients with or without chemotherapy can be compared in their survival times after conditioning their profiles.

The present study sought to determine the survival curves in patients with malignant pheochromocytoma and to evaluate whether CVD chemotherapy could extend patients' lives.

Patients and Methods

Diagnosis and evaluation of disease

Patients were diagnosed as having pheochromocytoma or paraganglioma based on a hormonal evaluation and imaging studies including computed tomography, magnetic resonance imaging, and ^{131}I-MIBG scans. The time when these results were obtained was defined as the time of pheochromocytoma diagnosis. Patients were diagnosed as having malignant tumors if metastases were present in nonchromaffin sites or when invasion of neighboring tissue was seen. Sites of metastases were classified as follows: pulmonary, bone, liver, or local. Local metastases included invasion into neighboring tissues, recurrence at the site where the primary tumor had been excised, and dissemination into the abdominal cavity and regional lymph nodes. The time of the discovery of metastasis or invasion was defined as the time of metastasis diagnosis. As described below, pheochromocytoma and metastasis were diagnosed at the same time in 14 patients. Urinary excretion of metanephrines (metanephrine and normetanephrine) was measured as described previously (6).

Inclusion and exclusion criteria for patients

Thirty-two patients were diagnosed and treated as suffering from malignant pheochromocytomas in our hospital between 1985 and 2006. They were registered in a clinical database. Twenty-three patients were referred to our hospital as metastatic pheochromocytoma patients. Among these, 14 patients were already found to have metastases at the time of diagnosis of pheochromocytoma. Nine patients were diagnosed as having malignant pheochromocytoma after primary tumors had been surgically removed previously in our hospital. Of the 32 patients in our study, 18 had died and 14 were alive at the last follow-up on June 30, 2008. Their survival periods were measured from two different time zero

points: the time of pheochromocytoma diagnosis, and the time of metastasis diagnosis.

In our study on the efficacy of chemotherapy, seven patients were excluded; six had not been treated by surgical excision of the primary tumor, and one had died due to intestinal bleeding after the primary excision. Of the remaining 25 patients, 16 were treated with chemotherapy using the CVD regimen (CVD group) and nine (control group) were not. Two women in the CVD group stopped this therapy after one or two rounds because of severe adverse effects including nausea, vomiting, and general malaise. The other CVD patients were treated with CVD therapy at least four times. Survival time was compared between the control and CVD groups by Kaplan-Meier survival analysis. The time zero for survival was the time of diagnosis of metastasis because this also represented the time of diagnosis of malignant pheochromocytoma and was the closest event to the initiation of CVD chemotherapy.

Therapy with or without CVD

CVD chemotherapy was administered according to the original method of Keiser *et al.* (7): a combination of cyclophosphamide, 750 mg/m² body surface on d 1; vincristine, 1.4 mg/m² body surface on d 1; and dacarbazine, 600 mg/m² body surface on d 1 and 2, with this protocol repeated every 21–28 d.

^{131}I-MIBG radiotherapy (8, 9), transcatheter arterial embolization (TAE), and surgical debulking of metastasized tumors were also performed in some patients (Table 1).

All of these therapies except ^{131}I-MIBG radiotherapy are physically taxing on patients. Therefore, according to the principles of our institution, they were given only to patients with a relatively stable condition and were not given to patients who were estimated to be too ill to benefit from a new and aggressive therapy. There were no standard criteria for the selection of therapies for different patients. The risk and benefit of therapies were dependent on patient's condition and nature (site and number) of metastatic tumor in general and, therefore, differ case by case. We always evaluated patients carefully, along with surgeons and radiologists with excellent skills, before the choice of therapy. Patients made the final decision.

Statistics

Data are presented as means and SD values. An unpaired *t* test or Fischer's exact test was used to compare two groups. Survival was estimated by the Kaplan-Meier method using Statistical Analysis System software, ver. 9.1.3 (SAS Institute Inc., Cary, NC). Equality of each group in Kaplan-Meier was estimated by the log-rank test.

Results

Survival analysis of 32 patients

Fourteen women and 18 men were included in the study. Eighteen patients died, and 14 were alive at the last follow-up. Twenty patients (62.5%) had paraganglioma. The primary tumor was surgically excised in 26 patients. CVD chemotherapy was given to 19 patients. Additional therapies were carried out in some patients: six patients underwent an additional debulking operation, four patients were treated with ^{131}I-MIBG, and three patients were treated with TAE.

A survival curve of 32 patients was analyzed from the time of diagnosis of pheochromocytoma by Kaplan-Meier survival analysis (Fig. 1A). The interval from time zero to the last follow-up ranged from 0.5 to 39.7 yr (mean ± SD, 10.7 ± 9.4). The 75, 50, and 25% survival rates were estimated to be 5.5 yr [95% confidence interval (CI), 2.3–12.2], 14.7 yr (95% CI, 8.2–32.4), and 32.4 yr (95% CI, 18.5–39.7), respectively. Ex-

TABLE 1. Profiles of patients and disease

Profiles	Control (n = 9)	CVD (n = 16)	P value[a]
Female gender	5 (55.6)	5 (31.3)	0.234
Patients with paragangliomas	6 (66.7)	9 (56.3)	0.610
Other treatments			
Surgery[b]	2 (22.2)	7 (43.8)	0.282
MIBG	1 (11.1)	2 (12.5)	0.918
TAE	0	3 (18.8)	0.166
Deceased	3 (33.3)	10 (62.5)	0.161
At the time of pheochromocytoma diagnosis			
Age (yr)	44.8 ± 16.9	42.8 ± 14.9	0.758
Patients with metastasis	4 (44.4)	5 (31.3)	0.509
Pulmonary metastasis	0	0	
Bone metastasis	2 (22.2)	2 (12.5)	0.524
Liver metastasis	1 (11.1)	0	0.174
Local metastasis	1 (11.1)	2 (12.5)	0.918
At the time of metastasis diagnosis			
Age (yr)	46.9 ± 17.8	50.4 ± 12.1	0.572
Years after surgery	2.2 ± 3.0	7.7 ± 2.2	0.107
Patients with metastasis	9 (100)	16 (100)	
Pulmonary metastasis	2 (22.2)	1 (6.3)	0.238
Bone metastasis	3 (33.3)	9 (56.3)	0.271
Liver metastasis	3 (33.3)	3 (18.8)	0.412
Local metastasis	4 (44.4)	5 (31.3)	0.509

Data represent number (%), unless otherwise described.

[a] An unpaired *t* test (two-tailed) or Fischer's exact test was used.

[b] Surgery was for debulking the metastasis or local invasion, not for the primary tumor.

pressed differently, the 5-, 10-, and 20-yr survival rates were 77.2, 61.3, and 39.5%, respectively. The survival rate declined continuously and linearly.

The survival curve was also analyzed from the time of diagnosis of metastasis (the time of malignant pheochromocytoma diagnosis) (Fig. 1B). The survival curve declined continuously and linearly until 10 yr and then became flat until 23 yr, suggesting that the curve was composed of two groups, *i.e.* patients with short lives (n = 26) after metastasis and those with long lives after metastasis (n = 6; 18.8%). The 75, 50, and 25% survival rates were estimated to be 3.5 yr (95% CI, 1.4–5.8), 7.6 yr (95% CI, 4.3–15.3), and 15.3 yr (upper range of 95% CI, 7.4), respectively. The profiles of the six patients with long survival were as follows: two were women and four were men, all had paraganglioma, all had excised primary tumors, three of these patients showed metastasis at the time of pheochromocytoma diagnosis, and three were treated with CVD (4, 8, and 20 times). Their average age at the time of metastasis diagnosis was younger than that of the other 26 patients (37.0 ± 13.8 *vs.* 52.3 ± 13.1 yr; *P* = 0.016).

We next examined the effects of gender, tumor type (adrenal pheochromocytoma or extraadrenal paraganglioma), and time of metastasis (presence or absence of metastasis at the time of pheochromocytoma diagnosis) on a survival curve after the time of metastasis diagnosis. Gender had no effect on the survival curve (Fig. 2A). Tumor type also had no effect ($\chi^2 = 1.412$; $P = 0.2347$ at log-rank test) (Fig. 2B). Patients with metastases at the time of pheochromocytoma diagnosis (termed early metastasis) had a worse survival rate during the first 5 yr, but then had a better survival rate than those without metastases at the time of pheochromocytoma diagnosis (termed late metastasis). Overall,

the difference in survival time between patients with early or late metastasis was statistically not significant ($\chi^2 = 1.589$; $P = 0.2074$) (Fig. 2C). Five patients who had not undergone surgical excision of their primary tumors were included among the patients with early metastasis who died during the first 5 yr.

Comparison of profiles of 25 patients selected to examine the effects of CVD chemotherapy

We next compared the profiles of the control (n = 9) and CVD (n = 16) groups. Gender, age, tumor type (adrenal pheochromocytoma or extraadrenal paraganglioma), treatments other than CVD, mortality, sites of metastasis, and time from surgery to metastasis were compared both at the time of pheochromocytoma diagnosis and at the time of metastasis diagnosis (Table 1). No significant differences were observed in any of these factors. The period from primary surgery to metastasis appeared to be somewhat longer in the CVD group (7.7 ± 2.2 yr) than in the control group (2.52 ± 3.0 yr), but this difference was not statistically significant (*P* = 0.107).

Effect of CVD chemotherapy on survival

Chemotherapy with the CVD regimen was initiated at times ranging from 13 to 1271 d after the diagnosis of metastasis and was repeated one to 21 times (mean ± SD, 8.9 ± 6.5). Nineteen patients were treated with CVD. In 13 patients, urinary metanephrines decreased to 52.4 ± 27.5% of basal level (ranging between 6.4 and 86%), suggesting the successful antineoplastic effect of CVD chemotherapy. Among these patients, urinary metanephrines returned to basal levels after 12.9 ± 12.0 months (ranging from 2 to 36 months) in 10 patients. Three other patients still had decreased levels on the last follow-up day, *i.e.*
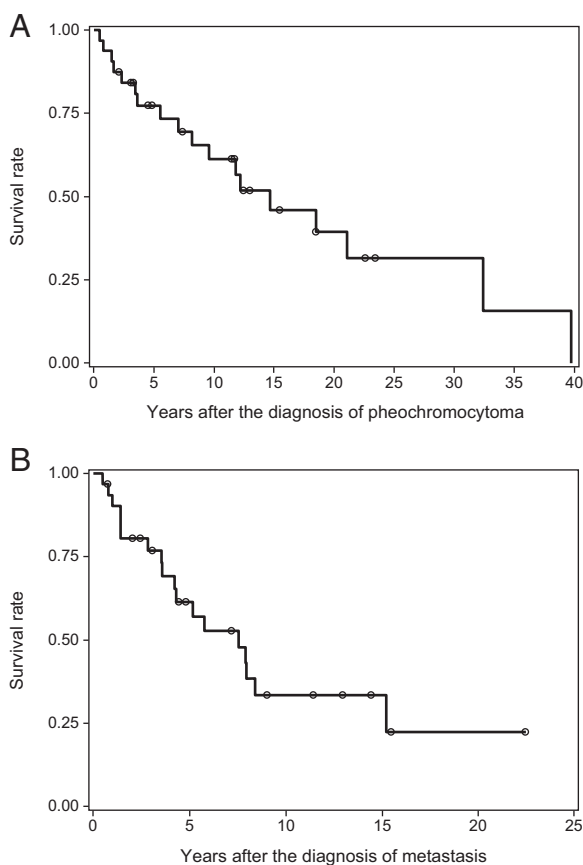
FIG. 1. Survival curve for all 32 patients. A, Time zero set at the time of pheochromocytoma diagnosis. B, Time zero set at the time of metastasis diagnosis. *Open dots* represent censored observations.

periods to the last follow-up day were 8, 24, and 31 months. In six patients, urinary metanephrines never decreased to less than 90% of the basal level, and in some of these patients they even increased. Complete remission has never been observed in any patient with malignant pheochromocytoma.

Survival curves were compared between the control and CVD groups both after the time of pheochromocytoma diagnosis and after the time of metastasis diagnosis. From time zero for the diagnosis of pheochromocytoma, the curves were nearly identical for the control and CVD groups ($\chi^2 = 0.2029$; $P = 0.6524$) (Fig. 3A). From time zero for the diagnosis of metastasis, however, the control group appeared to have a slightly better survival rate than the CVD group, although statistically, this difference was not significant ($\chi^2 = 2.7989$; $P = 0.0943$) (Fig. 3B).

The effects of CVD were then analyzed after stratification for gender, tumor type, and time of metastasis in the nine controls and 16 patients treated with CVD. In terms of gender, women without CVD treatment had a significantly better survival rate than those who received CVD treatment ($\chi^2 = 8.6406$; $P = 0.0345$) (Fig. 4A). In men, CVD chemotherapy had no effect on survival. In terms of tumor type, patients with adrenal pheochromocytoma who received CVD treatment had a significantly worse survival rate than all other groups ($\chi^2 = 11.5049$; $P = 0.0093$) (Fig. 4B). In patients with paragangliomas, CVD chemotherapy had no effect on survival. In terms of time of metastasis, patients with early metastases had better survival rates
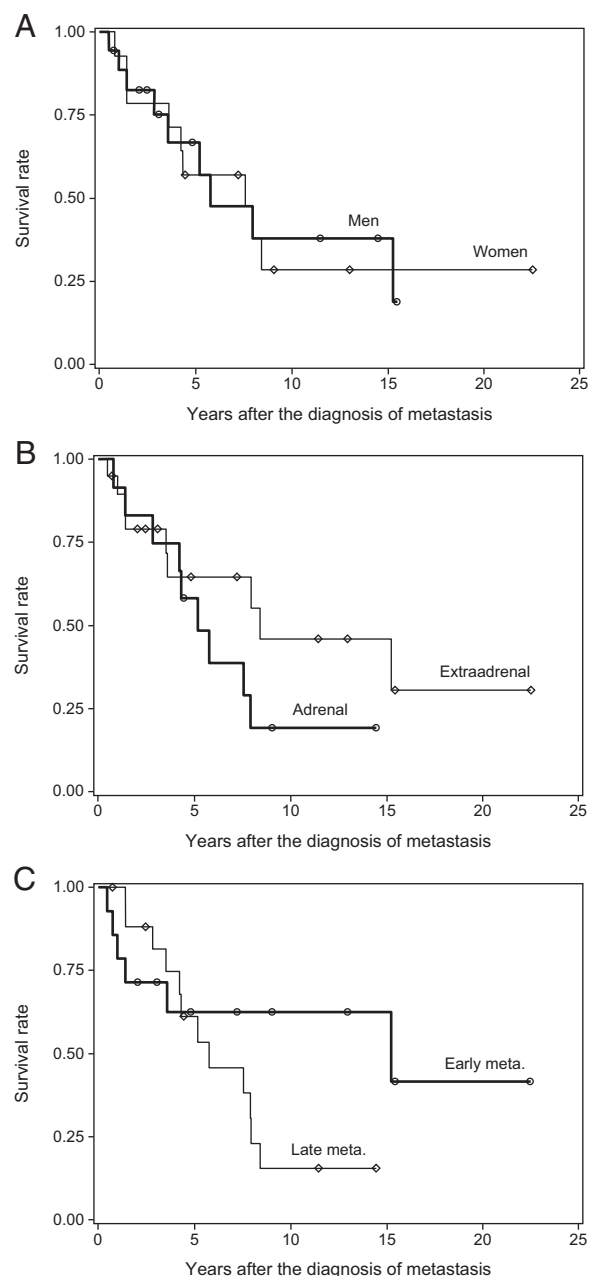

FIG. 2. Effects of patient and disease characteristics on the survival curve for all 32 patients. A, Effect of gender. Men (*thick line*) and women (*thin line*) had nearly identical survival curves ($\chi^2 = 0.0061$; $P = 0.9377$ with log-rank test). B, Effect of tumor type. Patients with extraadrenal paraganglioma (*thin line*) appeared to have slightly longer survival than those with adrenal pheochromocytoma (*thick line*), although statistically this difference was not significant ($\chi^2 = 1.4122$; $P = 0.2347$). C, Effect of time of metastasis. Patients who already showed metastasis at the time of pheochromocytoma diagnosis (Early meta., *thick line*) appeared to have slightly longer survival than those who did not (Late meta., *thin line*), although statistically this difference was not significant ($\chi^2 = 1.5894$; $P = 0.2074$). *Open dots* represent censored observations.

independent of CVD therapy than those with late metastases ($\chi^2 = 10.7436$; $P = 0.0013$) (Fig. 4C). The survival curves of patients with early and late metastases are shown in Fig. 2C. The difference between Fig. 2C and Fig. 4C reflects the difference in whether patients whose primary tumors had not been excised surgically were included (Fig. 2C) or not (Fig. 4C).
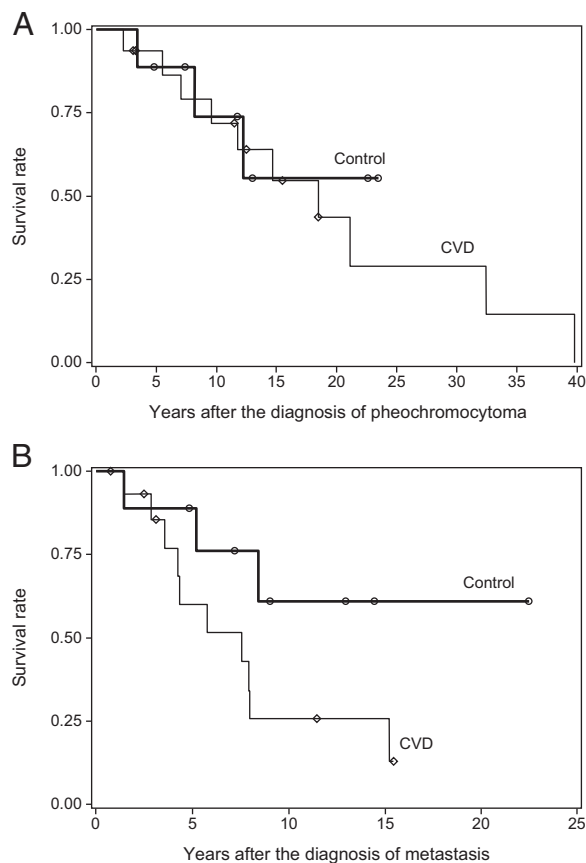
FIG. 3. Survival curves of control and CVD-treated patients. Nine controls (*thick lime*) and 16 patients (*thin line*) who received CVD therapy were compared after seven patients were excluded from the study by the exclusion criteria (see text). A, Time zero set at the time of pheochromocytoma diagnosis. B, Time zero set at the time of metastasis diagnosis. *Open dots* represent censored observations.

Discussion

The prognosis of a disease is evaluated in several ways. Mortality or the survival period of remaining life is an essential marker in a potentially lethal disease. In a malignant neoplasm with a low incidence and with an expectation of a long remaining life, information is ordinarily accumulated by an inception cohort study, and a survival curve is estimated by Kaplan-Meier survival analysis. However, to the best of our knowledge, such analysis has never been reported in patients with malignant pheochromocytoma. A few descriptive studies about mortality have been published. John *et al.* (10) studied 10 patients and reported that their survival rate was 20% at 5 yr and 0% at 10 yr. Huang *et al.* (2) studied 10 patients and reported that two of them died within 2 yr after diagnosis, but others reportedly had long survival periods. Cases with long survival were also reported by others (11, 12). Kimura *et al.* (13) studied 30 patients and reported that 5- and 10-yr survival rates were 60.6 and 42.4%, respectively. However, this study did not describe whether survival time was counted from the time of pheochromocytoma diagnosis or from time of metastasis diagnosis. The present study with 32 patients demonstrated that the 50% survival period was 14.7 yr and that the 10-yr survival rate was 61.3% from the time of pheochromocytoma diagnosis. We have thus confirmed that the survival period is variable but long, on average. Furthermore, the survival
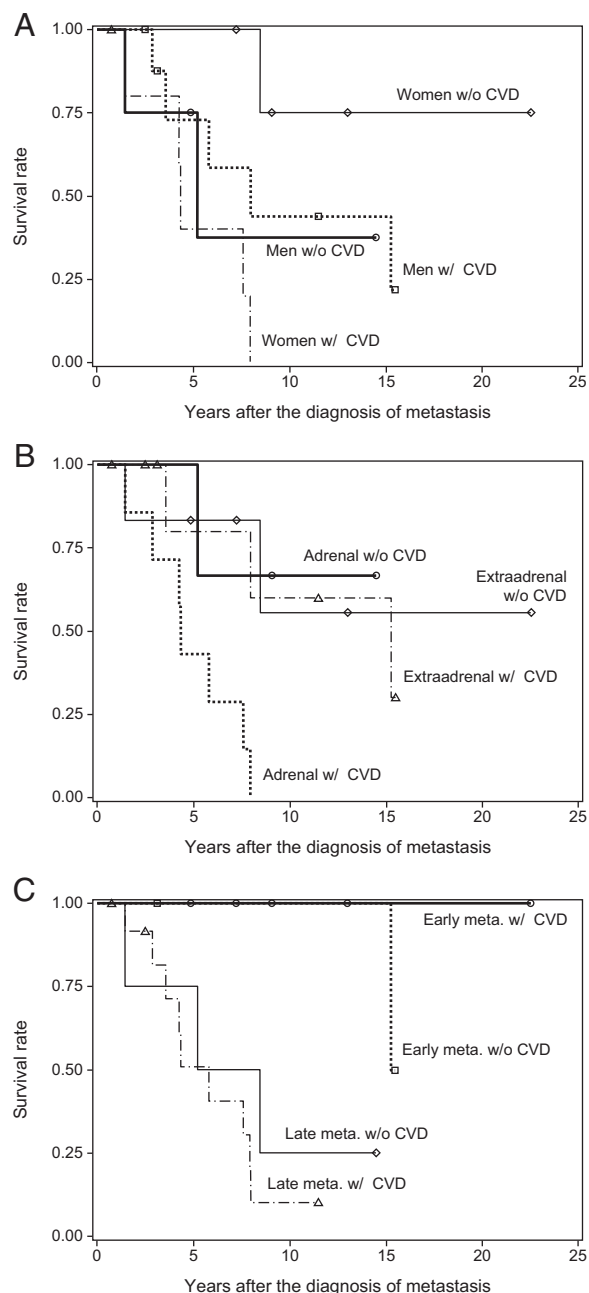

FIG. 4. Effects of patient and disease characteristics and CVD therapy on survival curves. Nine controls and 16 patients who received CVD therapy were compared after seven patients were excluded from the study by the exclusion criteria (see text). A, Effect of gender. Women without CVD (Women w/o CVD, *thin solid line*; n = 5) showed longer survival than men without CVD (Men w/o CVD, *thick solid line*; n = 4), men receiving CVD (Men w/ CVD, *broken line*; n = 11), or women receiving CVD (Women w/ CVD, *dotted line*; n = 5) (χ^2 = 8.6406; P = 0.0345). B, Effect of tumor type. Patients with adrenal pheochromocytoma receiving CVD (Adrenal w/ CVD, *dotted line*; n = 7) had shorter survival than those with extraadrenal paraganglioma without CVD (Extraadrenal w/o CVD, *thin solid line*; n = 6), those with adrenal pheochromocytoma without CVD (Adrenal w/o CVD, *thick solid line*; n = 3), and those with extraadrenal paraganglioma receiving CVD (Extraadrenal w/ CVD, *broken line*; n = 9) (χ^2 = 11.5049; P = 0.0093). C, Effect of time of metastasis. Patients who already showed metastasis at the time of pheochromocytoma diagnosis and who were treated with CVD (Early meta. w/ CVD, *thick solid line*; n = 5) or not (Early meta. w/o CVD, *dotted line*; n = 3) had longer survival than those who did not initially have metastases and who were treated with CVD (Late meta. w/ CVD, *broken line*; n = 13) or not (Late meta. w/o CVD, *thin solid line*; n = 4) (χ^2 = 10.7436; P = 0.00132). *Open dots* represent censored observations.

curve in our study showed a continuous and linear decline from the time of diagnosis for at least 20 yr. When the curve was analyzed from the time of metastasis diagnosis, it was linear for the first 10 yr and then became flat. This finding supports the idea that some (6 of 32; 18.8%) malignant pheochromocytoma patients have an extremely long survival time. The only significant difference we found between patients with short survival and those with long survival was average age. Patients with long survival were younger than the others.

We also analyzed the effects of gender, tumor type, and time of metastasis. No significant effects were observed for any of these factors (Fig. 2, A–C). However, patients with early metastasis had a worse survival rate during the initial 5 yr but then had better survival than those with late metastasis. From the standpoint of clinical practice, an estimation of survival time is important when a patient is diagnosed with a lethal disease. Therefore, a major goal of our study was to estimate the survival rate and curve of malignant pheochromocytoma patients from the time of metastasis, particularly in those patients whose primary tumors could be surgically excised.

We found that CVD chemotherapy decreased urinary metanephrine excretion in most patients. However, this effect did not continue for long periods of time as Scholz *et al.* (5) reported. The overall survival rate after the time of metastasis diagnosis was not statistically different between the CVD and control groups; however, it did approach statistical significance ($P = 0.0943$). We analyzed the effects of CVD after the stratification of patients by gender, tumor type, and time of metastasis onset. Women without CVD had better survival than women with CVD or men with or without CVD (Fig. 4A). Two of the women in our study received chemotherapy only once or twice and then stopped due to the adverse effects of chemotherapy toxicity. They were included in the CVD group based on the principle of intention-to-treat. This suggested that there is a greater toxicity of chemotherapy in women than in men. There have been no previous reports suggesting that gender differences may affect the survival time of patients with malignant pheochromocytoma. However, in another malignant tumor, advanced non-small cell lung cancer, survival time is significantly longer in women than in men, and chemotherapy toxicity is generally greater in women than in men (14). The present study raises the possibility that female gender is a negative prognostic factor for CVD chemotherapy. Next, we analyzed the effects of tumor type and found that patients who had adrenal pheochromocytoma and underwent CVD therapy had worse survival than other groups (Fig. 4B). Therefore, adrenal pheochromocytoma may be a negative prognostic factor for CVD chemotherapy. Finally, we analyzed the effects of time of metastasis onset. Patients with early metastases had better survival than those with late metastases independent of the absence or presence of CVD chemotherapy (Fig. 4C). As shown in Fig. 2C, patients with early metastases had worse survival during the first 5 yr and then showed better survival than those with late metastasis. This initial poor survival was due to patients with a poor prognosis who had not undergone surgical excision of their primary tumors. After excluding these patients, the survival rates were statistically significantly better in patients with early metastases than those with late metastases (Fig. 4C).

This observation was unexpected and cannot be explained based on the present study. However, this is an important finding suggesting that initial diagnosis with metastatic pheochromocytoma does not indicate a worse prognosis. We also observed that the period from the time of pheochromocytoma diagnosis to the time of metastasis diagnosis tended to be shorter in the CVD group than in the control group. Others have reported that a long tumor-free period after surgical excision of the primary tumor was not associated with a greater overall longevity than that seen in patients whose residual malignancy was observed sooner (1, 13). Taken together, these findings suggest that pheochromocytoma of adrenal origin and female gender are negative prognostic factors for CVD chemotherapy and that the patients' prognosis is not worsened by the finding of metastasis at the time of pheochromocytoma diagnosis if their primary tumors are surgically excised.

This study was a retrospective and nonrandomized control study. It should be noted that some biases and confounders could not be avoided in our study design. For example, patients without metastasis can be cured by surgical excision of the primary tumor alone and were not diagnosed with malignant pheochromocytoma. Therefore, they were not enrolled in this study. In our comparison between the control and CVD groups, several biases could not be excluded. Although we did not observe any differences in patient or disease profiles between these two groups, it is possible that the CVD group may have contained patients with more aggressive and imminently threatening disease, whereas the control group may have contained more patients with a stable condition (selection bias). The CVD group had a longer period from the diagnosis of pheochromocytoma to diagnosis of metastasis than the controls. If this time difference reflects lead time bias, the CVD group might have had more advanced metastatic tumors at the time of metastasis diagnosing. Additional unknown factors may also have affected our results. The present study is the first report using survival analysis to determine the efficacy of CVD chemotherapy on malignant pheochromocytoma, but our study may have limitations based on the study design. More cohort studies are needed to confirm the efficacy of CVD chemotherapy. Since our study was based on an inception cohort, data from new patients in future studies could be added to our data.

In conclusion, we have shown that the survival rate of patients with malignant pheochromocytoma declined continuously and linearly. Some patients had extremely long survival times. Although some patients already showed metastases at the time of disease diagnosis, we found that these patients had even longer survival than those with late metastases after surgical excision of the primary tumor. CVD chemotherapy using the standard regimen did not appear to be effective for extending patients' survival. We also found that female gender and adrenal pheochromocytomas may be negative prognostic factors for CVD chemotherapy.

Acknowledgments

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