

ORIGINAL ARTICLE

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Decrease of creatinine clearance rate with aging in patients with head and neck cancer in Japan

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Abstract

Background. We aimed to clarify the reason for the lower dosage of *cis*-platinum (CDDP) in patients with head and neck cancer in Japan compared with that in other countries, by evaluating renal function.

Methods. We studied 375 patients with head and neck cancer who had been hospitalized from January 1998 to October 2005, to evaluate and treat the disease. The creatinine clearance rate (Ccr) was calculated at least three times before beginning the treatments, and the average Ccr was estimated to evaluate the renal function.

Results. The Ccr decreased with aging, and the percentages of patients with Ccr lower than 65 ml/min per 1.73 m² were 27.1% of patients in their fifties, 36.8% in their sixties, 62.3% in their seventies, and 87.5% in their eighties. There was no correlation between renal function and the Japanese lifestyle (i.e., diet, water consumption).

Conclusion. The renal function of Japanese decreases rapidly with aging, whereas that of Americans is maintained for longer periods. The poor renal function of Japanese is one of the causes of the need to reduce the dosage of or avoid the administration of CDDP in cancer patients.

Key words Head and neck cancer · Ccr · CDDP

Introduction

More than 90% of head and neck cancers are squamous cell carcinomas. The definitive treatment method for locore-

gionally advanced head and neck squamous cell carcinoma (HNSCC) is radiotherapy and/or operation. Because of the anatomical features, preserving organs is important to maintain functions such as phonation and deglutition, and to minimize changes in the esthetic appearance. Some recent articles have described the efficacy of concurrent chemoradiotherapy and neoadjuvant chemotherapy in preserving function for patients with advanced HNSCC,^{1–3} because HNSCC is relatively sensitive to some chemotherapeutic agents. The main chemotherapeutic regimens for HNSCC consist of *cis* platinum (CDDP) and 5-fluorouracil (5-FU). The dose of CDDP is 70–100 mg/m² per day in most countries;^{1,2,4} however, a CDDP dose of 60–70 mg/m² per day is given to HNSCC patients in Japan. The reason for the lower doses is the poor renal function of the Japanese. Here we report on the renal function of patients with head and neck cancer (predominantly HNSCC) in Japan, by evaluating the creatinine clearance rate (Ccr.).

Patients and methods

Patient characteristics are summarized in Table 1. Three hundred and seventy-five patients with head and neck cancer, including 4 patients with synchronous double cancer and 3 with synchronous triple cancer, with no renal disease, hospitalized in the Department of Otorhinolaryngology, Head and Neck Surgery, Yokohama City University, Yokohama, Japan, from January 1998 to October 2005 were evaluated. The formulas used to calculate Ccr and body surface area (BSA) were as follows:

$$\text{Ccr} = (\text{urine creatinine}) \times (\text{urine volume per day}) / (24 \times 60 \times \text{serum creatinine}) \times (\text{BSA}) / 1.73 \text{m}^2$$
$$\text{BSA} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}$$

The Ccr in all patients was calculated at least three times, before beginning the treatments, and the average Ccr was estimated. The individual average Ccr was also processed to calculate the generational average in each age decade. Statistical analysis was done by Student's *t*-test to compare

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Table 1. Patients' characteristics, including four patients with synchronous double cancer and three patients with synchronous triple cancer

Sex (number of patients)	
Male	311
Female	64
Age (years)	
Mean	63.9
Range	16–89
10–19	1 (Number of patients)
20–29	2
30–39	14
40–49	18
50–59	85
60–69	125
70–79	106
80–89	24
Tumor site (number of patients)	
Larynx	91
Nasopharynx	19
Oropharynx	54
Hypopharynx	80
Nasal cavity, paranasal sinus	47
Oral cavity	39
Salivary gland	13
Ear	9
Eyelid	1
Esophagus	7
Lung	1
Stomach	1
Lymph node	22
Delayed metastasis	6
Malignant lymphoma	6
Primary unknown metastasis	10
Pathological diagnosis (number of patients)	
Squamous cell carcinoma	330
Poorly differentiated	100
Moderately differentiated	130
Well-differentiated	80
Carcinoma in situ	8
Not classified	12
Acinic cell carcinoma	1
Adenocarcinoma	12
Adenoidcystic carcinoma	3
Adenosquamous carcinoma	2
Basal cell carcinoma	1
Chondrosarcoma	1
Malignant lymphoma	6
Malignant melanoma	3
Mucoepidermoid carcinoma	3
Neuroendocrine carcinoma	4
Olfactory neuroblastoma	5
Salivary duct carcinoma	3
Small-cell carcinoma	3
Spindle-cell carcinoma	1
Undifferentiated carcinoma	4
Verrucous carcinoma	2

the Ccr in patients aged less than their fifties with that in patients in other age decades.

Results

The average Ccr decreased with aging, with a significant difference between the age decades (Fig. 1). In our department, we have been administering CDDP to patients with an average Ccr of more than 65 ml/min per 1.73 m². All the patients aged less than the fifties had a Ccr of more than

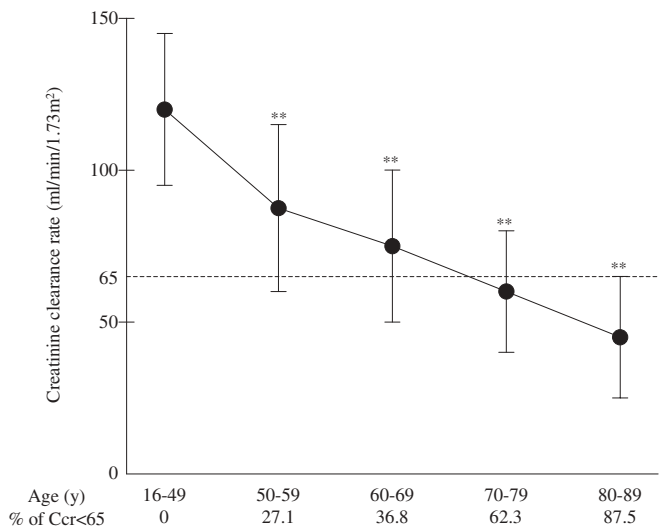


Fig. 1. The average creatinine clearance (Ccr) decreased in an age-dependent manner, with significant differences between the age decades. y, years; black closed circles, average, Bars. SD. ** $P < 0.01$

65 ml/min per 1.73 m²; the average was 119.5 ml/min per 1.73 m² and the range was from 69.6 to 168.7 ml/min per 1.73 m². The percentage of patients with low renal function, whose Ccr was less than 65 ml/min per 1.73 m², increased in an age-dependent manner. Only 3 of 24 patients in their eighties showed a Ccr of more than 65 ml/min per 1.73 m².

Discussion

Squamous cell carcinoma accounts for more than 90% of malignant head and neck tumors. The definitive treatment for locoregionally advanced HNSCC is operation and/or radiotherapy. Most HNSCC patients are at advanced stages (III and IV) at their first hospital visit, so there are few patients with early stages (I and II) who have a possibility of being cured completely by radiotherapy or partial resection. Because of the anatomical features of advanced HNSCC, surgical resection for these patients might diminish their quality of life, in terms of such functions as phonation and deglutition, as well as causing mental and emotional problems about esthetic changes. Therefore, worldwide, organ-preservation treatment has been used to cure patients with advanced HNSCC.¹⁻³ HNSCC is sensitive to some chemotherapeutic agents and some articles have reported the efficacy of concurrent chemoradiotherapy and neoadjuvant chemotherapy, mostly using CDDP, 5-FU, and/or taxanes, in patients with advanced HNSCC. Of these agents, CDDP is a key drug in the treatment of HNSCC.

The major adverse effects of CDDP are myelosuppression, emesis, and renal toxicity. To protect renal function, sufficient hydration is given prior to and after CDDP administration and a neutralizing drug, e.g. chiosulfate is given during the CDDP administration. In addition to these protective methods, it is important to evaluate the patient's renal function precisely to avoid the administration of

Fig. 2. Worldwide incidence of end-stage renal disease (ESRD) in 2002. All rates are unadjusted. Data from Israel, Japan, Luxembourg, and Taiwan represent dialysis only

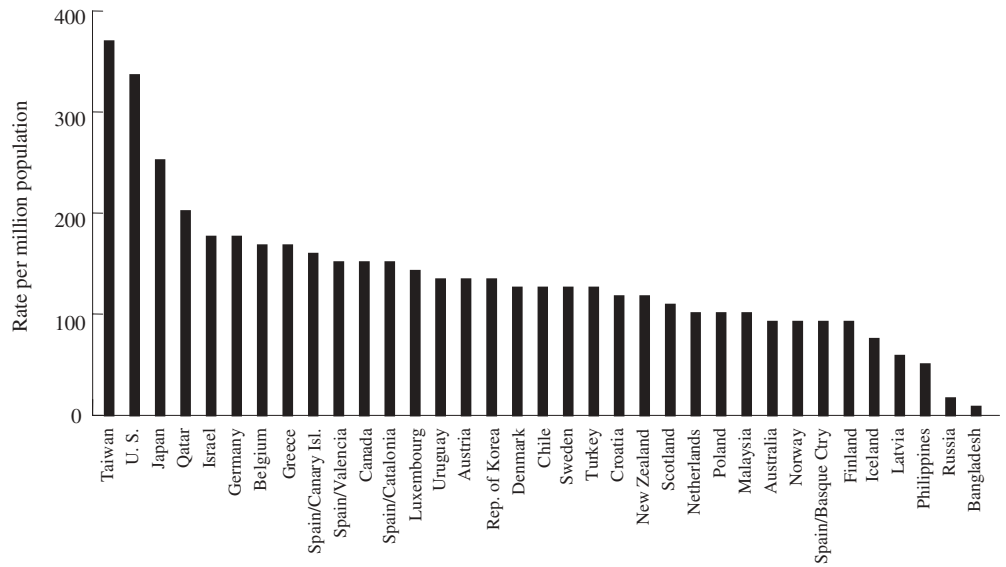
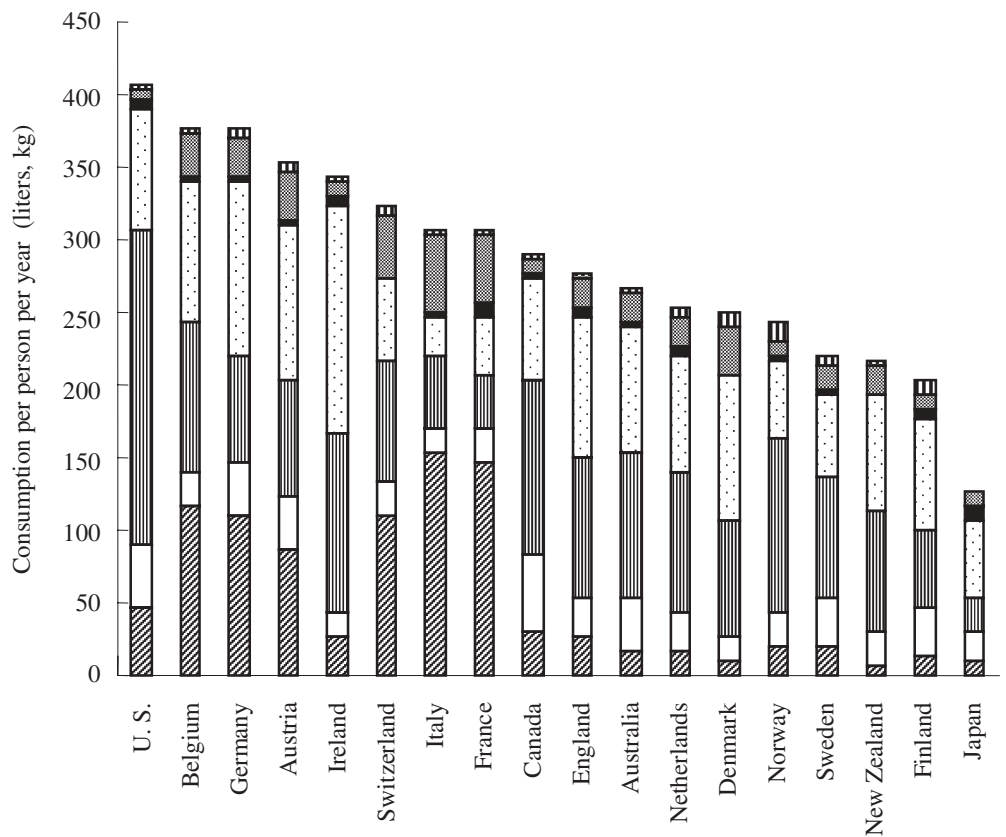


Fig. 3. Worldwide consumption of drink products per person per year in 2002. Legend: bottled water (l); fruit juice (l); carbonated soft drink (l); beer (l); total sprit (l); wine (li); coffee (kg); tea (kg)



CDDP in patients with poor renal function. In our department, each patient's renal function has been evaluated by serum creatinine and Ccr before the first treatment. We calculate the average Ccr, using at least three different measurements, and when the average exceeds 65 ml/min per 1.73 m², the patient is treated with CDDP at the dose of 60–70 mg/m² per day. In patients with an average Ccr of less than 60 ml/min per 1.73 m², other platinum derivatives are given; e.g., carboplatin at a dose of AUC = 5–6. Because Ccr is modified by aging, total muscle volume, diet, and

other factors, the most precise index of renal function is the glomerular filtration rate (GFR). However, the measurement of GFR is so complicated that it is impractical to evaluate renal function frequently with the GFR. So Ccr has been used for the evaluation of renal function throughout the treatment of patients with head and neck cancer with chemotherapeutic agents, especially CDDP.

In Western countries and Asian countries except for Japan, HNSCC patients are treated with CDDP at a dose of 70–100 mg/m² per day.^{1,2,4} The average GFR values in

Fig. 4. Relationship and regression line between incidence of ESRD and amounts of drink products consumed in 14 countries

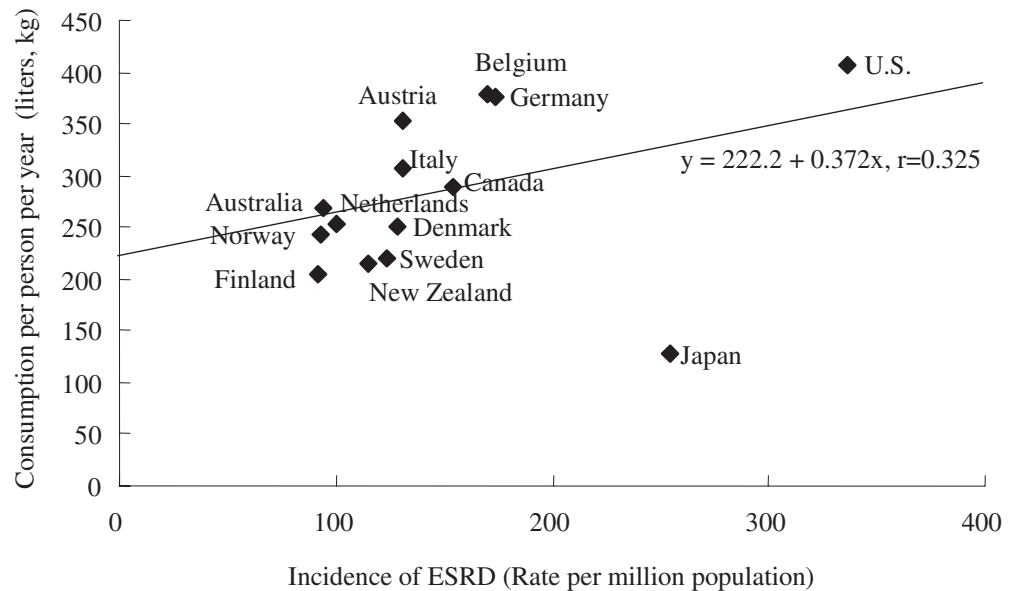
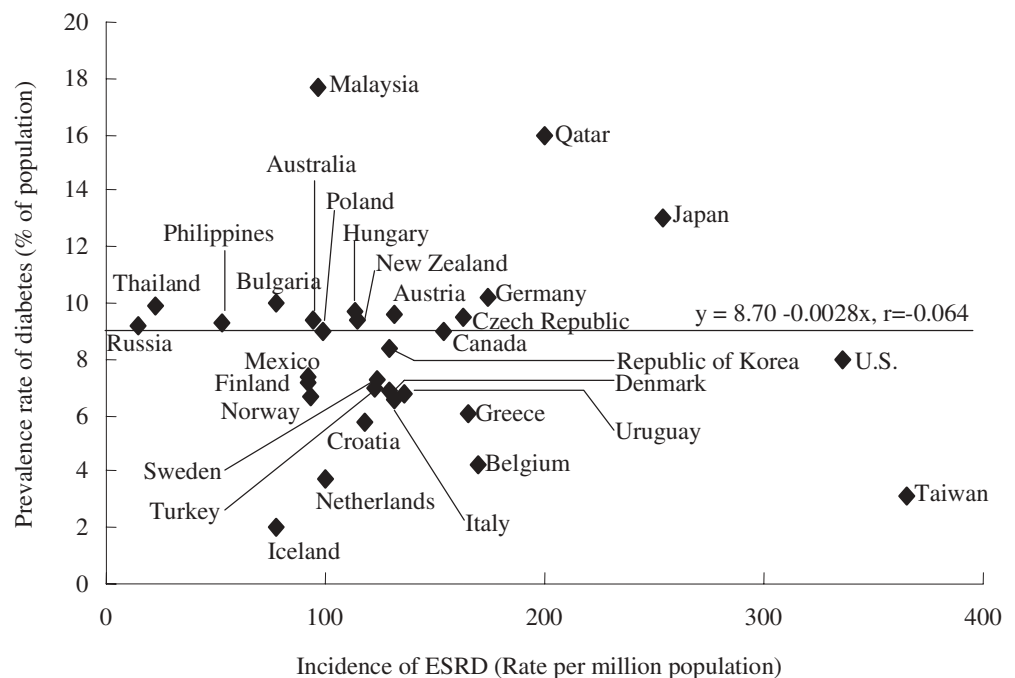


Fig. 5. Relationship and regression line between incidence of ESRD and the prevalence rates of diabetes in 31 countries



healthy people in the United States are as follows; in their twenties, 116 ml/min per 1.73 m²; the thirties, 107 ml/min per 1.73 m²; the forties, 99 ml/min per 1.73 m²; the fifties, 93 ml/min per 1.73 m²; the sixties, 85 ml/min per 1.73 m²; and over seventies, 75 ml/min per 1.73 m².⁵ Epstein,⁶ Wesson,⁷ and Adler et al.⁸ have also reported reductions in GFR with aging in European and United States populations. Their results have indicated that the GFR for the over-seventies is 70 ml/min for both sexes. This value represents sufficient renal function for the administration of CDDP at 70–100 mg/m² per day. Hosoya et al.⁹ have reported that renal function in aged Japanese is lower than that in their Western counterparts and they also reported that the average Ccr in healthy Japanese in their eighties was 54.5 ml/min per

1.73 m² in men and 52.5 ml/min per 1.73 m² in women. Our results in Japanese in their eighties showed an average Ccr of 44.3 ml/min per 1.73 m² in both sexes, and this value was also lower than that in Western people.

Figure 2 shows the worldwide incidence 175 of end-stage renal disease (ESRD) (<http://www.usrds.org>). It is known that sufficient hydration improves renal function, including Ccr.¹⁰ Therefore we summarized the worldwide consumption of drink products (shown in Fig. 3; <http://www.nation-master.com>). The relationship between these data in 14 countries was analyzed to make a regression line (Fig. 4). The results indicated no correlation among them ($r = 0.325$; $P > 0.05$). We also analyzed the relationship between the incidence of ESRD and the prevalence rate of diabetes

(<http://www.eatlas.org>) – which is the main disease underlying renal dysfunction – in 31 countries (Fig. 5). The results did not indicate any correlation ($r = -0.064$; $P > 0.05$). It is well known that renal function decreases with aging and that morphologic changes, e.g., decrease of kidney weight, the appearance of sclerotic glomeruli,¹¹ and intimal proliferation in the renal artery,¹² are considered to be some of the causes of renal dysfunction. The average Ccr values in Asian, Caucasian, and Hispanic people are 85.8, 101.1, and 105.9 ml/min per 1.73 m², respectively,¹³ and it is considered that Asians potentially have less renal function than other ethnic groups. Taiwan has the highest incidence of ESRD (Fig. 2). Though we could not find data for changing renal function with aging in healthy Taiwanese, the incidence of ESRD in Taiwan had dramatically increased in those of middle age (over 45 years; <http://www.usrds.org>). Taiwan is well known as a high-incidence area for nasopharyngeal cancer, and the incidence is highest in those in their twenties and forties in the United States and European countries, those in their fifties have the highest average incidence of HNSCC. The mean age of our patients was 63.9 years, and we consider this high age as one of reasons for the difference between the CDDP doses in Japan and other countries, based on renal function. We were unable to identify a clear reason for the rapid deterioration of renal function in the Japanese. Based on the present results, we have to pay more attention to renal toxicity in chemotherapy and chemoradiotherapy. Furthermore, the doses of chemotherapeutic agents used in elderly patients with HNSCC should be considered in relation to renal function.

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