中國醫藥大學

醫務管理學研究所碩士論文

編號：IHASEP-039

不同透析方式對病患罹患泌尿道癌之相對風險分析

Risk of Urinary Tract Cancer on Different Dialysis Modality Patients in Taiwan

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中華民國九十九年六月

摘要

目地: 本研究探討台灣末期腎病病患罹患泌尿道癌之情形並分析不同透析方式對末期腎病病患罹患泌尿道癌之相對風險。

方法: ：利用 1997 年至 2007 年的全民健康保險研究資料庫，以回溯性世代研究法， 將這 11 年間所有新接受透析治療超過三個月之末期腎病病患納入分析。 研究對象計有 78,568 位新接受透析治療之末期腎病病患 ，其中有 73,961 位病患接受血液透析，4,607 位病患接受腹膜透析)。除描述性統計及雙變項分析外，使用 Cox proportional hazard regression models 分析造成透析病患罹患泌尿道癌之相關因子。

結果: 總共計有 1,824 位透析病患罹患泌尿道癌(佔所有新接受透析治療之末期腎病病患的 2.49%)。Cox proportional hazard models 結果顯示，在控制其他變項後，接受血液透析病患較接受腹膜透析者有較高的罹癌機率(罹癌相對風險性為 1.968，95%信賴區間: 1.472-2.632)。其他顯著相關因素還包括；年齡層大於 40 歲有較高的罹癌機率(年齡層 41-50 歲, 51-60 歲, 61-70 歲, 及> 70 歲其罹癌相對風險性分別為 4.5，6.653， 6.28 及 5.952)、女性病患(罹癌相對風險性為 1.235，95%信賴區間: 1.119-1.363)、後天性腎囊腫(罹癌相對風險性為 1.612，95%信賴區間: 1.336-1.944)、高血壓(罹癌相對風險性為 0.475，95%信賴區間: 0.431-0.524)、糖尿病(罹癌相對風險性為 0.304，95%信賴區間: 0.269-0.342)及不同的透析機構層級(於醫學中心接受透析治療病患較於其他層級機構接受透析治療病患有較高的罹癌機率)。

結論: 接受腹膜透析之末期腎病患者較接受血液透析之患者有顯

著較低罹患泌尿道癌的機率。雖然腎臟專科醫師的偏好以及保險支付制度皆會影響病患對透析方式的選擇，本研究卻有不同的建議，選擇使用腹膜透析作為首選的腎臟替代療法的確值得更大力的推廣。

關鍵字：腹膜透析，血液透析，腎臟細胞癌，移形性細胞癌

Acknowledgement

致謝

此次碩士論文得以順利的提出，首先要感謝我的指導教授蔡文正所長在研究生涯的兩年裡的細心指導、體諒與包容，於課業上諄諄教誨與生活上的關心，使我能在兼顧多重角色下順利完成。特別感謝蔡教授在研究資源上的大方幫助以及研究工作的指導與斧正，使困難得以解決，論文更加充實與完整。在此對老師獻上最誠心的謝意。

感謝系上的所有老師，謝謝您們於課堂中鉅細靡遺、不厭其煩的指導，讓我得一窺醫務管理殿堂的浩瀚，大大的擴展了我的視野。

感謝口試委員李亞欣博士及謝淑惠副教授，對於本論文的指正與寶貴意見，使本論文能更加的詳實及嚴謹。

特別感謝一同努力走過這一段人生歷程的所有同學與學長姐、學弟妹，無論研究經驗的傳承、平日的打氣與鼓勵、課業上的配合、討論與傾囊相授，謝謝您們所給予最大的支持與關照，謝謝您們為我的人生加了這一段滿滿的美好的回憶。

最要感謝親愛的家人，你們的關懷與支持是我研究生活最大的動力。

謹以本文獻給所有關心我的人。

佳隴　謹誌 2010.06

Abstract

Objective: This study investigated the relationship between end-stage renal disease (ESRD) patients and urinary tract cancer and also examined the impact of dialysis modality on the incidence of the urinary tract cancer.

Methods: The retrospective cohort study was based on 11-year nationwide dialysis patients obtained from the National Health Insurance Research dataset. The study subjects included 78,568 new dialysis patients and of which 73,961 new hemodialysis (HD) patients and 4,607 new peritoneal dialysis (PD) patients were included. Besides bivariate analysis, this study used Cox proportional hazards regression models to examine the related factors influencing the dialysis patients to suffer from the urinary tract cancer.

Results: The incident rates of the urinary tract cancer are 2.49% (1,824) for dialysis patients. The Cox regression models indicated that the following variables were significant factors associated with urinary tract cancer: hemodialysis (Relative risk (RR): 1.968, 95% CI: 1.472-2.632), age group 41-50 years, 51-60 years, 61-70 years, > 70 years (RR: 5.143, 7.428, 6.980, 6.855 respectively), female gender (RR: 1.235, 95% CI: 1.119-1.363), acquired cystic kidney disease (ACKD) (RR: 1.612, 95% CI: 1.336-1.944), hypertension (RR: 0.475, 95% CI: 0.431-0.524), diabetes mellitus (DM) (RR: 0.304, 95% CI: 0.269-0.342) and level of dialysis facilities.

Conclusion: Peritoneal dialysis patients have a urinary tract cancer-specific advantage as compared to hemodialysis patients in Taiwan. Although the nephrologist's preference and the reimbursement system would influence the under-utilization of peritoneal dialysis, peritoneal dialysis deserved more

promotion as treatment options to ESRD patients.

Key words: Peritoneal dialysis, Hemodialysis, Transitional cell carcinoma, Renal cell carcinoma

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Chapter 1 Introduction

1. Research Background and Questions

As comparing to international data using the United States Renal Data System 2009 Annual Data Report (USRDS 2009 ADR), the incident and prevalent rates of end-stage renal disease patients in 2007 were greatest in Taiwan at 415 per million populations and 2,288 per million populations. The incidence and prevalence of dialysis patients in Taiwan were also steadily increased throughout the 1990–2001 (Yang & Hwang, 2008). The prevalent hemodialysis population in 2007 is nearly 2.38 times larger than in 1997, and topped 45,894 patients in 2007 (National Kidney Foundation R.O.C. [NKF], 2009). The number of peritoneal dialysis patients peaked at 4,181 in 2007, and now accounts for 8.5 percent of dialysis patients, a ratio that continues to increase from 1997 of nearly 4.4 percent per year.

Patients on maintenance hemodialysis, once initially diagnosed to be a victim of bladder cancer, were often found to have higher grade bladder transitional cell carcinoma (TCC) than normal population in clinical practice (Horiuchi, et al., 2004). Although several potential sources of bias, including closer surveillance of ESRD patients than of the general population; all patients with prevalent cancers from the cohort may not be excluded, were mentioned, dialysis ESRD patients are at increasing risk for cancers, especially urological cancers (Maisonneuve, et al., 1999). Although the cancer risks show no association with type of dialysis (Ishikawa, 1992; Stewart, et al., 2003), the reported difference in the results of several studies comparing development of transitional cell carcinoma and mortality risk among continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis patients is so variable (Nolph, 1996; Ou, et al., 2000).

Younger and female ESRD patients have significantly increased cancer risks, especially urinary bladder and kidney cancer (Maisonneuve, et al., 1999). Cancer of the kidney but not of the bladder (although not reaching significance, the risk of bladder cancer even fell) was associated with duration of dialysis (Stewart, et al., 2003). Contrary to Western countries, transitional cell carcinoma of the urinary bladder seem have more observed cases than renal cell carcinoma (RCC) of kidney in maintenance dialysis patients in Taiwan and Japan (Chang, Yang, & Yang, 2007; Inamoto, et al., 1991; Ou, et al., 2000; Wu, et al., 2006). However, there was no detailed and massive investigation on the related factors between patients on dialysis and urinary tract cancers, yet.

2. Research Objectives

The study will investigate the related factors between urinary tract cancers and ESRD dialysis patients. The objectives of this study are the following:

a. To understand the circumstances of the urinary tract cancers on dialysis patients in Taiwan.

b. To find out the relationship between the urinary tract cancers and the dialysis.

c. To investigate the impact of the dialysis modality on the incidence of the urinary tract cancers.

Chapter 2 Literature Review

This chapter discusses and introduces the relative literature in the following 5 sessions, including: Chronic kidney disease, ESRD and renal replacement therapy; demographic and epidemiologic features of ESRD dialysis patients; demographic and epidemiologic features of urinary tract cancer; urinary tract cancer of ESRD patients; and comparison of hemodialysis and peritoneal dialysis.

1. Chronic Kidney Disease, End Stage Renal Disease and Renal Replacement Therapy

(1) Symptoms and Signs of Chronic Kidney Disease

Chronic kidney disease (CKD) is a progressive loss of renal function over a period of months or years and should be differentiated from reversible acute renal failure. The symptoms of worsening kidney function are unspecific, and might be initially detected as an increase in serum creatinine or protein in the urine. As the kidney function decreases, symptoms and signs include ("K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification," 2002):

a. Blood pressure is increased due to fluid overload and production of vasoactive hormones, increasing one's risk of developing hypertension and/or suffering from congestive heart failure.
b. Urea accumulates, leading to azotemia and ultimately uremia (symptoms ranging from lethargy to pericarditis and encephalopathy). Urea is excreted by sweating and crystallizes on skin ("uremic frost").
c. Potassium accumulates in the blood (hyperkalemia with a range of

symptoms including malaise and potentially fatal cardiac arrhythmias).

d. Erythropoietin synthesis is decreased (anemia, which causes fatigue).
e. Fluid volume overload - symptoms may range from mild edema to life-threatening pulmonary edema.
f. Hyperphosphatemia - due to reduced phosphate excretion, associated with hypocalcemia (due to vitamin D3 deficiency). The major sign of hypocalcemia being tetany. Later this progresses to tertiary hyperparathyroidism, with hypercalcaemia, renal osteodystrophy and vascular calcification that further impairs cardiac function.
g. Metabolic acidosis due to accumulation of sulfates, phosphates, uric acid, etc. This may cause altered enzyme activity by excess acid acting on enzymes and also increased excitability of cardiac and neuronal membranes by the promotion of hyperkalemia due to excess acid (acidemia) (Adrogue & Madias, 1981).
h. Accelerated atherosclerosis and cardiovascular disease.

Often, CKD is diagnosed as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a blood relative with chronic kidney disease. CKD may also be identified when it leads to one of its recognized complications, such as cardiovascular disease, anemia or pericarditis. (National Institute for Health and Clinical Excellence, [NICE], 2008).

(2) Staging of CKD

Recent professional guidelines classify the severity of CKD in five stages (Crowe, Halpin, & Stevens, 2008; K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification," 2002):

a. Stage 1 CKD

Slightly diminished function; Kidney damage with normal or relatively high GFR (>90 mL/min/1.73 m2). Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

b. Stage 2 CKD

Mild reduction in GFR (60-89 mL/min/1.73 m2) with kidney damage. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

c. Stage 3 CKD

Moderate reduction in GFR (30-59 mL/min/1.73 m2). British guidelines distinguish between stage 3A (GFR 45-59) and stage 3B (GFR 30-44) for purposes of screening and referral.

d. Stage 4 CKD

Severe reduction in GFR (15-29 mL/min/1.73 m2). Preparation for renal replacement therapy.

e. Stage 5 CKD (also known as ESRD)

Established kidney failure (GFR <15 mL/min/1.73 m2), or permanent renal replacement therapy (RRT).

(3) Etiology and Prognosis of CKD

The most common causes of CKD are diabetic nephropathy, hypertension, and glomerulonephritis. Together, these cause approximately 75% of all adult cases. Others are polycystic kidney disease, urinary tract obstruction, reflux nephropathy, drug- or medication-induced kidney problems, and bacteria such as E. coli or streptococcus infections. Other problems, such as kidney stones, Alport syndrome, Fabry disease, and Wilms' cancer, can also affect the kidneys.

The prognosis of patients with chronic kidney disease, guarded as epidemiological data, has shown that all cause mortality increases as kidney function decreases (Perazella & Khan, 2006). The leading cause of death in patients with CKD is cardiovascular disease, regardless of whether there is progression to stage 5 (Perazella & Khan, 2006; Tonelli, et al., 2006). In ESRD patient, particularly among patients age 65 and older, all-cause mortality has sharp peak in months two and three after the initiation of RRT; mortality due to cardiovascular disease and infection also peak in these months. The decline from the higher mortality rates seen in the early and mid-1980s may be explained by advances in the delivery of dialysis, including, as mentioned in the chapter introduction, the use of Kt/V to quantitate dialysis dose, the replacement of acetate with bicarbonate dialysate, the introduction of new dialyzer membranes, and the use of ultrafiltration control equipment to stabilize weight removal during the dialysis run.

(4) ESRD and Renal Replacement Therapy

When one reaches stage 5 CKD (ESRD), renal replacement therapy (RRT), a term used to encompass life-supporting treatments for renal failure, is required. The number of patients coming to ESRD continued to increase annually, challenging the existing system of renal replacement therapy. These patients, on average, are older at the onset of ESRD and are living longer after the initiation of RRT. These treatments, including hemodialysis, peritoneal dialysis, hemofiltration and renal transplantation, do not cure but just are palliative treatments for ESRD.

a. Modalities of renal replacement therapy

Hemodialysis

Hemodialysis is a method for removing waste products such as potassium and urea, as well as free water from the blood when the kidneys are in renal failure. It involves diffusion of solutes across a semipermeable membrane. HD utilizes counter current flow, where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit. Counter-current flow maintains the concentration gradient across the membrane at a maximum and increases the efficiency of the dialysis. Fluid removal (ultrafiltration) is achieved by altering the hydrostatic pressure of the dialysate compartment, causing free water and some dissolved solutes to move across the membrane along a created pressure gradient. The dialysis solution that is used is a sterilized solution of mineral ions. Urea and other waste products, potassium, and phosphate diffuse into the dialysis solution. However, concentrations of sodium and chloride are similar to those of normal plasma to prevent loss. Sodium bicarbonate is added in a higher

concentration than plasma to correct blood acidity. A small amount of glucose is also commonly used.

A prescription for dialysis by a nephrologist will specify various parameters for a dialysis treatment. These include frequency (how many treatments per week), length of each treatment, and the blood and dialysis solution flow rates, as well as the size of the dialyzer. The composition of the dialysis solution is also sometimes adjusted in terms of its sodium and potassium and bicarbonate levels. In general, the larger the body size of an individual, the more dialysis he or she will need.

Longterm complications of HD include amyloidosis, neuropathy and various forms of heart disease. Cardiovascular disease is the leading cause of death among patients with ESRD (USRDS 2009 ADR). Left ventricular hypertrophy and chronic inflammation are independent risk factors for cardiovascular death among patients receiving maintenance hemodialysis. Short daily hemodialysis significantly increased cumulative dialysis dose and ultrafiltration. Increasing the frequency and length of treatments has been shown to improve fluid overload, phosphorus management, and enlargement of the heart that is commonly seen in such patients (Ayus, et al., 2005; Weinreich, De los Rios, Gauly, & Passlick-Deetjen, 2006).

Peritoneal Dialysis

Peritoneal dialysis (PD) uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. PD is used as an alternative to HD though it is far less common. PD may also be used for patients with cardiac instability as it does not result in rapid and significant alterations to body fluids, and for patients with insulin-dependent

diabetes mellitus due to the ability to control blood sugar levels through the catheter. It has comparable risks and expenses with HD, with the primary advantage being the ability to undertake treatment without visiting a medical facility. The primary complication with PD is a risk of infection due to the presence of a permanent tube in the abdomen (Khanna & Nolph, 1989; La Greca, et al., 2001; Maher, 1990; Nolph, 1979).

During each session of PD, a large volume of fluid is introduced to the abdomen over the next ten to fifteen minutes. After a variable period of time depending on the treatment (usually 4-6 hours), the fluid is removed and replaced with fresh fluid. This can occur automatically while the patient is sleeping (automated peritoneal dialysis, APD), or during the day by keeping two liters of fluid in the abdomen at all times, exchanging the fluids four to six times per day (CAPD). Though there are several different shapes and sizes of catheters that can be used, different insertion sites, number of cuffs in the catheter and immobilization, there is no evidence to show any advantages in terms of morbidity, mortality or number of infections, though the quality of information is not yet sufficient to allow for firm conclusions (Strippoli, Tong, Johnson, Schena, & Craig, 2004).

PD is less efficient at removing wastes from the body than hemodialysis, and the presence of the tube presents a risk of peritonitis due to the potential to introduce bacteria to the abdomen. Peritonitis can be as frequent as once every 15 months (0.8 episodes per patient year) and is best treated through the direct infusion of antibiotics into the peritoneum with no advantage for other frequently used treatments such as routine peritoneal lavage or use of urokinase (Rabindranath, et al., 2007; Wiggins, Craig, Johnson, & Strippoli, 2008).

Complications of PD include hypotension (due to excess fluid exchange

and sodium removal), low back pain and hernia or leaking fluid due to high pressure within the abdomen. Hypertriglyceridemia and obesity are also concerns due to the large volume of glucose in the fluid, which can add as many as 1200 calories to the diet per day.

In a 2009 worldwide survey of patients in end stage renal disease (USRDS 2009 ADR), HD is the most common mode of dialysis therapy worldwide. Evidenced data showing that, in nearly 75 percent of reporting countries, at least 80 percent of patients are on this mode of therapy. Only 8.5% of patients, respectively, use CAPD/APD in Taiwan. However, in countries such as Hong Kong and Jalisco, peritoneal dialysis is provided to 80 and 66 percent of patients in 2007, respectively.

Hemofiltration

Hemofiltration is a renal replacement therapy similar to HD which is used almost exclusively in the intensive care setting. Thus, it is almost always used for acute renal failure. It is a slow continuous therapy, usually last between 12 to 24 hours in each session and is usually performed daily. A recent Cochrane database review of available trials could not find a definite benefit of hemofiltration vs. hemodialysis in terms of outcomes (Rabindranath, et al., 2006).

Renal transplantation

Renal transplantation is the organ transplant of a kidney in a patient with end-stage renal disease. Kidney transplantation is typically classified as deceased-donor (formerly known as cadaveric) or living-donor transplantation depending on the source of the recipient organ. Living-donor renal transplants are further characterized as genetically related

(living-related) or non-related (living-unrelated) transplants, depending on whether a biological relationship exists between the donor and recipient. Immunosuppressant drugs are used to suppress the immune system from rejecting the donor kidney. Having medications to suppress the immune system was essential. Suppressing an individual's immune system places that individual at greater risk of infection and cancer (particularly skin cancer and lymphoma), in addition to the side effects of the medications.

Complications of renal transplantation include: transplant rejection (hyperacute, acute or chronic); infections and sepsis due to the immunosuppressant drugs that are required to decrease risk of rejection; post-transplant lymphoproliferative disorder; imbalances in electrolytes including calcium and phosphate; side effects of medications including gastrointestinal inflammation and ulceration of the stomach and esophagus, hirsutism, hair loss, obesity, acne, diabetes mellitus (type 2), and hypercholesterolemia.

The average lifetime for a donor kidney is ten to fifteen years. When a transplant fails a patient may opt for a second transplant, and may have to return to dialysis for some intermediary time. This modality of renal replacement therapy is associated with improved survival and quality of life when compared with other modes of dialysis (Becker & Stone, 1997).

b. Initiation and timing of renal replacement therapy

No standardized criteria yet exist to define when a patient with progressive renal failure should start RRT. There are a number of clinical indications to initiate dialysis in patients with CKD. These include("K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification," 2002):

- Pericarditis or pleuritis (urgent indication).
- Progressive uremic encephalopathy or neuropathy, with signs such as confusion, asterixis, myoclonus, wrist or foot drop, or, in severe cases, seizures (urgent indication).
- A clinically significant bleeding diathesis attributable to uremia (urgent indication).
- Fluid overload refractory to diuretics.
- Hypertension poorly responsive to antihypertensive medications.
- Persistent metabolic disturbances that are refractory to medical therapy: include hyperkalemia, metabolic acidosis, hypercalcemia, hypocalcemia, and hyperphosphatemia.
- Persistent nausea and vomiting.
- Weight loss or signs of malnutrition.

Optimum timing of treatment for patients with CKD prevents serious and uremic complications, including malnutrition, fluid overload, bleeding, serositis, depression, cognitive impairment, peripheral neuropathy, infertility, and increased susceptibility to infection. However, all forms of kidney replacement therapy entail important trade-offs. As GFR decreases, patients and physicians must weigh many risks and benefits. Decision making is more complex for older and more fragile patients. Together, patients and physicians must continually reconsider whether the anticipated physiological benefits of solute clearance and extracellular fluid (ECF) volume control now outweigh the physical risks and psychosocial toll of therapy.

c. Choice of renal replacement therapy

The choice of RRT modality that is best suited for a particular patient is increasingly important. Important factors to consider include not only mortality and morbidity, but also quality of life, patient age and social circumstances, evidence of cardiovascular disease, patient preference, available of suitable living related donor, economic factors and the etiology of ESRD. Considering the optimum choice of RRT modality, two important aspect of RRT could be used to gauge the best RRT modality (Becker & Stone, 1997):

Patient survival

The most fundamental outcome for RRT that can be analyzed is survival. Historical comparisons of survival data from ESRD programs are confounded by factors such as improvements in transplantation graft and patient survival; selection bias that steer patients toward one RRT modality; and co-morbid conditions as the ESRD population ages. In addition, in the United States, Health Care and Financing Administration (HCFA) data do not include the first 90 days on dialysis. Patients may have a significant mortality rate (11-25%) during this period. Overall and across causes, mortality is highest in the third month of dialysis and then falls back to levels close to or lower than those in month one. Thus, the comparison of risks of death for different RRT modalities continue to show contradictory findings.

However, living-related donor transplantation was associated with a fare better patient survival, with expected lifetimes 62–70 percent as long as those in the general population, than the other RRT modalities. For patients treated with HD, PD, and cadaveric renal transplantation, there are no significant difference in survival (USRDS 2009 ADR).

Quality of life

The other important aspect of RRT that can be used to gauge the best RRT modality for a particular individual is quality of life.

Patients undergoing dialysis did not work or function at the same level as individuals in the general population and also experienced an increased rate of psychological and sexual problems, a reduction in social activities, and an increase in marital problems. Successful transplantation may offset a number of these problems. Dialysis patients undergoing treatment at home experienced a higher quality of life than other dialysis. PD patients, having superior psychosocial adaptation to their condition, had an improved quality of life compared to in-center HD patients.

Transplantation recipients displayed a "higher" quality of life based on subjective measures such as life satisfaction and general well-being. Renal transplantation patients are more likely to be employed (75%) versus PD (35%) or in-center HD (19%) (Evans, et al., 1985; Julius, et al., 1989).

2. Demographic and Epidemiologic Features of Dialysis ESRD Patients

As of December 31, 2007, data by National Kidney Foundation of Taiwan [NKF] (2009) exhibited total 45,894 patients were receiving hemodialysis therapy (91.65 percent of dialysis patients), 4,181 (8.35 percent of dialysis patients) were on peritoneal dialysis, but only 2,054 had ever received renal transplantation from 1997-2007 (The Transplantation Society of Taiwan, 2009), that's about 0.4 percent of Dialysis patients. Jalisco (Mexico), the United States, Norway, and the Netherlands reported

transplant rates of 59.3, 58.1, 55.2, and 50.7 per million populations in 2007. The reported rate was less than 10 per million, in contrast, in Hong Kong, Bosnia and Herzegovina, Thailand, Malaysia, Russia, Romania, Bangladesh and Taiwan. The annual rate of growth has slowed in the prevalent hemodialysis population, from 13 percent in 1997 to 8.3 percent in 2007. Taiwan and Japan (dialysis only) continue to report the greatest prevalent rates of ESRD, at, 2,288 and 2,060 per million populations, respectively, in 2007. The next highest rate was reported by the United States, at 1,698. The lowest rates, of 74 and 99 per million population, were reported by the Philippines and Bangladesh.

In U.S. (USRDS 2009 ADR), chronic glomerulonephritis (CGN) was the main cause of ESRD, comprising 38.6% of incident patients and 47.1% of prevalent patients, diabetes mellitus (DM) caused 24.7% of incident patients and 14.6% of dialysis prevalent patients in 1990. According to the USRDS 2009 ADR, the annual numbers of patients who have diabetes and are admitted to RRT in the United States are more than doubled between 1995 and 2007, and there was a striking increase in the percentage of incident ESRD patients with diabetes as the primary diagnosis (30.4% in 1987, 45.2% in 2000 and 54% in 2007). However, diabetes was the primary cause of ESRD for 54 percent of new patients in 2007; one in three patients had a primary diagnosis of hypertension. The incident rate of diabetic ESRD fell 3.3 percent between 2006 and 2007, to 155 per million population — just 0.6 percent greater than the rate seen in 2000. The rate of ESRD caused by hypertension, in contrast, has grown 8.0 percent since 2000, to 99 per million population, while ESRD due to glomerulonephritis has fallen 21.3 percent, to 24.3., returning to levels seen in the early 1990s. It is not clear if this finding is related to improved blood pressure control and greater use of

ACE-Is or ARBs, or if hypertension and diabetes are now so common that there is some misclassification of primary diagnosis. In many countries, ESRD patients with diabetes is increasing dramatically worldwide and diabetes has become the single most frequent cause of ESRD. In Taiwan, DM was the main primary cause of ESRD, comprising 43.1 percent of prevalent patients in 2007.

USRDS data also show that adjusted rates of all-cause mortality are 6.7–8.5 times higher for dialysis patients than for their counterparts in the general population. In 2007, mortality for patients on therapy 5+ years was 20.6% greater than the rate among the newest patients. Five-year survival for 1998–2002 incident patients reached 0.38 overall, a 7.5% increase compared to survival in 1993–1997. Admissions for cardiovascular disease are highest in patients age 75 and older, at 0.62 per patient year. Mortality is highest in the third month of dialysis, then falls to levels close to or lower than those in month one. Among prevalent hemodialysis patients age 75–84, the cumulative probability of incident walking disability at one year after stroke is 51%. Among prevalent hemodialysis patients age 75–84 with a stroke, 60% die within one year of the stroke. Jalisco (Mexico), the United States, Norway, and the Netherlands reported transplant rates of 59.3, 58.1, 55.2, and 50.7 per million populations in 2007. The reported rate was less than 10 per million, in contrast, in Hong Kong, Bosnia and Herzegovina, Thailand, Malaysia, Russia, Romania, Bangladesh and Taiwan.

3. Demographic and Epidemiologic Features of Urinary Tract Cancer

In 2008, the 10 leading causes of death in Taiwan remained unchanged

from the previous year, accounting for 75.6 percent of all deaths. Malignant tumors, been the leading cause of death in Taiwan since 1982, were again the No. 1 killer, causing 27.3 percent of all deaths, that's nearly 39,000 people died of cancer per year (2008 statistics of causes of death, Department of health, Taiwan). Urinary tract cancer is a general term for cancer in the kidney, bladder, and the tubes that connect them. With the age-standardized incident rates at about 28 per 100,000 populations in 2006, there were 1,200 deaths from urinary tract cancer in 2008 (about 9.5 per 100,000 population age-standardized mortality rates). Bladder cancer accounts for around 1.9% of male deaths and 1.6 % of female deaths from cancer in Taiwan and is the 12th. and the 13th. most common cause of cancer death in men and woman. Renal cancer accounts for around 1.2% of male deaths and 1.6 % of female deaths from cancer in Taiwan and is the 14th. and the 12th. most common cause of cancer death in men and woman.

Etiologic factors of urinary tract cancer include: smoking(Vogelzang & Stadler, 1998); chemical carcinogens [Asbestos (Enterline, Hartley, & Henderson, 1987), organic solvents (Vamvakas, Bruning, et al., 1998), cadmium (Kolonel, 1976), aristolochia (Nortier, et al., 2000)]; radiation (Boice, et al., 1988; Vogelzang, Yang, Goldman, Vijayakumar, & Steinberg, 1998) ; physical activity (Murai & Oya, 2004); analgesics and diuretics (Lindblad, McLaughlin, Mellemgaard, & Adami, 1993); Von Hippel-Lindau disease (Maxwell, et al., 1999); acquired cystic disease (Dunnill, Millard, & Oliver, 1977); and even obesity (Amling, 2004) and diet (Asal, Risser, et al., 1988).

(1) Etiology of Bladder Cancer

We do not yet know exactly what causes bladder cancer, but we do

know the following risk factors have been linked to bladder cancer:

a. Smoking: Smoking is the greatest risk factor for bladder cancer. Smokers get bladder cancer twice as often as people who don't smoke. Certain chemicals in tobacco smoke are absorbed from the lungs into the blood. From the blood, they are filtered by the kidneys and collect in the urine. These chemicals in the urine damage the cells that line the inside of the bladder and increase the risk of cancer.
b. Work exposure: Some chemicals used in the making of dye have been linked to bladder cancer. Industries that use certain chemicals may put workers at risk if good safety practices are not followed. The industries with highest risks include the makers of rubber, leather, textiles, and paint products, as well as printing companies. Workers with a higher risk of bladder cancer include painters, hairdressers, machinists, printers, and truck drivers. Smoking can increase the risk among these workers.
c. Race: Whites are twice as likely to get bladder cancer as are African Americans and Hispanics. Asians have the lowest rate of bladder cancer. We do not know the reason for this.
d. Age: The risk of bladder cancer goes up with age.
e. Gender: Men get bladder cancer 4 times as often as women.
f. Chronic bladder inflammation: While urinary infections, kidney stones, and bladder stones don't cause bladder cancer, they cause ongoing inflammation and have been linked to it.
g. Personal or family history of bladder cancer: People who have had bladder cancer have a higher chance of getting another

tumor. People whose family members have had bladder cancer also have a higher risk. There are some diseases that run in families that are known to increase bladder cancer risk, too.

h. Bladder birth defects: Very rarely a connection between the belly button and the bladder doesn't go away as it should before birth and it can become cancerous. There is another, very rare, birth defect called exstrophy which can lead to bladder cancer.

i. Earlier treatment: Some drugs or radiation used to treat other cancers can increase the risk of bladder cancer.

j. Arsenic: Arsenic in drinking water has been linked to a higher risk of bladder cancer.

k. Not drinking enough liquids: People who drink lots of liquids each day have a lower rate of bladder cancer.

(2) Etiology of Kidney Cancer

Risk factors of kidney cancer included medical history, radiation exposure, predominant lifetime occupation, exposure to high-risk industries, body mass index, education, smoking, beverage use, and artificial sweeteners. We do not yet know exactly what causes kidney cancer, but we do know the following risk factors have been linked to kidney cancer (Asal, Geyer, et al., 1988; Asal, Risser, et al., 1988):

a. Lifestyle-related and job-related risk factors

- Smoking: Smoking increases the risk of getting kidney cancer. The risk seems to be linked to how much you smoke and drops if you stop smoking.
- Weight: Severe or “morbid” obesity, especially in women, has

been linked to a higher risk of kidney cancer (Amling, 2004). Weight control at an early age might help to prevent the occurrence of a significant proportion of kidney cancer. Obesity also is a modifiable risk factor that may impact the clinical course of kidney cancer.

- Job hazards: Work in petroleum-related and dry-cleaning industries were associated with elevated risk. Many studies suggest that exposure to certain chemicals on the job increases the risk of kidney cancer. Some of these are asbestos, cadmium, some herbicides, benzene, and organic solvents, particularly trichloroethylene.

b. Other risk factors

- Inherited risk factors:

  Kidney cancer can be caused by some rare inherited conditions such as those listed below. People who have these conditions have a much higher risk for getting kidney cancer, although they account for only a small portion of cases overall.

  - Von Hippel-Lindau disease
  - Hereditary papillary renal cell carcinoma
  - Hereditary leiomyomatosis and renal cell carcinoma
  - Birt-Hogg-Dube syndrome
  - Hereditary renal oncocytoma

- Family history: People with family members who have kidney cancer (especially a brother or sister) have a much higher chance of getting the disease.

- High blood pressure: The risk of kidney cancer is higher in

people with higher blood pressure(Chow, Gridley, Fraumeni, & Jarvholm, 2000). The combination of obesity and high diastolic blood pressure is particularly risky. People with high blood pressure are often treated with drugs, so it is hard to tell if the higher risk is caused by the drugs, by the high blood pressure itself, or both.

- Certain medicines: A once popular pain-reliever (called phenacetin) has been linked to kidney cancer. But this medicine has not been used in the United States for over 20 years, and it no longer appears to be a major risk factor. Some drugs used to treat high blood pressure have also been linked to kidney cancer. It's not clear whether the higher risk is caused by the drugs or the high blood pressure. But people who need these drugs should not avoid them to try to reduce their risk of kidney cancer.
- Advanced kidney disease: People with advanced kidney disease who need to be on dialysis have a higher risk of kidney cancer. Dialysis is a treatment used to remove toxins from the body in people whose kidneys are not working.
- Gender: Kidney cancer is found about twice as often in men as in women. The reasons for this are not clear (Ochsner, Brannan, Pond, & Goodier, 1973).
- Race: African Americans have a slightly higher rate of renal cell cancer than whites. The reasons for this are not clear.

4. Urinary Tract Cancer of ESRD Patients

In Stewart study of 831,804 patients with ESRD treated by maintenance dialysis followed for 2,045,035 person-years, the increased risk of kidney cancer and bladder cancer occurred in every category of primary renal disease but fewer observed cases and lower standardized incidence ratios (SIR) in bladder cancer (Stewart, et al., 2003). Risks were relative more in younger than older patients and more in female patients. During average follow-up of 2.5 years, 25,044 (3%) of 831,804 patients developed cancer compared with an expected number of 21,185 (standardized incidence ratio 1.18). The excess risk can largely be ascribed to effects of underlying renal or urinary-tract disease, or of loss of renal function, on the kidney and bladder, and to increased susceptibility to viral carcinogenesis. The relative risk, which is especially high in younger patients, gradually diminishes with age (Maisonneuve, et al., 1999). Potential sources of bias of this relative high risks include: closer surveillance of ESRD patients than of the general population, all patients with prevalent cancers from the cohort, some positive results are likely to be chance findings due to the large size of the dataset.

The association of ESRD with acquired cystic kidney disease and renal cancers was first recognized in 1977 (Dunnill, et al., 1977). End-stage kidney disease (ESKD) under HD or PD is associated with 50% cystic degenerative changes (acquired cystic kidney disease [ACKD]) and higher incidence of renal cell carcinoma (Gronwald, et al., 1999; Maisonneuve, et al., 1999).

Factors associated with chronic renal failure (CRF) and the dialysis treatment itself may contribute to increased cancer formation and cancer progression in those patients. Increasing oxidative stress caused

deoxyribonucleic acid (DNA) damage (Davies, 2000; Durak, Kacmaz, Elgun, & Ozturk, 2004), impaired DNA repair in the course of long-term hemodialysis (Herman, et al., 2008; Vamvakas, et al., 1996), reduced antioxidant defense and accumulation of carcinogenic compounds due to reduced renal elimination (Mimic-Oka, Simic, Djukanovic, Reljic, & Davicevic, 1999), chronic infection and inflammation especially in the urinary tract (Chow, et al., 1997; Vamvakas, Bahner, & Heidland, 1998), a weakened immune system, previous treatment with immunosuppressive or cytotoxic drugs, nutritional deficiencies and the persistent metabolic changes associated with renal insufficiency may all contributed partly to increased cancer formation. In addition, the underlying disease leading to renal failure and the development of certain complications, such as acquired renal cystic disease, may predispose to cancer (Ishikawa, 1992).

5. Comparison of Hemodialysis and Peritoneal Dialysis

Compared to hemodialysis, PD allows greater patient mobility, produces fewer swings in symptoms due to its continuous nature, and phosphate compounds are better removed, but large amounts of albumin are removed which requires constant monitoring of nutritional status. The costs and benefits of hemodialysis and PD are roughly the same - PD equipment is cheaper but the costs associated with peritonitis are higher. PD patients achieve better elimination of middle molecular weight substances, have less severe uremia-induced immunological impairment (Schollmeyer & Bozkurt, 1988) but have lower serum albumin and total protein concentrations in blood . PD patients also have better preservation of residual renal function through: absence of acute fluid shifts; hemodynamic stability and prevention

of glomerular ischemia; stable and high BUN levels; reduced dietary protein; reduced protein losses in dialysate; and absence of cytokine-mediated responses to extracorporeal membrane treatment. DNA repair synthesis in PD was significantly reduced to only 69% of the control, whereas the repair of HD patients was close to normal (86%) (Zevin, Malachi, Gafter, Friedman, & Levi, 1991).

There is insufficient research to adequately compare the risks and benefits between CAPD and automated peritoneal dialysis (APD). A Cochrane Review of three small clinical trials found no difference in clinically important outcomes (i.e. morbidity or mortality) for patients with end stage renal disease, nor was there any advantage in preserving the functionality of the kidneys. The results suggested APD may have psychosocial advantages for younger patients and those who are employed or pursuing an education(Rabindranath, et al., 2007).

As compared to renal transplantation, optimal dialytic therapy should never be adequate to normalize the hematologic, biochemical, neurobehavioral, and nutritional abnormalities. It also cannot completely reverse all signs and symptoms of uremia.

Chapter 3 Theoretical Framework and Research Design

The chapter will be divided into six sections, including conceptual framework, hypotheses, subjects and data sources, measurement, analytical methods, and expected contribution of this study.

1. Conceptual Framework

In order to comprehend the relationship between urinary tract cancer and ESRD dialysis patients, the samples in this study are the ESRD dialysis patients. The independent variables are characteristics of ESRD dialysis patients, characteristics of dialysis facilities, dialysis modalities and ESRD comorbidities. The dependent variables are "Yes or No suffering from urinary tract cancer". The conceptual framework is as Figure 3-1:

2. Hypotheses

According to the research purpose, literature review, and the conceptual framework of this study, the following study hypotheses will be tested:

a. Characteristics of chronic dialysis patients and medical institutes are significantly correlated with urinary tract cancer.
b. Comorbidities of ESRD dialysis patients are significantly correlated with urinary tract cancer.
c. Dialysis modalities are significantly correlated with the incidence of the urinary tract cancer in ESRD dialysis patients.

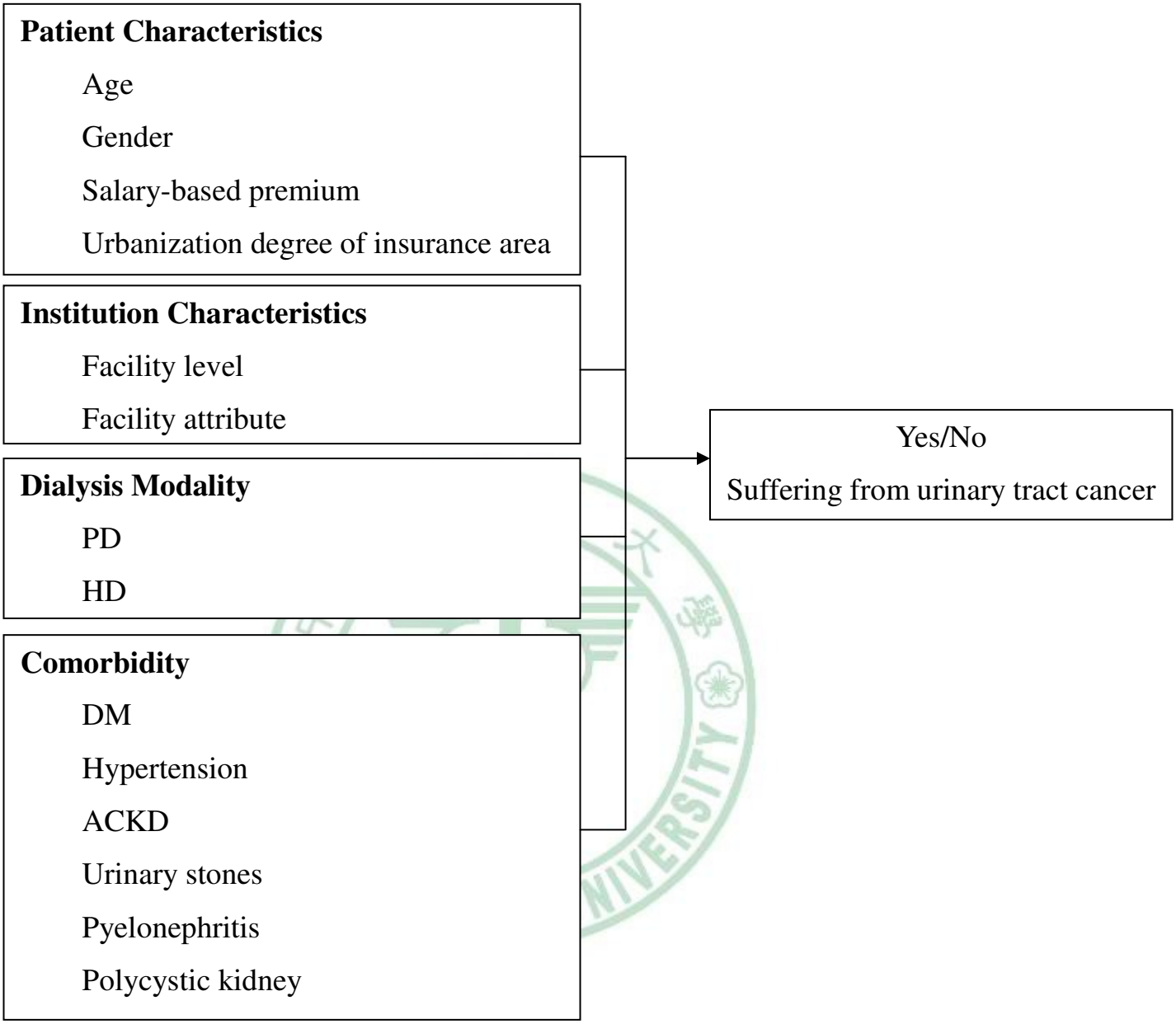

Figure 3-1 The conceptual framework of the study: the relationship between urinary tract cancer and dialysis ESRD patient

3. Study Subjects and Data Sources

(1) Study Subjects

The retrospective cohort study was based on 11-year nationwide dialysis patients obtained from the National Health Insurance Research dataset. The subjects are 80,855 new chronic dialysis patients receiving dialysis for more than 3 months under BNHI reimbursement from February 1997 to December 2007. In this 11-year period, those who switched their dialysis modality between HD and PD for more than 3 months; in whom the diagnosis of cancer was made within 6 months since their first dialysis (N=138); and in whom the diagnosis of cancer was made before their first dialysis (N=2149) were excluded. A total of 78,568 new dialysis patients, of which 1,824 new urinary tract cancer patients were included, were identified and included for further analysis.

(2) Data Sources

The data sources of this study are 11-year nationwide dialysis patients files obtained from the 1997–2007 National Health Insurance Research Database (NHIRD) in Taiwan. The NHIRD, organized and managed by the National Health Research Institutes, is derived from the National Health Insurance Program (NHIP). The NHIP has been implemented since 1995 to provide mandatory comprehensive medical care coverage to all civilian residents in Taiwan. The NHIP coverage rate was estimated to be 98.7% in 2004, and reasons for non-enrollment included living abroad, missing or untraceable, or simply unable to pay the National Health Insurance (NHI) premiums.

The medical claimed data set includes the following files:

a. Registration files for contracted medical facilities (HOSB)

b. Registration files for medical personnel (PER)

c. Ambulatory of care expenditures by visits (CD)

d. Details of ambulatory care orders (OO)

e. Inpatient expenditures by admissions (DD)

f. Details of inpatient orders (DO)

g. Registration files for beneficiaries (ID)

The related disease's ICD-9-CM codes are show in table 3-1:

Table 3-1 Enrolled ICD-9-CM codes for Systematic sampling

188 Malignant neoplasm of bladder
– 188.0 Trigone of urinary bladder
– 188.1 Dome of urinary bladder
– 188.2 Lateral wall of urinary bladder
– 188.3 Anterior wall of urinary bladder
– 188.4 Posterior wall of urinary bladder
– 188.5 Bladder neck (Internal urethral orifice)
– 188.6 Ureteric orifice
– 188.8 Other specified sites of bladder
– 188.9 Bladder, part unspecified
189 Malignant neoplasm of kidney and other and unspecified urinary
– 189.0 Kidney parenchyma, except pelvis
– 189.1 Renal pelvis, Renal calyces,Ureteropelvic junction
– 189.2 Ureter
– 189.3 Urethra
– 189.4 Paraurethral glands
– 189.8 Other specified sites of urinary organs
– 189.9 Urinary organ, site unspecified

4. Measurement

(1) Independent Variables

The purpose of this study was to investigate the relationship between urinary tract cancers and ESRD dialysis patients, especially the relationship between dialysis modalities (PD and HD) and urinary tract cancers. According to this purpose, the independent variables are characteristics of dialysis ESRD patients, dialysis modalities, characteristics of dialysis

facilities and comorbidities of end-stage renal disease (Table 3-2).

Table 3-2 The operational definitions of the independent variables

	Variables	Operation Definition	Variable attribute
Patient Characteristics	**Age**	< 20 y/o; 21~30 y/o; 31~40y/o; 41~50y/o; 51~60 y/o; 61~70 y/o; >70 y/o;	**Ordinal**
	Gender	Male, Female	**Nominal**
	Salary-based premium	Insured dependant <15,840NTD; 16,500-22,000; 24,000-28,800; 30,300-45,800; 48,200-57,800; 60,800-72,800; 76,500-87,600;	**Ordinal**
	Urbanization degree of insurance area	Urbanization degree 1 to 8	**Ordinal**
Institution's Characteristics	**Facility level**	Center, regional, or district hospital, and clinic	**Nominal**
	Facility attribute	Public, private, non-profit	
Dialysis Modality	**HD**		**Nominal**
	PD		
Comorbidity	**DM**		**Nominal**
	Hypertension		
	ACKD		
	Urinary stones		
	Pyelonephritis		
	Polycystic kidney		

(2) Dependent Variable

According to the purpose of this study, the dependent variable is "Yes or No suffering from urinary tract cancer". The conceptual and operational definition of the dependent variable is as Table 3-3.

Table 3-3 The operational definition of the dependent variable

Dependent Variable	Operation Definition	Variable Attribute
Urinary tract cancer	Yes/No suffering from urinary tract cancer	**Nominal**

5. Analytical Methods

The statistical methods included the descriptive and inferential statistics. The statistical data were analyzed by SAS 9.0 software. While comparing different modalities of dialysis, those who switched treatment modalities between HD and PD were excluded. Chi-square test was used to determine whether there is some association between two variables with enumeration data. Cox proportional hazard models were used to explore the explanatory relationship between independent variables and dependent variable (suffering from urinary tract cancer or not). As survival analysis, those who have their first cancer attack diagnosis during the study period are event cases; cancer-free patients at the end of the study, transplantation, death or initially alive but loss follow up will be considered as censor cases (Figure 3-2). The effect of covariates estimated can thus be reported as hazard ratios.

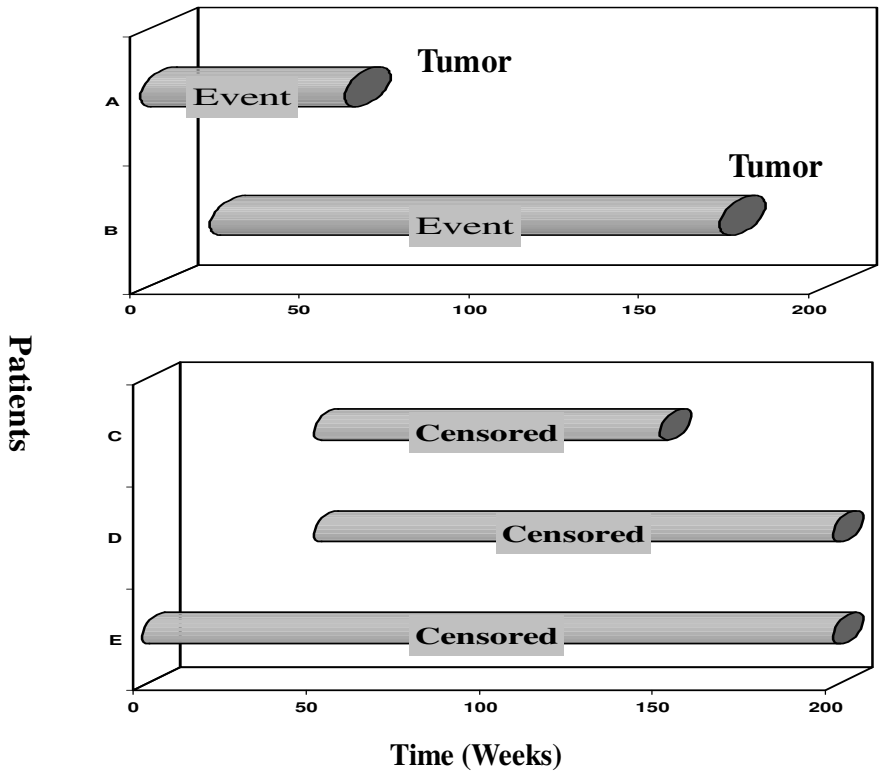

Figure 3-2. Cox Proportional Hazard Model

6. Expected Contribution

The study will investigate the related factors between urinary tract cancer and ESRD dialysis patients in Taiwan. Although there are plenty oversea researches about the dialysis patients and urinary tract cancer in western population, especially renal cell carcinoma, there is little about the transitional cell carcinoma and little about the eastern population. The massive comprehensively explanatory data from this study, especially the relationship between the dialysis modalities and the cancer occurrence, may contribute to establish a BNHI reimbursed formal periodic screening protocol for urinary tract cancer survey in high risk dialysis patients and also can extrapolate to all Chinese who live in the East.

Chapter 4 Research Result

1. Baseline characteristics of the study cohort

Excluded those who switched their treatment modalities between HD and PD for more than 3 months, the original datasets contained information on 80,855 dialysis patients. We then totally excluded 2,287 patients: 138 with diagnosis of cancer within 6 months since their first dialysis; and 2149 with diagnosis of cancer before their first dialysis. The final study cohort therefore consisted of 78,568 patients undergoing treatment for ESRD by hemodialysis (94.14%) or peritoneal dialysis (5.86%); initiating dialysis between February 1997 and November 2007; and followed up until end of the study period, last visit, transplantation, or death. Hypertension was the commonest comorbidity (53.28%), followed by diabetes (50.87%), ACKD (2.4%), Urinary stones (1.8%) and pyelonephritis (1.2%). The mean age at start of dialysis was 59.34±12.75 years in cancer group and 60.92±14.47 years in group without cancer. Female patients (51.5%) were relatively more than male patients (Table 4-1). There were 1,824 incident urinary tract cancer identified (including 1495 TCC and 333 RCC in HD group and 48 TCC and 14 RCC in PD group) when 209 urinary tract cancers were expected (Table 4-2).

2. Inferential result

(1)Bivariate analysis

Result of bivariate analysis, comparing the characteristics of patients with and without urinary cancer, is shown in Table 4-1. The unadjusted relative ratio (RR) and 95% confidence interval (95% CI) are also illustrated in Table 4-3. The excess of cancer risk was observed in hemodialysis

modality (as compared to PD), in age group more than 30 year-old (as compared to age less than 20 year-old), in female gender, in insured dependant and salary-based premium 17,281 to 22,800 NTD group (as compared to group of salary-based premium < 17,280 NTD), in ACKD comorbidity of ESRD, in urbanization degree 8 of insurance area (as compared to the urbanization degree 1 area) , and in facility level other than medical center; but it was relatively more pronounced in the relative younger age group.

(2) In urinary tract cancer category

The relationship between independent variables and subsequent cancer-specific risk was explored for the entire cohort and the adjusted hazard ratios with 95% CI for each covariate are shown in Table 4-3. The Cox regression models indicated that the following variables were significant factors associated with urinary tract cancer: dialysis modality, age-stratification, gender, comorbidities, and level of dialysis facilities. As compared to PD, hemodialysis had a significantly higher cancer risk (RR=1.968, 95% CI: 1.472-2.632). As compared to patients less than 20 year-old, those groups older than 30 years all have significant higher cancer risk but seem to be relatively higher in the relative younger age group (31-40 years, 41-50 years, 51-60 years, 61-70 years, and > 70 years (RR=2.964, 5.143, 7.428, 6.980, 6.855, respectively). In the contrary to general population, a reverse gender effect to cancer risk was impressed. Female ESRD dialysis patients had significantly higher cancer risk than male ESRD dialysis patients (RR=1.235, 95% CI: 1.119-1.363). No doubt, comorbidity ACKD had significant result (RR=1.612, 95% CI: 1.336-1.944). Patient receiving dialysis in the medical center had significant higher cancer risk

than in other level of dialysis facilities (RR= 0.685, 0.601 and 0.510 at regional hospital, district hospital and clinic, respectively). Interestingly, the unadjusted and adjusted cancer-specific relative risk was significantly lower for patients with diabetes and hypertension (RR=0.304, 95% CI: 0.269-0.342; RR= 0.475, 95% CI: 0.431-0.524, respectively).

Adjusted Cox regression curves were estimated for peritoneal dialysis- and hemodialysis-treated patients as shown in Figures 4-1. No matter what dialysis modality received, the progressive increased urinary tract cancer-specific risk in ESRD dialysis patients was closely correlated with duration of dialysis.

(3) In urothelial cancers and renal parenchymal cancers category

While separating the urinary tract cancers into urothelial cancer (TCC) group and renal parenchymal cancer (RCC) group, the Cox proportional regression analysis was performed for each group. As shown in Table 4-3, the significant variables associated with urothelial cancers were almost the same as urinary tract cancer group but only ACKD (RR=1.789, 95% CI 1.176-2.722) and clinic level of dialysis facilities were significant factors associated with renal parenchymal cacer risk (Table 4-4). However, diabetes and hypertension still have significantly negative effect (protective effect) in all 3 groups.

As shown in Figures 4-2 and 4-3, adjusted Cox regression curves were estimated for peritoneal dialysis- and hemodialysis-treated patients for urothelial cancer group and renal parenchymal cancer group separately. Still, the cancer-specific risk in both groups increased gradually depending on the duration of dialysis.

Chapter 5 Discussion

1. Cancer-specific advantage of PD

We have demonstrated, using the National Health Insurance Research Database (NHIRD), that patients initiating renal replacement therapy (RRT) in Taiwan from the 1997–2007 and selected for HD have a 97% increase in urinary tract cancer risk when compared to patients selected for PD. Despite peritoneal dialysis has positive effect on hemodynamic stability, volume regulation, better residule renal function preservation(Lysaght, et al., 1991), and is generally less expensive than HD to the payer, hemodialysis was widely provided to ESRD patients as primary renal replacement therapy in Taiwan. The findings of this study, proposing a new point of view as concerning the cancer-specific advantage of PD, suggest the contrary.

Although important prognostic factors, such as information about predisposing factors, cause-effect etiology of urinary tract cancer, even data on dialysis adequacy, patient compliance, nutritional status, and comorbid condition severity, were not available in this retrospective population-based cohort study, it is not obvious whether they would differ systematically and change our analytic results. However, the underlying assumption of the Cox proportional hazard model is that the hazard ratio associated with a given predictor is constant over the entire follow-up period. So severity of comorbidities (such as adequacy of diabetes or hypertension control or severity of pyelonephritis) may exert impact on hazard changes during follow-up and produce biased results due to this non-proportionality of risks. Further, interaction between risk factors may also contribute to study bias. Predictors of mortality, health-related quality of life in dialysis patients (such as age, gender, diabetes, peritonitis, residule renal function, nutritional status

and comorbidities) and the financial seduction of NHI reimbursement system may affect the selection process of the choice of dialysis modalities by the patients and the nephrologist. The selection bias may be small in U.S. (Nolph, 1996; Patient selection to peritoneal dialysis versus hemodialysis according to comorbid conditions," 1992; Port, Wolfe, Bloembergen, Held, & Young, 1996), but it would be large and important in Taiwan even some of those factors mentioned above was adjusted in our model.

Even those possible bias and limitation may influence our study results, there's abundant study suggested the suspected higher carcinogenic effect of HD compared with PD:

a. Acquired cystic disease in PD patients was comparable to the prevalence seen in hemodialysis patients. The overall prevalence of renal cell carcinoma accompanying acquired cystic disease in CAPD patients was 2 of 375 (0.4%), which is lower than the prevalence of 1.5% (17/1103) in hemodialysis patients, although not statistically significant (Ishikawa, 1992).
b. HD related renal ischemia secondary to intratreatment hypovolemia and/or nephrotoxic effects of the inflammatory mediators of extracorporeal circulation (Lysaght, et al., 1991).
c. Blood membrane interaction, specific to hemodialysis, might be carcinogenic (Akizawa, Kinugasa, & Koshikawa, 1994).
d. Human mononuclear cell apoptosis were significantly increased in HD as compared with CAPD (Martin-Malo, et al., 2000).
e. Spontaneous DNA repair increases during hemodialysis in order to overcome the newly produced DNA damage (Herman, et al., 2008).
f. Significant residule renal function preservation at least in the first 2 years of PD but not in HD was well known.

g. PD has better cellular immunity, a significant reduction of the percentage of E-rosette inhibition, than HD due to removal of as yet unidentified solutes (Schaubel, Morrison, & Fenton, 1998).

As we know, intravesical Bacillus Calmette-Guérin (BCG) against superficial bladder carcinoma recurrences is regarded as the most successful immunotherapy. A complex local immune response for tumor control is induced by BCG in the human bladder. The local ratio of T-helper/ T-suppressor cells in the bladder wall before the start of therapy was about 1:2. After completion of the intravesical BCG therapy, the infiltrate of mononuclear cells in the bladder wall, consisted mainly of T-cells, with a distinct predominance of CD4+ (so-called T-helper/inducer) cells compared with CD8+ (so-called T-suppressor/cytotoxicity) cells. The ratio of CD4+/CD8+ T-cells detectable in the submucosa was 2:1, which represents a reversal of the original ratio found in the normal bladder. The sequelae of an impaired and altered immune system in uremia are well known. The depression of the lymphocytes in peripheral blood of chronic hemodialysis patients is well established. Although all depressed, the general immune defense in PD patients is superior to hemodialysis patients. As comparing T-lymphocyte subset and suppressor-cell activity in PD patients and in HD patients, PD has a significant depression of T-suppressor cell and an increase in the T4-helper/T8-suppressor ratio (Schollmeyer & Bozkurt, 1988). Those findings were compatible with the proposed therapeutic immune reaction of BCG-induced tumor control and maybe one of the causes contributing to the lower cancer risk of PD patients than HD patients.

Comparing to general population in Taiwan (Cancer Registry Annual Report, 2007), incident urinary tract cancer in ESRD on dialysis patients

significantly increased and was closely correlated with duration of dialysis (Fig. 2) especially in the HD group. As shown in Table 2 and 3, urothelial cancer, as compared to renal parenchymal cancer, significantly increased in HD group but not in the PD group. Concerning the extremely high proportion of patients receiving HD but not PD in Taiwan, that would be why we have so many urothelial cancers but not renal parenchymal cancers in dialysis patients as contrary to Western countries.

2. Among diabetics or hypertensions with ESRD on dialysis

Why patients with ESRD due to diabetic nephropathy or hypertension should have a relatively small excess (protective) risk of urinary tract cancer? In a population-base case-control study among men from Montreal, risks of pancreatic and liver cancers, but not bladder and kidney cancers, increased among diabetics (Rousseau, Parent, Pollak, & Siemiatycki, 2006). As shown by USRDS 2009 ADR, cancer risk increases gradually in the process of CKD progresses to ESRD and is closely related to exposure duration of chronic renal insufficiency. Kidney cancer risk in ESRD on dialysis patients increased significantly with time since first dialysis (Stewart, et al., 2003). CKD patients with diabetes or hypertension progress to ESRD more rapidly and also have shorter life expectancy (Liem, Wong, Hunink, de Charro, & Winkelmayer, 2007). So the protective effect from cancers in diabetic patients may due to the shorter duration of exposure to chronic renal failure or shorter life expectancy (as we treat mortality as censored value in our model).

Research indicates that over half of all cancers in developed countries could be prevented if we implemented population-wide measures to promote

the following behaviors: reduce tobacco use, increase physical activity, control weight, improve diet, limit alcohol, utilize safer sex practices, get routine cancer screening tests, and avoid excess sun exposure (Stein & Colditz, 2004). Smoking and obesity seem to be risk factors for RCC. Reducing these behaviors and conditions may also reduce the risk of RCC. Healthier eating habits (fruits and vegetables, and a lower caloric intake) and more physical activity may also reduce the risk of RCC and breast cancer (Monninkhof, et al., 2007; Moyad, 2001; Voskuil, Monninkhof, Elias, Vlems, & van Leeuwen, 2007). Therefore, it is possible that the relatively small excess risk of urinary tract cancer may also be due, in part, to more regular and healthier lift style factors of diabetes and hypertensive patients that have been on the increase over the past years due to the NHI system.

The hypoglycemic agents or anti-hypertensive medication may also play a role, in part, in reducing the excess risk of cancers. There is increasing evidence about the protective effect of both drugs classes. Pioglitazone (Actos®) inhibited tumor cell proliferation. Other glitazones, troglitazone and ciglitazone, had similar effects. The combination of pioglitazone with 2-deoxyglucose, a potent inhibitor of glycolysis, had an additive effect on the inhibition of cell proliferation and led to MCTS disintegration (Gottfried, et al., 2010). Sponsored by U.S. National Cancer Institute, one phase II trial is studying the effectiveness of pioglitazone in preventing head and neck cancer in patients who have oral leukoplakia. Chemoprevention therapy with pioglitazone may be effective in preventing head and neck cancer. Although systemic and coronary arteriosclerosis were significantly higher in diabetics than non-diabetics, the rate of carcinomas in the diabetic group with nodular and diffuse glomerulosclerosis was 2.5- and 1.9-fold, respectively, significant lower than in the non-diabetic group (Nerlich, Hagedorn, Boheim,

& Schleicher, 1998). Microangiopathy, arteriosclerosis and altered cell-matrix interaction exerted by chronic TGF-beta overexpression in diabetes may play a crucial role both in diabetes, carcinogenesis and tumor progression. In hypertensive patients with type 2 diabetics and microalbuminuria, combination angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARB) therapy resulted in better blood pressure control than either agent alone, as well as greater reductions in microalbuminuria. Compared with monotherapy, dual renin-angiotensin system (RAS) inhibition reduced the occurrence of a doubling of the serum creatinine concentration or end-stage renal disease by 60% to 62% in patients with nondiabetic renal disease (Weir, 2007). Derangements of the RAS may contribute to hypertension and renal injury, particularly in patients with types 1 or 2 diabetics. ACE inhibitors have been proven to be beneficial in patients with hypertension and diabetes by preventing or delaying the development and progression of proteinuria and glomerulosclerosis. Renoprotective effects for ACE inhibitors are independent of and additive to their systemic antihypertensive actions (Hollenberg, 2000).

3. Why women but not men?

All over the world, men have higher urinary tract cancer incidence than women in general population (2.4 fold more in urothelial cancer, 1.9 fold more in renal parenchyma cancer in Taiwan). Although unknown etiology, malignant degeneration in cysts of ACKD and those cysts developed more quickly in men than women would be one of the causes (Ishikawa, et al., 1997). Compared with male patients, female patients had lower stage and grade renal parenchyma cancers and less frequent metastasis at diagnosis

along with better cancer-specific survival. Younger female patients had more cancer with unfavorable histology, and higher stage and grade compared to older female patients (Chen, Shi, Zhang, Jiang, & Xu, 2009; Schrader, et al., 2008).

Why men have a relative small excess risk of urinary tract cancer after dialysis than women is still not obvious. With increasing the duration of CAPD, dialysate CA125 levels were significantly lower 6 months after the start of CAPD in the men as compared to the women (Mojahedi, Hami, Shakeri, & Hekmat, 2007). Male gender is a significant characteristic associated with increased risk of early death (die within the first 90 days after beginning dialysis) in dialysis patients (Soucie & McClellan, 1996). Standardized mortality rate (SMR) of men on renal replacement therapy is twice as high as SMR of women (Schrander-v d Meer, van Saase, Roodvoets, & van Dorp, 1995). As we treat those patients die within the study period without cancer diagnosis as censored value in our study, these results suggest that the increased risk of early death in male patients may substantially influences the cancer-specific risk of male gender.

Some kinds of medication may also play a role, in part, in non-proportional increasing the risk of cancers between men and women. In a population-based cohort study, risk of kidney parenchyma cancer, and to a lesser extent, cancer of the renal pelvis and ureter, among patients using analgesics and diuretics was higher for women than for men (Lindblad, et al., 1993). If the association between diuretics/analgesics and renal parenchyma cancer is causal, this would have an impact on public health, due to the widespread use of these medication.

4. Higher cancer risk in medical center!

Receiving dialysis in the medical center would have significantly higher cancer risk than in other level of dialysis facility? Interestingly, in all 3 groups analyzed, “clinic” level has the lowest adjusted cancer risk, and the risk seems to gradually increase as the facility level upgraded. That cancer diagnosis was made in relatively higher percentage of the dialysis population of medical center would be one of the answers. Although seldom mentioned in the literature, it would be not far from truth that the nephrology physicians at the academic medical center used more testing and requested consultations more often than those practicing in a community hospital; and that the dialysis clinic and region hospital had potential barriers to implementation of adequate or new techniques for cancer screening, not mentioned the trade-off between the expected costs and the expected increase in quality of care due to the NHI global budget reimbursement system. Further study to investigate the potential barriers of accurate cancer diagnosis and the adequate periodic cancer screening programs would be necessary to clarify the reimbursement policy decision.

Chapter 6 Conclusion and Recommendations

Although important factors, other than cancer risk, in selecting dialysis modality for an individual patient would include HD- and PD-associated quality-of-life and a patient's personal preference, the tremendous under-utilization of peritoneal dialysis is still a problem necessitated serious consideration. The influence of the nephrologist's preference and the NHI reimbursement system should play a very important role in patients' decision making. From our findings, we conclude that peritoneal dialysis patients have a urinary tract cancer-specific advantage as compared to hemodialysis patients in Taiwan. Also, the benefit of the relative lower cancer risk become more and more enormously as the duration of dialysis increase. In this point of view, peritoneal dialysis deserved more promotion as treatment option to ESRD patients.

The findings of this study also raise the question of the correct approach to cancer screening in ESRD dialysis patient. It is difficult to attribute the large increased relative risk of cancer in the dialysis population of medical center to the effects of bias. In our clinical experience, more testing, more requested consultations and more advanced diagnostic facilities in the medical center really would greatly raise the accurate diagnosis rate of relatively silent cancers. But what would be the most effective trade-off between the expected costs and the expected increase in quality of care? Till now, there is no regular follow-up protocol suggested for those ESRD dialysis patients. Considering the higher cancer risk of ESRD dialysis patient and the subsequent healthcare expenditure, we recommend a further cost-effectiveness study to propose an active cancer screening program for ESRD dialysis patients in the future.

Chapter 7 Research Limitations

Information about predisposing factors or cause-effect etiology of urinary tract cancer origin, such as smoking, chemical carcinogens (asbestos, organic solvents, cadmium, aristolochia) exposure, analgesics and diuretics consumption and even obesity and diet, etc., were not available in NHRI database. Adequacy of dialysis, comorbidities, immune and nutritional status was also unknown and may have different non-proportional contributions to development of urinary tract cancer in the Cox model. Age, comorbidities, urinary tract infection and even general health condition may have some interaction between and some impact to proper prescriptions of different dialysis modalities and dialysis adequacy. We should have more persuasive results if we could treat those factors as controlled variables.

Table 4-1 Baseline characteristics of the study cohort (N=78,568)

	Urinary tract cancer Yes		Urinary tract cancer No		
	Case No.	(%)	Case No.	(%)	P
Case No.	1824	(2.32)	76744	(97.68)	
Mean age	59.34±12.75		60.92±14.47		<.001[a]
Dialysis modality					<.001
HD	1766	(2.39)	72195	(97.61)	
PD	58	(1.26)	4549	(98.74)	
Age					<.001
< 20 year	5	(0.91)	543	(99.09)	
21-30 year	14	(0.75)	1865	(99.25)	
31-40 year	117	(2.38)	4808	(97.62)	
41-50 year	360	(2.97)	11777	(97.03)	
51-60 year	478	(2.83)	16393	(97.17)	
61-70 year	484	(2.31)	20485	(97.69)	
> 71 year	366	(1.72)	20873	(98.28)	
Gender					<.001
Male	722	(1.89)	37395	(98.11)	
Female	1102	(2.72)	39349	(97.28)	
Salary-based premium (NTD)					<.001
Insured dependant	581	(2.24)	25302	(97.76)	
< 17280	287	(1.85)	15217	(98.15)	
17281-22800	714	(2.56)	27186	(97.44)	
22801-28800	64	(3.02)	2056	(96.98)	
28801-36300	36	(2.11)	1668	(97.89)	
36301-45800	51	(2.49)	2001	(97.51)	
45801-57800	22	(3.09)	690	(96.91)	
> 57801	24	(2.70)	865	(97.30)	
Missing data	45		1759		
Comorbidity					
ACKD	124	(6.51)	1780	(93.49)	<.001
Pyelonephritis	43	(4.57)	897	(95.43)	<.001
Urinary stones	62	(4.45)	1332	(95.55)	<.001
Polycystic kidney	3	(3.66)	79	(96.34)	0.421
Hypertension	715	(1.71)	41143	(98.29)	<.001
DM	359	(0.90)	39612	(99.10)	<.001

* a : t test (p value)

Table 4-1 Baseline characteristics of the study cohort (N=78,568) (cont')

	Urinary tract cancer Yes		Urinary tract cancer No		
	Case No.	(%)	Case No.	(%)	P
Urbanization degree of insurance area					0.055
1	281	(2.15)	12779	(97.85)	
2	498	(2.64)	18331	(97.36)	
3	283	(2.24)	12358	(97.76)	
4	159	(2.34)	6628	(97.66)	
5	219	(2.18)	9827	(97.82)	
6	152	(2.31)	6430	(97.69)	
7	128	(2.14)	5864	(97.86)	
8	43	(1.97)	2144	(98.03)	
Missing data	61		2383		
Facility attribute					<.001
Public	242	(1.97)	12049	(98.03)	
Private	1022	(2.59)	38471	(97.41)	
Non-profit	560	(2.09)	26224	(97.91)	
Facility level					<.001
Medical center	368	(2.44)	14734	(97.56)	
Region hospital	450	(1.96)	22511	(98.04)	
District hospital	471	(2.34)	19693	(97.66)	
Clinic	535	(2.63)	19806	(97.37)	

* a : t test (p value)

Table 4-2 New ESRD dialysis patients with and without urinary tract cancer/RCC/TCC by treatment modalities (HD/PD) (N=78,568)

		HD		PD	
		No.	(%)	No.	(%)
Urinary tract cancers					
	Yes	1766	(2.39)	58	(1.26)
	No	72195	(97.61)	4549	(98.74)
Subgroup					
(1) TCC					
	Yes	1495	(2.02)	48	(1.04)
	No	72466	(97.98)	4559	(98.96)
(2) RCC					
	Yes	333	(0.45)	14	(0.30)
	No	73628	(99.55)	4593	(99.70)

Table 4-3 Predictors of urinary tract cancer in new ESRD dialysis patients in Taiwan (N=78,568)

	Unadjusted RR	(95%CI)	Adjusted RR	(95%CI)
Dialysis modality				
PD (ref.)				
HD	1.706 ***	(1.294-2.248)	1.968 ***	(1.472-2.632)
Age				
< 20 year (ref.)				
21-30 year	0.747	(0.266-2.094)	0.855	(0.304-2.406)
31-40 year	2.530 *	(1.033-6.197)	2.964 *	(1.204-7.298)
41-50 year	3.810 **	(1.576-9.212)	5.143 ***	(2.115-12.506)
51-60 year	4.554 ***	(1.886-10.996)	7.428 ***	(3.061-18.026)
61-70 year	4.313 **	(1.786-10.415)	6.980 ***	(2.879-16.921)
> 71 year	4.858 ***	(2.008-11.750)	6.855 ***	(2.823-16.646)
Gender				
Male (ref.)				
Femal	1.325 ***	(1.205-1.457)	1.235 ***	(1.119-1.363)
Salary-based premium (NTD)				
< 17280NTD (ref.)				
Insured dependant	1.333 ***	(1.157-1.536)	1.171 *	(1.012-1.357)
17281-22800	1.278 ***	(1.114-1.466)	1.118	(0.969-1.290)
22801-28800	1.275	(0.967-1.681)	1.228	(0.928-1.623)
28801-36300	0.822	(0.581-1.162)	0.854	(0.603-1.211)
36301-45800	0.983	(0.726-1.331)	0.980	(0.722-1.332)
45801-57800	1.227	(0.795-1.893)	1.302	(0.841-2.015)
> 57801	1.102	(0.726-1.671)	1.043	(0.685-1.588)
Comorbidity				
ACKD	1.658 ***	(1.378-1.996)	1.612 ***	(1.336-1.944)
Pyelonephritis	1.165	(0.860-1.578)	0.995	(0.732-1.353)
Urinary stones	1.269	(0.979-1.646)	1.132	(0.871-1.470)
Polycystic kidney	0.956	(0.308-2.964)	0.883	(0.284-2.742)
Hypertension	0.418 ***	(0.380-0.460)	0.475 ***	(0.431-0.524)
DM	0.317 ***	(0.282-0.356)	0.304 ***	(0.269-0.342)

* p<0.05 ; ** p<0.01 ; *** p<0.001

Table 4-3 Predictors of urinary tract cancer in new ESRD dialysis patients in Taiwan (N=78,568) (cont')

	Unadjusted RR	(95%CI)	Adjusted RR	(95%CI)
Urbanization degree of insurance area				
1 (ref.)				
2	1.074	(0.910-1.267)	1.125	(0.951-1.332)
3	1.126	(0.927-1.368)	1.106	(0.908-1.346)
4	1.077	(0.903-1.286)	1.061	(0.884-1.274)
5	1.182	(0.970-1.439)	1.131	(0.921-1.388)
6	1.132	(0.918-1.395)	1.062	(0.853-1.322)
7	1.108	(0.804-1.528)	1.161	(0.837-1.610)
8	1.245 **	(1.075-1.441)	1.189 *	(1.026-1.379)
Hospital attribute				
Public (ref.)				
Private	0.975	(0.846-1.125)	1.071	(0.898-1.278)
Non-profit	0.964	(0.827-1.124)	0.854	(0.728-1.001)
Hospital attribute				
Medical center (ref.)				
Region hospital	0.852 *	(0.740-0.980)	0.685 ***	(0.586-0.801)
District hospital	0.858 *	(0.746-0.986)	0.601 ***	(0.499-0.725)
Clinic	0.807 **	(0.704-0.925)	0.510 ***	(0.415-0.627)

* p<0.05 ; ** p<0.01 ; *** p<0.001

Table 4-4 Predictors of TCC in new ESRD dialysis patient in Taiwan (N=78,568)

		Unadjusted RR	(95%CI)	Adjusted RR	(95%CI)
Dialysis modality					
	PD (ref.)				
	HD	1.722 ***	(1.271-2.332)	1.972 ***	(1.433-2.715)
Age					
	< 20 year(ref.)				
	21-30 year	0.516	(0.173-1.540)	0.574	(0.192-1.721)
	31-40 year	1.873	(0.760-4.617)	2.133	(0.860-5.290)
	41-50 year	3.215 **	(1.328-7.783)	4.218 **	(1.731-10.278)
	51-60 year	3.977 **	(1.646-9.610)	6.419 ***	(2.641-15.601)
	61-70 year	3.800 **	(1.572-9.183)	6.147 ***	(2.532-14.922)
	> 71 year	4.131 **	(1.705-10.006)	5.822 ***	(2.393-14.166)
Gender					
	Male (ref.)				
	Female	1.381 ***	(1.245-1.533)	1.289 ***	(1.157-1.436)
Salary-based premium					
	< 17280 NTD (ref.)				
	Insured dependant	1.307 ***	(1.120-1.527)	1.110	(0.946-1.303)
	17281-22800 NTD	1.297 ***	(1.117-1.506)	1.110	(0.950-1.297)
	22801-28800 NTD	1.381 *	(1.033-1.847)	1.318	(0.982-1.769)
	28801-36300 NTD	0.885	(0.615-1.274)	0.936	(0.648-1.350)
	36301-45800 NTD	0.846	(0.596-1.200)	0.852	(0.598-1.213)
	45801-57800 NTD	1.311	(0.831-2.069)	1.445	(0.912-2.290)
	> 57801 NTD	0.971	(0.601-1.567)	0.919	(0.567-1.489)
Comorbidity					
	ACKD	1.388 **	(1.121-1.720)	1.344 **	(1.083-1.669)
	Pyelonephritis	1.154	(0.832-1.602)	1.021	(0.733-1.422)
	Urinary stones	1.244	(0.938-1.650)	1.119	(0.842-1.486)
	Polycystic kidney	0.742	(0.185-2.967)	0.697	(0.174-2.790)
	Hypertension	0.415 ***	(0.374-0.461)	0.475 ***	(0.427-0.528)
	DM	0.294 ***	(0.258-0.335)	0.278 ***	(0.243-0.318)

* p<0.05 ; ** p<0.01 ; *** p<0.001

Table 4-4 Predictors of TCC in new ESRD dialysis patient in Taiwan (N=78,568) (cont')

	Unadjusted RR	(95%CI)	Adjusted RR	(95%CI)
Urbanization degree of insurance area				
1 (ref.)				
2	1.349 ***	(1.147-1.587)	1.280 **	(1.086-1.508)
3	1.146	(0.955-1.376)	1.195	(0.991-1.440)
4	1.249 *	(1.010-1.544)	1.210	(0.976-1.500)
5	1.201	(0.990-1.457)	1.161	(0.951-1.418)
6	1.296 *	(1.044-1.609)	1.215	(0.971-1.521)
7	1.228	(0.976-1.544)	1.120	(0.881-1.425)
8	0.951	(0.646-1.401)	0.972	(0.656-1.441)
Hospital attribute				
Public (ref.)				
Private	1.008	(0.861-1.179)	1.113	(0.917-1.352)
Non-profit	0.987	(0.833-1.168)	0.872	(0.732-1.039)
Facility level				
Medical center (ref.)				
Region hospital	0.848 *	(0.728-0.989)	0.670 ***	(0.564-0.795)
District hospital	0.848 *	(0.728-0.988)	0.578 ***	(0.471-0.709)
Clinic	0.813 **	(0.701-0.942)	0.497 ***	(0.397-0.623)

* p<0.05 ; ** p<0.01 ; *** p<0.001

Table 4-5 Predictors of RCC in new ESRD dialysis patient in Taiwan (N=78,568)

	Unadjusted RR	(95%CI)	Adjusted RR	(95%CI)
Dialysis modality				
PD(ref.)				
HD	1.318	(0.757-2.295)	1.507	(0.835-2.719)
Age				
< 20 year (ref.)				
21-30 year	1.731	(0.208-14.375)	2.158	(0.257-18.100)
31-40 year	3.656	(0.500-26.727)	4.801	(0.648-35.561)
41-50 year	3.485	(0.484-25.107)	5.167	(0.707-37.749)
51-60 year	3.851	(0.536-27.668)	6.386	(0.878-46.460)
61-70 year	3.612	(0.503-25.948)	5.821	(0.802-42.246)
> 71 year	4.727	(0.658-33.987)	6.553	(0.902-47.583)
Gender				
Male (ref.)				
Female	1.038	(0.838-1.286)	0.982	(0.787-1.227)
Salary-based premium				
<17280 NTD (ref.)				
Insured dependant	1.216	(0.896-1.651)	1.211	(0.880-1.666)
17281-22800 NTD	1.029	(0.760-1.394)	1.072	(0.781-1.471)
22801-28800 NTD	0.481	(0.193-1.196)	0.503	(0.201-1.255)
28801-36300 NTD	0.537	(0.216-1.335)	0.544	(0.217-1.359)
36301-45800 NTD	1.221	(0.672-2.219)	1.191	(0.650-2.184)
45801-57800 NTD	0.785	(0.247-2.502)	0.732	(0.228-2.348)
> 57801 NTD	1.289	(0.558-2.979)	1.202	(0.515-2.805)
Comorbidity				
ACKD	1.839 **	(1.217-2.778)	1.789 **	(1.176-2.722)
Pyelonephritis	1.182	(0.585-2.389)	0.997	(0.488-2.035)
Urinary stones	1.606	(0.940-2.744)	1.474	(0.858-2.531)
Polycystic kidney	1.771	(0.249-12.608)	1.737	(0.243-12.411)
Hypertension	0.471 ***	(0.379-0.585)	0.497 ***	(0.398-0.620)
DM	0.516 ***	(0.407-0.652)	0.516 ***	(0.404-0.658)

* p<0.05 ; ** p<0.01 ; *** p<0.001

Table 4-5 Predictors of RCC in new ESRD dialysis patient in Taiwan (N=78,568) (cont')

	Unadjusted RR	(95%CI)	Adjusted RR	(95%CI)
Urbanization degree of insurance area				
1 (ref.)				
2	0.848	(0.624-1.154)	0.838	(0.614-1.145)
3	0.774	(0.545-1.099)	0.826	(0.577-1.182)
4	0.723	(0.465-1.123)	0.728	(0.466-1.137)
5	0.704	(0.476-1.041)	0.724	(0.483-1.085)
6	0.640	(0.398-1.030)	0.635	(0.388-1.039)
7	0.628	(0.379-1.039)	0.624	(0.369-1.055)
8	1.345	(0.760-2.382)	1.416	(0.786-2.550)
Facility attribute				
Public (ref.)				
Private	0.674 **	(0.504-0.902)	0.800	(0.551-1.163)
Non-profit	0.688 *	(0.501-0.945)	0.650 *	(0.468-0.903)
Facility level				
Medical center (ref.)				
Region hospital	0.908	(0.663-1.242)	0.780	(0.551-1.102)
District hospital	0.870	(0.635-1.193)	0.709	(0.469-1.072)
Clinic	0.727 *	(0.530-0.997)	0.552 *	(0.346-0.882)

* p<0.05 ; ** p<0.01 ; *** p<0.001

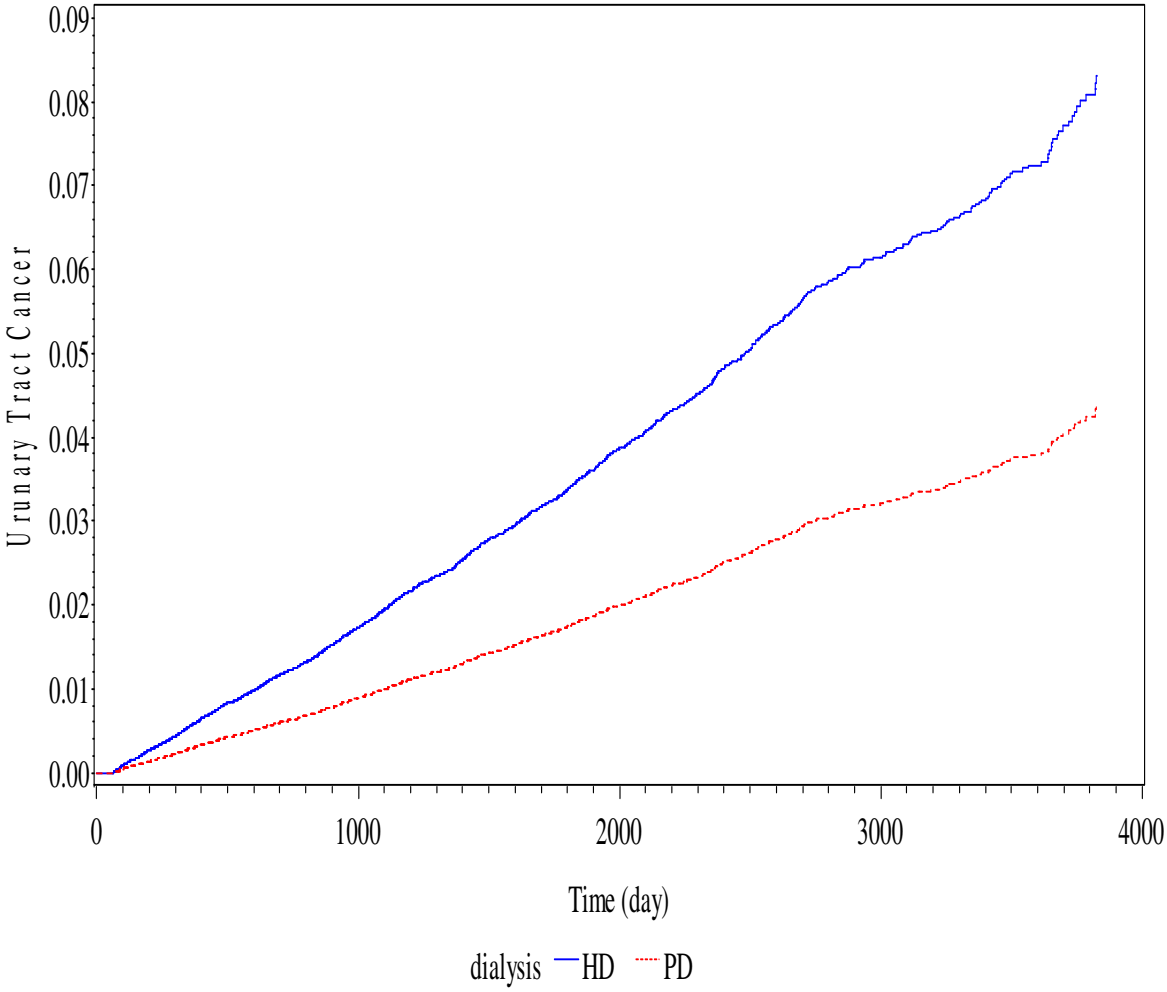

Figure 4-1 Adjusted Cox regression curves for new ESRD dialysis patients with and without urinary tract cancer treated with PD versus HD

*For HD/PD comparison, p<.001

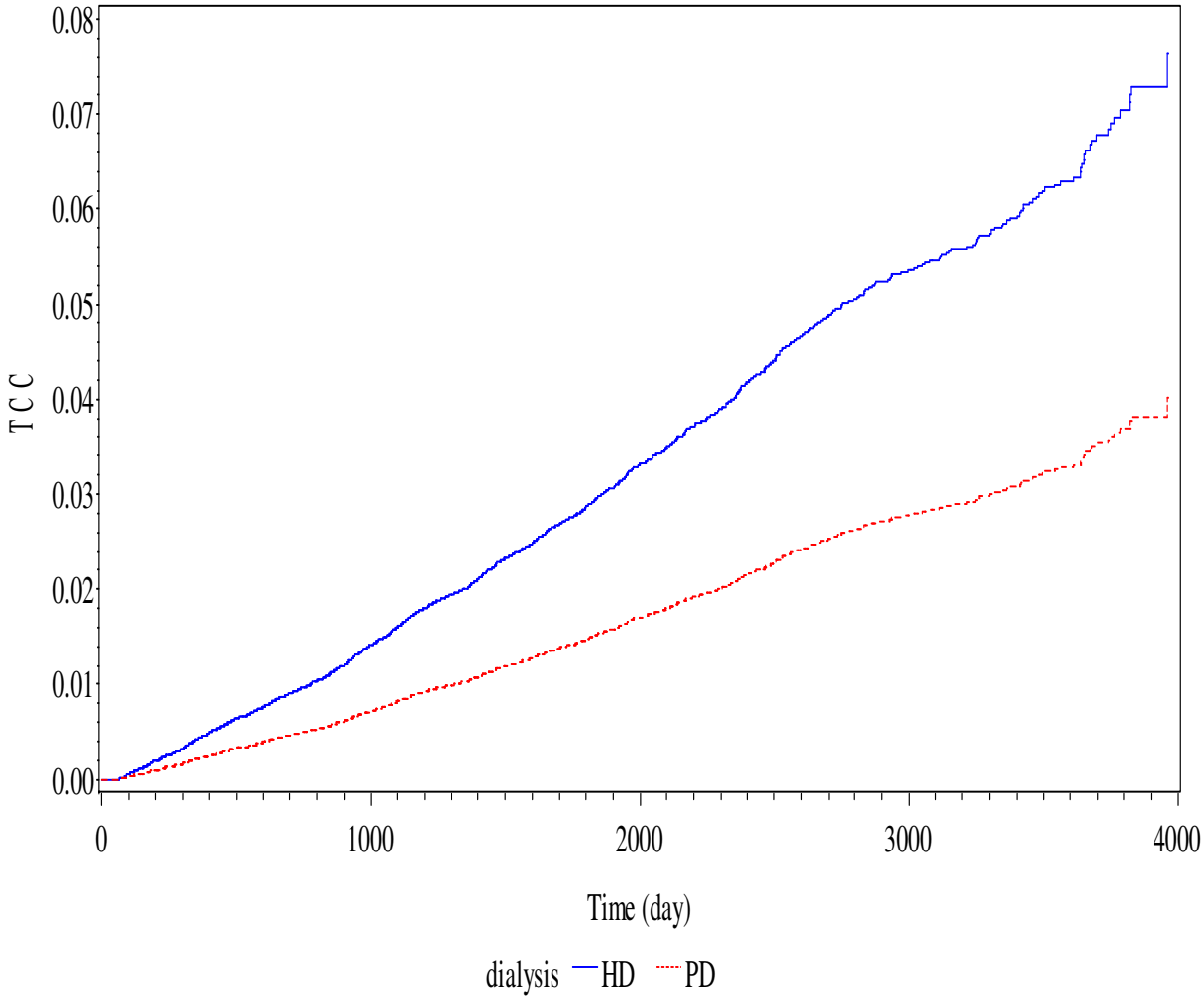

Figure 4-2 Adjusted Cox regression curves for new ESRD dialysis patients with and without TCC treated with PD versus HD

*For HD/PD comparison, p<.001

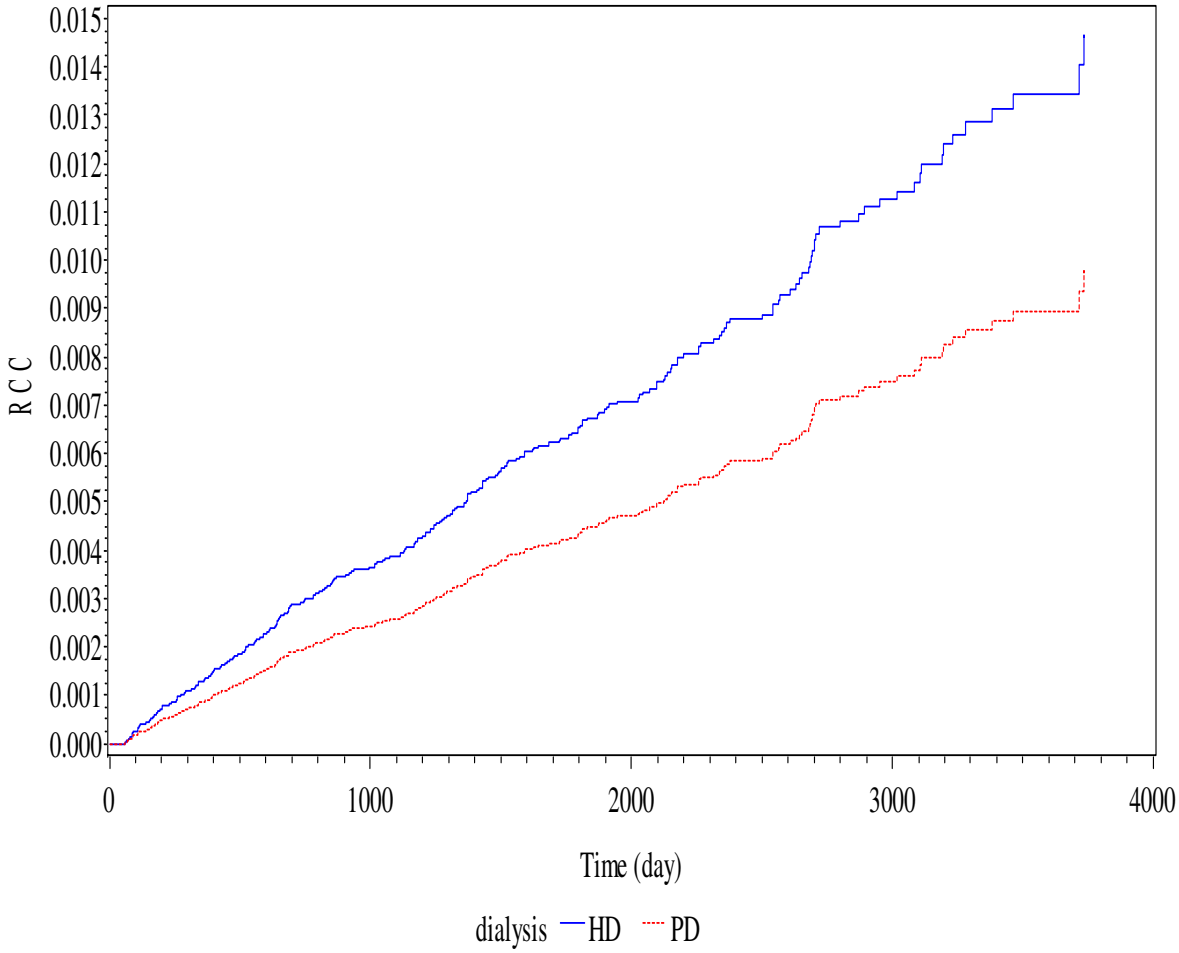

Figure 4-3 Adjusted Cox regression curves for new ESRD dialysis patients with and without RCC treated with PD versus HD

*For HD/PD comparison, p=0.173

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