INTRODUCTION

Malignant tumors are the leading cause of death in the general population worldwide. Although cardiovascular disease is the most common cause of death in patients with chronic kidney disease (CKD) (1, 2), the incidence of malignant diseases is growing in this population due to increased life span. Many studies have reported that patients who received kidney transplant are at higher risk of malignant disease (3-6). However, whether CKD patients undergoing dialysis treatment have similar risks of developing malignancies is still controversial (6-10), although most studies have shown that this risk of developing malignant disease in CKD patients (with or without dialysis) is increased in comparison with the general population (3, 7, 11). The exact mechanisms responsible for this increased incidence of cancer have not yet been fully elucidated but several factors such as impaired immune system, chronic infections, decreased antioxidant capacity, accumulation of carcinogenic compounds, and dialysis-related factors may promote malignant transformation and tumor formation (12-16).

As studies of cancer in CKD patients on dialysis in Korea have not yet been reported, we undertook this study to investigate the clinical features and outcomes of cancer in Korean dialysis patients.

MATERIALS AND METHODS

We conducted a retrospective study of a total of 4,562 end-stage renal disease (ESRD) patients who started hemodialysis (HD) or peritoneal dialysis (PD) at two centers at Yonsei University Health System from January 1996 to December 2005. We excluded patients in whom the diagnosis of cancer preceded dialysis or those who received renal allograft or started dialysis after renal allograft. Seventy-three (69%) of our subjects were male and 33 (31%) were female. The mean age at the time of cancer diagnosis was 57.9 ± 11.7 yr. The mean time from the start of dialysis to the diagnosis of cancer was 75.2 ± 63.9 months. The most common cancer site was gastrointestinal tract (GIT) (51%) followed by urinary tract (20%), lung (8%), and thyroid (7%). Sixty nine percent of the total mortality was due to cancer. The mean time from diagnosis to death was 2.9 ± 2.5 yr. In ESRD patients with cancer, there were no significant differences in mortality rates by dialysis modality. In ESRD patients, the most common cancer was GIT cancer followed by urinary tract cancer. Therefore, careful surveillance of these cancers in ESRD patients is highly recommended.

Key Words: Neoplasms; Kidney Failure, Chronic; Gastrointestinal tract; Urinary Tract
difference. The significance of differences in survival rates between HD and PD patients was determined using the Kaplan-Meier method. The standardized incidence rate (SIR: the ratio of observed to expected cancers) was used to estimate the relative risk and 95% confidence interval (CI) for these ratios were calculated with the assumption that the observed number of cancer cases followed a Poisson distribution. Data analysis was done with SAS software (version 6.12).

RESULTS

Cancer in the general population (2002 annual report of the Korea central cancer registry)

Of the total of 66,025 patients with malignancies registered from January 1 to December 31, 2002, 55,398 (55.9%) cases were male and 43,627 (44.1%) cases were female: a sex ratio of 1.27:1. The leading age groups in order of relative frequency were 60-64 yr of age (14.8%), followed by 65-69 (14.4%), 55-59 (11.7%), 70-74 (10.7%), 50-54 (9.9%), and 45-49 (9.0%). The relative frequencies of age groups below 45 and above 75 were 0.1-7.5% and 10.9%, respectively. The leading primary cancer sites in order of relative frequency were stomach (20.2%), followed by bronchus and lung (11.9%), liver and intrahepatic bile ducts (11.3%), colorectum (11.2%), breast (7.4%), thyroid (4.9%), uterine cervix (4.0%), hematopoietic systems (2.6%), pancreas (2.4%), and urinary bladder (2.2%).

In males, the leading primary cancer sites were stomach (24.0%), followed by bronchus and lung (15.0%), liver and intrahpatic bile ducts (15.4%), colorectum (11.6%), urinary bladder (3.2%), prostate (3.0%), esophagus (2.8%), hematopoietic systems (2.7%), pancreas (2.5%), and kidney (2.0%). In females, breast (16.8%) was the most common site, followed by stomach (15.3%), colorectum (10.7%), thyroid (9.5%), uterine cervix (9.1%), bronchus and lung (6.6%), liver and intrahpatic bile ducts (6.0%), ovary (3.6%), hematopoietic systems (2.5%), and pancreas (2.3%).

Cancer in the general population (from our hospital)

The mean age of the general population at the time of the diagnosis of a malignant tumor was 53.0±18.1 yr (male: female=28,335:25,385). The most common cancer was gastrointestinal tract (GIT) cancer (44%), followed by genital organ cancer (18%), lung cancer (9%), thyroid cancer (7%), and urinary tract cancer (4%). The remaining cancers were head and neck cancer (4%), hematologic cancer (3.3%), skin cancer (1%), and cancer of unknown origin (Fig. 1).

Baseline characteristics of ESRD patients with cancer

Among the 4,562 ESRD patients, 106 (2.3%) were diagnosed with malignant tumors. Seventy three patients were male (69%) and 33 were female (31%) (2.2:1). Unlike in the general population, malignancies developed predominantly in the males of our study population (p<0.05). Diabetic nephropa-

![Fig. 1. Types of cancer in the general population (%).](image1)

![Fig. 2. Types of cancer in ESRD patients (%).](image2)

Table 1. Baseline characteristics of patients

| Total ESRD patients (n=4,562) | ESRD patients with cancer (n=106) |
|-------------------------------|---------------------------------|
| Age* 50.7±14.6 (18-90)       | 57.9±11.7 (26-83)               |
| Sex (M:F) 2760:1802 (1.5:1)  | 73.33 (2.2:1)                   |
| Dialysis mode (%)            |                                 |
| HD 3011 (66)                 | 63 (59)                         |
| PD 1551 (34)                 | 43 (41)                         |
| Cause of ESRD (%)            |                                 |
| DM 2,052 (45)                | 44 (42)                         |
| Hypertension 912 (20)        | 19 (18)                         |
| Chronic GN 821 (18)         | 17 (16)                         |
| Others 319 (7)               | 6 (5)                           |
| Unknown 458 (10)             | 20 (19)                         |
| Time to discovery of cancer (months) | 75.2±63.9 (3-288) |

* age the time of diagnosis of cancer.
ESRD, end-stage renal disease; HD, hemodialysis; PD, peritoneal dialysis; GN, glomerulonephritis.
thy (42%), hypertensive nephropathy (18%), and chronic glomerulonephritis (16%) were the most common causes of ESRD. Among the 106 patients, 63 (59%) received HD, and 43 received PD (41%). The mean age at the time of diagnosis of the cancer was 57.9 ± 11.7 yr (26-83 yr), higher than the general population (57.9 ± 11.7 vs. 53.0 ± 18.1 yr, p < 0.05). The mean duration from the initiation of dialysis to diagnosis was 75.2 ± 63.9 months (3-288 months) (Table 1). Follow-up duration from diagnosis was 42.9 ± 47.3 months (1-240).

In ESRD patients, GIT cancer was the most common followed by urinary tract cancer, lung cancer, thyroid cancer, hematologic cancer, genital tract cancer, head and neck cancer, and the others (Fig. 2, Table 2).

### Table 2. Cancer types of ESRD patients

| Location (n, %) | Cancer type (n) |
|----------------|----------------|
| Gastrointestinal tract (54, 51%) | Stomach (13) |
| Liver (20) |
| Intestine (16) |
| Pancreatobiliary (5) |
| Urinary tract (21, 20%) | Kidney (12) |
| Bladder (9) |
| Lung (9, 8%) | Lung (9) |
| Thyroid (8, 7%) | Thyroid (8) |
| Genital tract (4, 4%) | Uterine (2) |
| Ovary (1) |
| Prostate (1) |
| Hematologic (3, 3%) | Multiple Myeloma (3) |
| Head & Neck (3, 3%) | Tongue (1) |
| Larynx (1) |
| Mandibular (1) |
| Skin (1, 1%) | Melanoma (1) |
| Others (3, 3%) | Unknown origin (1) |
| Retroperitoneal tumor (1) |
| Malignant fibroma (1) |

**ESRD, end-stage renal disease.**

### Table 3. Comparison of cancer sites between the general population and ESRD patients

| Site | General population | ESRD patients |
|------|-------------------|---------------|
|      | M (28,335) F (25,221) | M (73) F (33) |
| Stomach | 6,234 (22%) 3,056 (12.0%) 11 (15%) 2 (6.1%) |
| Liver | 4,611 (16.3%) 1,141 (4.5%) 17 (23.3%) 3 (9.1%) |
| Intestine | 3,055 (10.8%) 1,976 (7.7%) 13 (17.8%) 3 (9.1%) |
| Esophagus | 700 (2.5%) 56 (0.2%) 0 0 |
| Pancreatobiliary | 1,651 (5.8%) 1,175 (4.6%) 4 (5.5%) 1 (3.0%) |
| Lung | 3,474 (12.3%) 1,246 (4.9%) 5 (6.8%) 4 (12.1%) |
| Thyroid | 500 (1.8%) 3,369 (13.2%) 2 (2.7%) 6 (18.2%) |
| Urinary tract | 1,537 (5.4%) 514 (2.0%) 1 (1.3%) 10 (30.3%) |
| Hematologic | 1,003 (3.5%) 747 (2.9%) 2 (2.7%) 1 (3.0%) |
| Uterus | 4,956 (19.4%) 2 (6.1%) |
| Breast | 4,578 (17.9%) 0 (0%) |
| Testis & prostate | 936 (3.3%) 1 (1.3%) |

**ESRD, end-stage renal disease.**

### Comparison of cancer sites between the general population and ESRD patients

In the general population, common cancer sites were stomach (22.0%), liver (16.3%), lung (12.3%), and intestine (10.8%) in males, whereas in females, the incidence of female genital tract cancer, including uterine cervical cancer (19.4%) and breast cancer (17.9%), was the highest, followed by stomach (12.0%), thyroid (13.2%), and intestine (7.7%). On the other hand, in ESRD patients, liver was the most common cancer site followed by intestine and stomach in male patients. In female patients, urinary tract cancer showed the highest incidence rate (Table 3).

### The time to the development of cancer in ESRD patients

The earliest diagnosed cancer was multiple myeloma and the latest was cancer of liver (mainly hepatocellular carcinoma, HCC). For cancer of liver, kidney and thyroid, the interval to diagnosis of malignant tumors was relatively long (Table 4). Among the 106 patients, 18 (17%) were diagnosed with malignant tumors within 1 yr of beginning dialysis, and the remaining 88 (83%) were diagnosed within 10 yr (Table 5). The risk of cancer was slightly higher when cancer was diagnosed during the first year of dialysis.

When ESRD patients were divided into two groups according to age of 40, most malignancies developed after 40 yr of age (84%); Malignancies of patients older than 40 yr (n=89) includes 47 GIT cancers, 14 urinary tract cancer, 9 lung can-

### Table 4. Mean interval* to discovery of cancer in ESRD patients

| Type of cancer | Mean Interval (months) |
|----------------|------------------------|
| Liver | 90.4 ± 70.6 (19-288) |
| Colorectal | 47.3 ± 51.1 (5-168) |
| Stomach | 57.6 ± 43.8 (6-156) |
| Kidney | 142.7 ± 68.2 (60-276) |
| Bladder & Ureter | 59.1 ± 49.3 (14-154) |
| Lung | 30.6 ± 24.3 (4-69) |
| Thyroid | 88.0 ± 31.4 (27-123) |
| Hematologic | 3.3 ± 0.6 (3-4) |

* Mean time from the start of dialysis to the diagnosis of cancer.

### Table 5. Overall risk of cancer in ESRD patients by length of dialysis treatment

| Time after dialysis | n | SIR (95% CI) |
|---------------------|---|-------------|
| During year 1 | 18 | 1.3 (1.0-1.4) |
| During year 2 | 14 | 1.1 (1.0-1.2) |
| During year 3-6 | 23 | 1.2 (1.1-1.3) |
| During year 6-10 | 32 | 1.3 (1.0-1.4) |
| After year 10 | 19 | 1.1 (1.0-1.2) |

ESRD, end-stage renal disease; SIR, standardized incidence rate; CI, confidence interval.
cancers, 4 thyroid cancers, and 15 other cancers. In patients less than 40 yr of age (n=18), there were 7 GIT cancer, 7 urinary tract cancer, and 4 thyroid cancers (Fig. 3A). In the general patients older than 40 yr, the leading primary cancer sites were GIT (45%), followed by breast & uterine cervix (19%), lung (9%), and thyroid (7%). In the general patients younger than 40 yr, breast & uterine cervix (30%) was the most common site, followed by GIT (22%), thyroid (15%), and hematologic systems (5%) (Fig. 3B).

Comparison of cancer types according to dialysis modality in ESRD patients

Fig. 4 shows the cancer distribution with respect to dialysis modality. We found no significant difference between HD and PD treated patients. In HD (n=63) patients, GIT cancer was the most common (n=37, 58.7%), followed by urinary tract cancer (n=12, 19%) and lung cancer (n=4, 6.3%), with a similar pattern seen in PD (n=43) patients.
Survival of ESRD patients with cancer

The mean time from diagnosis to death was 2.9 ± 2.5 yr. Among the 106 cancer patients, the overall mortality rate was 53%. Thirty four patients (60%) died of cancer and 22 (40%) died of cause not related to cancer, such as cerebral hemorrhage (n=3), cardiovascular disease (n=2), sepsis (n=2), trauma (n=1) and unknown reasons (n=13). Deaths occurred in all patients with cancer of biliary tract system, in 2 out of 3 patients with hematologic cancer (67%), in 5 out of 9 patients with lung cancer (56%), and in 6 out of 13 patients with bladder cancer (46%) (Table 6).

The survival rate of ESRD patients without cancer was significantly higher compared to that of ESRD patients with cancer (p < 0.05). In ESRD patients with cancer, there were no significant differences in mortality rates by dialysis modality (Fig. 5). Five year survival rate was 44.0% and 46.6% in patients treated with HD and PD respectively.

DISCUSSION

CKD patients have a high incidence of cancer for several reasons, including: weakened immune system, previous immunosuppressive treatment, altered DNA repair, and chronic infection (12-16).

In 25,044 patients who received dialysis in the U.S.A., Europe, Australia, or New Zealand, the overall risk of cancer is increased (3%) compared with the general population (17). In one report, HD patients have a higher risk of developing malignant tumors than the general population, with malignancies diagnosed in 4.9% of patients (18). In a recent meta-analysis of 15 studies, it was found that the relative risk (observed cancer cases over expected cancer cases) averaged 7.6 in 10 studies (72,484 ESRD patients). In contrast, in the remaining 5 studies (35,407 ESRD patients) the average risk was 0.98 (19). Despite this lack of consensus, there is general agreement that CKD patients have a greater risk of cancer than the general population. A recent report showed that cancer incidence is increasing in Korea, with an incidence rate by the dialysis duration, 17% of all malignancies occurred within 1 yr of starting dialysis, with a gradually decreasing trend in the malignancy incidence rate afterwards. This finding was in line with a report by Inamoto et al., reporting that the incidence was very high during the first 6 months of dialysis treatment and rather low in the 7th-10th year. (25). However, compared to the study by Inamoto et al., only 17% of all malignancies occurred within 1 yr of starting dialysis in our study. This is partly because that our study include many cases of HCC, thyroid cancer, etc., which generally have a relatively delayed development, and that could explain why we found relatively few malignancies within 1 yr of beginning dialysis. The risk of cancer was slightly higher when cancer was diagnosed during the first year of dialysis. This finding might be due to increased detection of cancer and more detailed observation at the time of initial dialysis treatment.

Similar to the general population, GIT cancers were the most common cancer in HD patients as well as nondialysed uremic patients. Cengiz et al. (22) reported that 19% of CKD patients (regardless of dialysis treatment) had a urologic malignancy. In other reports, bladder cancer developed in 28.5% of HD patients (23) and kidney and bladder cancers (12 of 33) were the most common types of cancer in HD patients (5). Ishikawa et al. (24) also showed that the incidence of renal cell carcinoma in HD patients was 41 times that of the general population. In contrast, our study found GIT cancers to be the most common in ESRD patients, although urologic malignancy were more prevalent than in the general population, which is similar to the findings of a Japanese survey (25). In fact, these results are not surprising, as stomach cancer is the most frequent in Japan and Korea.

The mean age at the time cancer diagnosis in ESRD patients was higher than in the general population. This may be because the age of dialysis patients is relatively higher than the general population as a whole, thus causing the age at the time of cancer diagnosis to also be high. According to the incidence rate by the dialysis duration, 17% of all malignancies occurred within 1 yr of starting dialysis, with a gradually decreasing trend in the malignancy incidence rate afterwards. This finding was in line with a report by Inamoto et al., reporting that the incidence was very high during the first 6 months of dialysis treatment and rather low in the 7th-10th year. (25). However, compared to the study by Inamoto et al., only 17% of all malignancies occurred within 1 yr of starting dialysis in our study. This is partly because that our study include many cases of HCC, thyroid cancer, etc., which generally have a relatively delayed development, and that could explain why we found relatively few malignancies within 1 yr of beginning dialysis. The risk of cancer was slightly higher when cancer was diagnosed during the first year of dialysis. This finding might be due to increased detection of cancer and more detailed observation at the time of initial dialysis treatment.

Similar to the general population, GIT cancers were the most common cancer in our subjects, implying that early detection and aggressive treatment of these cancers is just as important as in ESRD patients as in the general population. In addition, the incidence of urinary tract cancer was substantially higher than in the general population, indicating that it is important to perform screening tests for this type of cancer as well. Unlike in transplant recipients (26-28), the types of cancers most commonly diagnosed in patients on dialysis are those most likely to be found in the general non-ESRD population. These results should reinforce the need for routine check-up to include renal and gastrointestinal tract can-
Increased surveillance should lead to detection of cancers at an earlier stage, which are not observed among GIT and urinary tract cancers.

Our findings showed that liver cancers were more prevalent in ESRD patients. Infection with HBV or HCV is a serious problem in dialysis patients. The fact that ESRD patients have greater exposure to hepatitis B and C viruses than normal patients, probably accounts for the observed excess of liver cancer (29). Therefore, widespread screening for HBV and HCV also should be encouraged.

It should be noted that all 3 hematologic malignancies which occurred in ESRD patients were multiple myeloma. Multiple myeloma (MM) is a common hematologic malignancy and also can be the cause of ESRD (30). Consequently, the diagnosis of MM might be missed at the time of the dialysis start and it is possible that its incidence could be underestimated.

Interestingly, in our study, thyroid cancer was fairly common, it was found in 8 (7.5%) patients. Thyroid disease, including hypothyroidism, goiter, nodules, and thyroid cancer, may occur more frequently in ESRD patients than in the general population (17, 31), and it has been suggested that chronic immunosuppression and secondary hyperparathyroidism may play a role (32, 33).

There are several limitations to the present study. First, we analyzed limited data from two centers in a retrospective review. Second, we had more limited follow-up and fewer observed cancer cases than those might be found in a larger cohort of dialysis patients. Third, the relationship between the underlying disease and malignancy was not evaluated. However, even with such limitations, this study contributes to a comprehensive assessment of cancer risk in ESRD patients, especially in Korea.

In conclusion, our data shows that ESRD patients in Korea have a higher risk of developing cancer than the general population, and the types of cancer most commonly diagnosed in ESRD patients are those most likely to be found in the general population. In addition, the incidence of urinary tract cancer is higher in ESRD patients compared to the general population, thus, careful surveillance for malignancies in ESRD patients, especially for those of the urinary tract, is highly recommended.

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