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ORIGINAL RESEARCH

Prognostic Value of Pretreatment Serum Cystatin C Level in Nasopharyngeal Carcinoma Patients in the Intensity-modulated Radiotherapy Era

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Purpose: Serum cystatin C has been considered as a significant prognostic factor for various malignancies. This study aimed to evaluate the relationship between serum cystatin C level before antitumor treatment and the prognosis of nasopharyngeal carcinoma (NPC) patients treated with intensity-modulated radiotherapy (IMRT).

Patients and Methods: A cohort of 2077 NPC patients were enrolled between April 2009 and September 2012. The Kaplan–Meier curves and log rank tests were used to determine the differences of overall survival (OS) and disease-free survival (DFS). Univariate and multivariate Cox regression analyses were used to determine independent prognostic factors.

Results: Overall, 362/2077 (17.4%) patients had high serum cystatin C level, and they were older and more male (both $P<0.001$), and they had higher TNM stage (all $P<0.05$). Kaplan–Meier analysis revealed that patients with high serum cystatin C had worse OS ($P<0.001$) and DFS ($P<0.001$). Univariate and multivariate Cox regression analysis showed that high serum cystatin C level was an independent prognostic predictor of OS (HR: 1.56, 95%CI: 1.25–1.95) and DFS (HR: 1.38, 95%CI: 1.13–1.68). Subgroup analysis based on TNM stage revealed that advanced-stage NPC patients with high serum cystatin C had poorer OS ($P<0.001$) and DFS ($P<0.001$).

Conclusion: Our results revealed that high serum cystatin C level before antitumor treatment can predict clinical outcomes of NPC patients treated with IMRT, and it can guide clinicians to formulate more personalized therapy for NPC patients.

Keywords: nasopharyngeal carcinoma, serum cystatin C level, survival prognosis, predictor

Introduction

Nasopharyngeal carcinoma (NPC) is a kind of head and neck squamous cell carcinoma and has a unique distribution, with the highest incidence in southeast Asia, especially in southern China.[1] Mainly originating from pharyngeal recess, an anatomical position close to skull base, NPC is sensitive to radiotherapy, alone or with chemotherapy.[2] With the advent of diagnostic methods and treatment strategies, survival rate has been obviously increased in locally advanced NPC patients recently,[3] but the number of patients dead from NPC keeps increasing across the whole world according to global cancer statistical data in 2018.[4] Distant metastasis has become the major obstacle of treatment failure in NPC patients.[5]

The TNM staging system, comprised of the T, N, M classification, is the most significant tool for prognostic judgment and the key measure of treatment strategies.[6] However, the TNM staging system is inadequate for predicting

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prognosis of NPC patients for depending largely on the anatomy and ignoring biological heterogeneity of the tumor.[7,8] Thus, it is still urgent to discover new biomarkers to predict the clinical outcome and the risk of distant metastasis of NPC patients. With the great development in the understanding of the molecular biology of NPC, numerous studies have found biomarkers for the prognosis or curative effect of NPC patients, such as albumin to globulin ratio,[9] lactate dehydrogenase,[10] C-reactive protein/albumin ratio,[11] serum bilirubin,[12] circulating lipoprotein,[13] and plasma EBV-DNA level.[14] Nevertheless, their clinical roles need to be confirmed and we are eager to find new and effective biomarkers to predict prognosis and guide treatment accurately.

Cystatin C, a 13-kD nonglycosylated protein and a cysteine protease inhibitor, is encoded by a housekeeping gene in almost all nucleated cells.[15] Cystatin C affects protein catabolism, antigen presentation, bone resorption, and hormone processing, and it can couple to cleavage of membrane and extracellular matrix proteins during tissue remodeling irregularly, and its homeostasis imbalance can lead to disease, including cancer.[16] Previous studies have shown that serum cystatin C level plays important roles in diagnosing and predicting human diseases, such as cirrhosis,[17] inflammation,[18] Parkinson's disease,[19] kidney disease,[20] and cardiovascular disease.[21] Many studies have reported that cystatin C plays important roles in predicting the prognosis and effect of clinical therapy of various cancers, such as myeloma,[22,] esophageal cancer,[23] renal carcinoma,[24] upper tract urothelial carcinoma,[25] non-Hodgkin's B-cell lymphoma,[26] and so on. One study has described the potential relationship between cystatin C and NPC treated with two-dimensional conformal radiotherapy (2D-CRT).[27] However, the clinical significance of cystatin C in NPC treated with intensity-modulated radiotherapy (IMRT) is still unclear.

Therefore, we performed this retrospective cohort study to discover and verify the prognostic value of serum cystatin C level at the first time of diagnosis in NPC in the IMRT era, in order to assist clinicians to formulate more individualized treatment strategies for NPC patients and improve their life quality and clinical outcome.

Patients and Methods

Patient Population

A total of 2077 patients newly diagnosed with NPC at Sun Yat-Sen University Cancer Center between April 2009 and September 2012 were analyzed retrospectively in this study. Patients were enrolled if (i) diagnosed as NPC by pathological biopsy; (ii) without distant metastasis; (iii) without previous anticancer treatment; (iv) without previous history of cancer; (v) with complete patient history and biochemical test results.

Pretreatment Evaluation

All patients participating in the study were assessed with routine pretreatment evaluation consisting of complete medical history, physical examination, routine blood test and biochemical analyses, nasopharyngoscopy, histopathological diagnosis, magnetic resonance imaging (MRI) of the nasopharynx and neck, chest radiography, abdominal ultrasonography, and whole body bone scan by single photon emission computed tomography (ECT) or 18^{F}-fluorodeoxyglucose positron-emission tomography/computed tomography (PET/CT). All patients were restaged according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. Two radiation oncologists specializing in head and neck cancer independently reviewed all imaging scans and divergence was resolved by consultation. This study was approved by the Institutional Ethical Review Board of Sun Yat-Sen University Cancer Center, and the written informed consent was waived by the Ethics Review Board due to the anonymity of the study. This study was also conducted in accordance with the Declaration of Helsinki.

Laboratory Measurements

All patients participating in this study had serum cystatin C levels measured in our hospital before having any antitumor treatment. Five milliliters of peripheral blood from each patient was separated by centrifugation at 3000 g for five minutes and the upper serum was carefully transferred to Eppendorf Pipes. Serum cystatin C level was determined using an automated analyzer (7600–020, Hitachi High-Technologies, Tokyo, Japan), and the coefficient of variance of serum cystatin C measurement was less than 5%.

Treatment

According to our institutional guidelines, the primary tumor and cervical malignant lymph nodes were treated with intensity-modulated radiation therapy (IMRT). The prescribed doses were 66–72 Gy (28–33 fractions) to the planning target volume (PTV) of the gross tumor volume of nasopharynx lesion (GTVnx), and 64–70 Gy (28–33

fractions) to the PTV of the gross tumor volume of the malignant lymph nodes (GTVnd). In principal, radiation therapy alone was used for stage I disease, concurrent chemoradiotherapy for stage II disease, and concurrent chemoradiotherapy (CCRT) with or without induction/adjuvant chemotherapy (IC/AC) for stage III–IVB disease. Three regimes of IC were commonly adopted: cisplatin (80 mg/m^2) plus 5-fluorouracil (750–1000 mg/m^2 per day for five days), cisplatin (75 mg/m^2) plus docetaxel (75 mg/m^2), and cisplatin (60 mg/m^2) plus docetaxel (60 mg/m^2) and 5-fluorouracil (600–750 mg/m^2 per day for five days) every three weeks for 2–4 cycles. CCRT adopted cisplatin (80–100 mg/m^2) every three weeks for 2–3 cycles or cisplatin (30–40 mg/m^2) weekly for five-to-seven cycles. AC was less often chosen because of its poor compliance. Reasons for deviation from guidelines included recruitment in clinical trials, patient's refusal, age, or organ dysfunction suggesting intolerance to treatment.

Follow-up

The process of the follow-up continued from the first day of antitumor treatment to the time of last visit or death. The median follow-up time was 96.3 months (range: 4.1–120.0 months). In our study, overall survival (OS) and disease-free survival (DFS) were two clinical indicators for outcome measure. OS was defined as from the first day of antitumor treatment to death, whatever the cause; DFS was to disease progression or death whatever the cause. After a whole therapy mentioned before, we reexamined patients every three months in the first two years, every six months in the subsequent three years, and once a year henceforth until the end.

Statistical Analysis

SPSS version 22.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analysis. Chi-squared or Fisher's exact test was used to analyze the differences between categorical variables. Kaplan–Meier curve was applied to the calculation of the cumulative survival rates, and log rank test was used to compare their differences. Univariate and multivariate analysis with Cox proportional hazards models were used to look for independent predictors of prognosis of NPC patients by backward elimination of confounding variables. Host factors included age, gender, WHO type, and TNM stage were used as covariates. All tests were two-side and a P-value <0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of 2077 NPC patients are shown in Table 1. The median age of patients with NPC was 45 years (range from 18 to 78 years). Among them, 527 (25.4%) patients were female and 1550 (74.6%) were male. According to the eighth AJCC/UICC staging system, the quantity of patients classified as stage I, II, III, and IV were 120 (5.8%), 414 (19.9%), 968 (46.6%), and 575 (27.7%), respectively. All of those patients went radical IMRT, and 1763 patients (84.9%) received

Table 1 Baseline Characteristics of 2077 Patients with Nasopharyngeal Carcinoma

Characteristics	No. of Patientsn (%)
Age, years	
Median	45
Range	18–78
Gender	
Female	527 (25.4)
Male	1550 (74.6)
WHO type	
I	11 (0.5)
II	98 (4.7)
III	1968 (94.8)
T category[a]	
T1	349 (16.8)
T2	344 (16.6)
T3	984 (47.4)
T4	400 (19.3)
N category[a]	
N0	352 (16.9)
N1	1178 (56.7)
N2	334 (16.1)
N3	213 (10.3)
TNM stage[a]	
I	120 (5.8)
II	414 (19.9)
III	968 (46.6)
IV	575 (27.7)
Chemotherapy	
No	314 (15.1)
Yes	1763 (84.9)
Comorbidity	
No	1377 (66.3)
Yes	700 (33.7)

Note: [a]According to the eighth AJCC/UICC staging system.

platinum-based chemotherapy, while 314 patients (15.1%) did not. Median follow-up was 96.3 months (range from 4.1 to 120.0 months).

Correlation of Higher Serum Cystatin C Level with Patient Characteristics

We defined patients who had serum cystatin C level above the upper limit of the normal range (0.59–1.03 mg/L) as being in the high cystatin C group (>1.03 mg/L), and the remaining patients as being in the low cystatin C group (≤1.03 mg/L). Then the baseline characteristics of the two groups were compared and the results were displayed in Table 2. For the whole cohort, 362/2077 (17.4%) patients were diagnosed as high serum cystatin C (>1.03 mg/L). Compared with those with low serum cystatin C level (≤1.03 mg/L), the NPC patients with high serum cystatin C level were older (P<0.001), and they were with higher T category (P<0.001), N category (P=0.037), TNM stage (P=0.004). Moreover, they tended to be more male (P<0.001) and complicated with more comorbidities (P<0.001) than those with low serum cystatin C. Additionally, there were no obvious statistical differences in terms of WHO type (P=0.194) and chemotherapy (P=0.116).

Prognostic Value of Serum Cystatin C Level in NPC

We first analyzed the relationship of serum cystatin C level with the survival probabilities of NPC patients by Kaplan–Meier analysis. As shown in Figure 1, the NPC patients with a high level of serum cystatin C level had worse OS (P<0.001), and DFS (P<0.001) compared with those with a low level of serum cystatin C.

We then used univariate and multivariate Cox proportional hazards models to assess whether serum cystatin C level can predict clinical outcome of NPC patients. Univariate analysis results showed that together with age, gender, WHO type and TNM stage, serum cystatin C level can predict the clinical outcome of NPC patients, specifically high serum cystatin C level was associated with worse OS (HR: 1.81, 95%CI: 1.46–2.24, P<0.001, Table 3), and DFS (HR: 1.54, 95%CI: 1.27–1.87, P<0.001, Table 3).

Multivariate analysis further indicated that serum cystatin C level can be an independent predictor of OS (HR: 1.56, 95%CI: 1.25–1.95, P<0.001, Table 4) and DFS (HR: 1.38, 95%CI: 1.13–1.68, P=0.002, Table 4) for NPC patients. Similarly, age, WHO type and TNM stage were independent predictors of OS and DFS for NPC patients (all P<0.05, Table 4).

Table 2 Baseline Characteristics of Nasopharyngeal Carcinoma Patients with Low or High Serum Cystatin C Levels

Characteristics	Serum Cystatin C level		*P*-value*
	≤1.03 mg/L, n (%)	>1.03 mg/L, n (%)	
Age			
≤ 45 years	1007 (58.7)	103 (28.5)	<0.001**
> 45 years	708 (41.3)	259 (71.5)	
Gender			
Female	482 (28.1)	45 (12.4)	<0.001**
Male	1233 (71.9)	317 (87.6)	
WHO type			
I+II	85 (5.0)	24 (6.6)	0.194
III	1630 (95.0)	338 (93.4)	
T category[a]			
T1	312 (18.2)	37 (10.2)	<0.001**
T2	266 (15.5)	78 (21.5)	
T3	821 (47.9)	163 (45.0)	
T4	316 (18.4)	84 (23.2)	
N category[a]			
N0	299 (17.4)	53 (14.6)	0.037**
N1	985 (57.4)	193 (53.3)	
N2	267 (15.6)	67 (18.5)	
N3	164 (9.6)	49 (13.5)	
TNM stage[a]			
I	109 (6.4)	11 (3.0)	0.004**
II	345 (20.1)	69 (19.1)	
III	810 (47.2)	158 (43.6)	
IV	451 (26.3)	124 (34.3)	
Chemotherapy			
No	269 (15.7)	45 (12.4)	0.116
Yes	1446 (84.3)	317 (87.6)	
Comorbidity			
No	1169 (68.2)	208 (57.5)	<0.001**
Yes	546 (31.8)	154 (42.5)	

Notes: *P-value was calculated using the chi-squared tests or Fisher's exact test. **P<0.05. [a]According to the eighth AJCC/UICC staging system.

Varying Impact of Serum Cystatin C Level by Stage

As shown in Table 2, two groups of NPC patients had different TNM stage distribution (P=0.004). Then, we performed a subgroup analysis based on clinical TNM stage by dividing the patients into two groups (I–II: early-stage group and III–IV: advanced-stage group). Survival

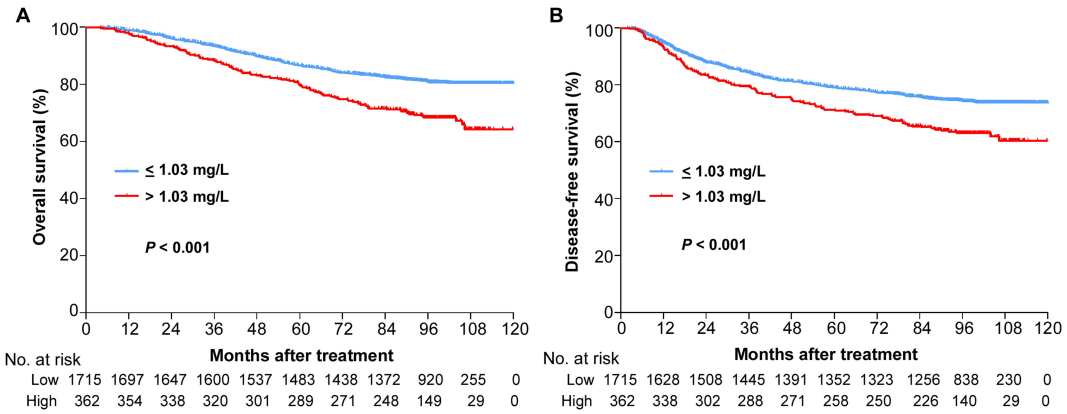

Figure 1 Kaplan-Meier curve analysis of survival probabilities of NPC patients stratified by the level of serum cystatin C. (**A**) Overall survival, (**B**) Disease-free survival.

analysis results showed that compared with patients with low serum cystatin C level, early-stage patients with high serum cystatin C level had poorer OS (P=0.018, Figure 2A), but had no significant statistical difference in DFS (P=0.252, Figure 2B), and advanced-stage patients with high serum cystatin C level had both poorer OS (P<0.001, Figure 2C) and DFS (P<0.001, Figure 2D).

Discussion

To the best of our knowledge, this study is the largest retrospective cohort study to assess the relationship between serum cystatin C level and the prognosis of NPC patients treated with IMRT. Our results revealed that high serum cystatin C level can independently predict poor clinical outcome of patients with NPC. Therefore, monitoring serum cystatin C level before antitumor treatment can assist clinicians to formulate more individualized treatment strategies for NPC patients and improve their life quality and survival.

The standard treatment for NPC is mainly effective in local symptomatic control, but not in distant metastasis.[28,29] Therefore, it remains an urgent problem to predict the prognosis and prolong the survival of NPC patients at different stages. At present, TNM staging system is the most commonly used tool to determine the

Table 3 Univariate Analysis of Prognostic Factors in Patients with Nasopharyngeal Carcinoma

Variables	Univariate Analysis		
	HR	95%CI	*P*-value*
Overall survival			
Age (>45 years vs ≤45 years)	1.58	1.31–1.90	<0.001**
Gender (female vs male)	0.75	0.60–0.94	0.014**
WHO type (III vs I+II)	0.58	0.41–0.81	0.002**
TNM stage (III–IV vs I–II)	3.01	2.24–4.04	<0.001**
Comorbidity (with vs without)	1.13	0.93–1.37	0.228
Serum cystatin C level (high vs low)	1.81	1.46–2.24	<0.001**
Disease-free survival			
Age (>45 years vs ≤45 years)	1.41	1.20–1.66	<0.001**
Gender (female vs male)	0.80	0.66–0.97	0.026**
WHO type (III vs I+II)	0.64	0.46–0.87	0.005**
TNM stage (III–IV vs I–II)	2.26	1.79–2.85	<0.001**
Comorbidity (with vs without)	1.06	0.89–1.26	0.505
Serum cystatin C level (high vs low)	1.54	1.27–1.87	<0.001**

Notes: *P-value was calculated using the univariate Cox proportional hazards model. **P<0.05.

Table 4 Multivariable Analysis of Prognostic Factors in Patients with Nasopharyngeal Carcinoma

Variables	Multivariate Analysis		
	HR	95%CI	*P*-value*
Overall survival			
Age (>45 years vs ≤45 years)	1.40	1.15–1.70	0.001**
WHO type (III vs I+II)	0.58	0.42–0.82	0.002**
TNM stage (III–IV vs I–II)	2.96	2.21–3.98	<0.001**
Serum cystatin C level (high vs low)	1.56	1.25–1.95	<0.001**
Disease-free survival			
Age (>45 years vs ≤45 years)	1.29	1.09–1.53	0.003**
WHO type (III vs I+II)	0.64	0.47–0.87	0.005**
TNM stage (III–IV vs I–II)	2.24	1.78–2.82	<0.001**
Serum cystatin C level (High vs Low)	1.38	1.13–1.68	0.002**

Notes: *-value was calculated using the multivariable Cox proportional hazards model. **P<0.05. The following parameters were included in the Cox proportion hazard model by backward elimination: age (≥45 vs <45 years), gender (female vs male), WHO type (type III vs type I+II), TNM stage (III–IV vs I–II), comorbidity (with vs without), and serum cystatin C level (high vs low) as covariates.

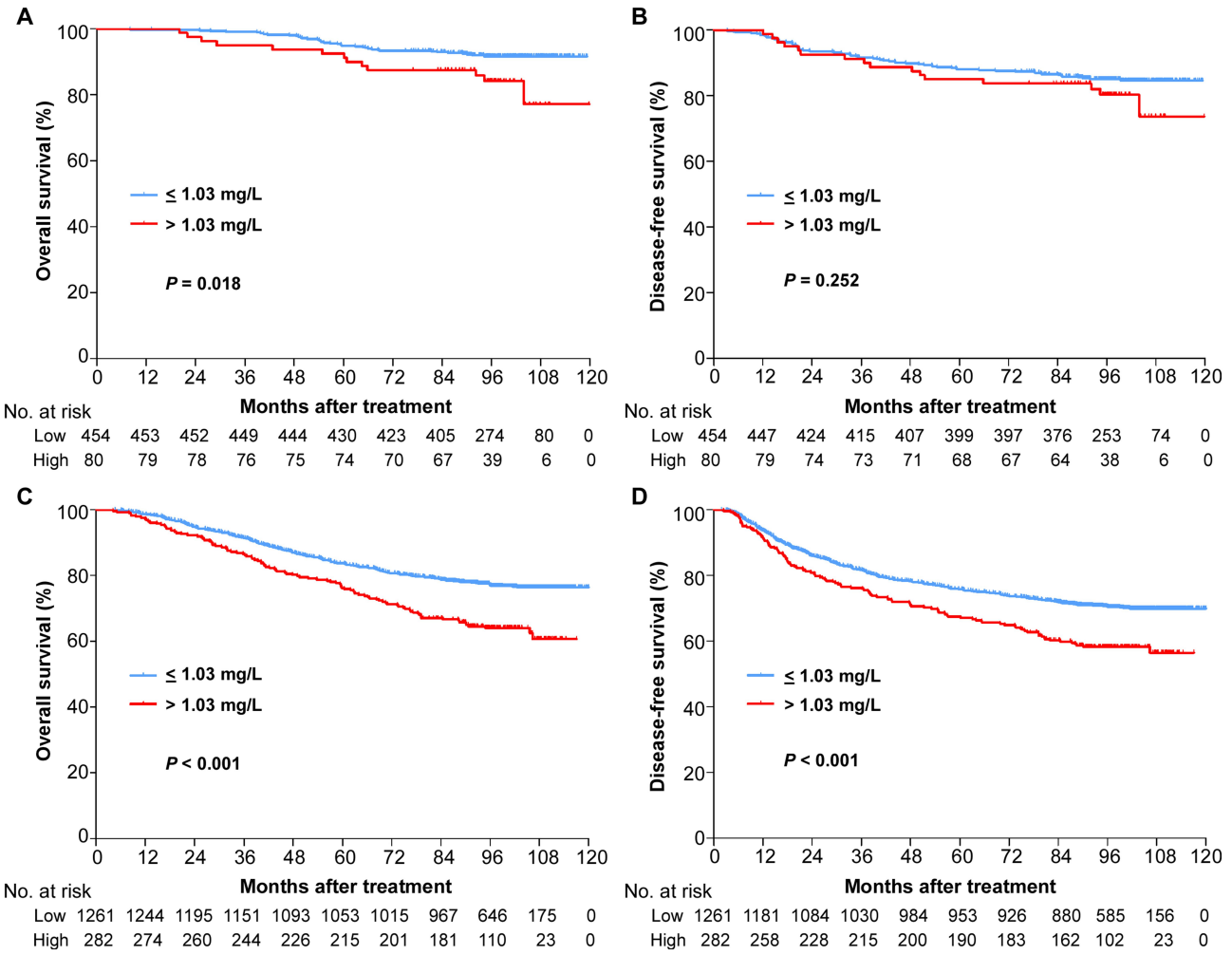

Figure 2 Kaplan-Meier curve analysis of survival probabilities of NPC patients stratified by TNM stage and the level of serum cystatin C. (**A**) Overall survival in early-stage, (**B**) Disease-free survival in early-stage, (**C**) Overall survival in advanced-stage, (**D**) Disease-free survival in advanced-stage.

prognosis of patients with NPC. However, studies have shown that patients with the same TNM stage have a different prognosis after receiving the same treatment regimen.[8] This shows that TNM staging has limitations in predicting the survival of patients with NPC, and new biomarkers are needed to increase the accuracy of TNM staging in predicting the prognosis of patients with NPC. Serum cystatin C is a cysteine protease inhibitor and has been reported to be a significant predictor to carry prognostic or diagnostic information in human diseases, including various malignant cancers.[17–26] However, a study regarding the predictive value of serum cystatin C on NPC patients treated with IMRT has not been reported yet.

Here, we conducted this retrospective study, with 2077 patients and a median follow-up time of 96.3 months (range from 4.1 to 120.0 months), to evaluate the impact of serum cystatin C on NPC patients treated with IMRT. Our results demonstrated that patients with high serum cystatin C level before antitumor treatment tend to get shorter OS, as well as shorter DFS. Furthermore, in multivariable analysis, we found that the pretreatment level of serum cystatin C level is a significant predictor of inferior prognosis in NPC patients. And the subgroup analysis based on TNM stage revealed that advanced patients with high serum cystatin C level had shorter OS and DFS, which was in accordance with the results inthe whole cohort of our patients.

The molecular role of serum cystatin C level in clinical outcome of NPC remains unknown. Cystatin C genes, sharing some common features with housekeeping genes, are expressed among most human tissues, such as lung, liver, kidney, stomach, pancreas.[30] Most of the cystatin C exist in cerebrospinal fluid, semen, and also in milk, synovial fluid, saliva, tears, serum, and urine.[31] Researchers

believe that the level of cystatin is associated with age.[32–34] Filler et al found that cystatin C is stable among 1~50-year-old people, while its level gets higher in the elderly due to renal impairment.[32] Odden et al reported that older people had a higher level of cystatin than younger people.[33] Stephen et al came to the same conclusion, and suggested that the burden of disease, depressive symptoms, physical inactivity, and BMI were partly to blame.[34] Due to its inhibiting activity on lysosomal cysteine proteinases, some in vitro and in vivo studies have reported that cystatin C acts as a tumor suppressor in some cancers to take control of key steps of cell proliferation, invasion, angiogenesis and metastasis in tumor biological process.[35–37] But different opinions showed that cystatin C can drive the biological process of a plenty of malignancies, such as ovarian cancer,[36] prostate cancer,[38] and so on. The precise molecular role of cystatin C in NPC biological process are still unclear.

In terms of molecular mechanism underlying cystatin C in cancers, Wegiel et al found that serum cystatin C inhibited tumor invasion via MAPK/ERK pathway and had a crosstalk with androgen receptor mediated pathways.[39] Yan et al identified that long noncoding RNA-*SNHG1* directly bound microRNA-338 to upregulate the expression of *CST3* (Cystatin C), leading to promote cancer cell growth.[40] Mori et al found that activated p53 upregulated cystatin C expression through p53 binding sequence in the first intron to increase adriamycin-induced apoptosis.[41] Only one study showed that the level of cystatin C, secreted by epidermal growth factor receptor, was decreased under TGF-α stimulation in NPC cell.[42] A recent study appealed uncontrolled cystatin C may result in tumor progression, as a consequence of unbalanced immune system.[43] The molecular mechanism underlying the relationship of cystatin C and prognosis of NPC patients and whether cystatin C can become a therapeutic target need to be further explored in in vivo and in vitro experiments.

Some limitations in our design should be stated, although our study has clear strengths including the larger database and complete clinical data of patients. Firstly, our study is based on a monocenter, indeed results of this study should be validated by more research institutions. Secondly, the existed selection bias and potential confounding factors in our retrospective study could not be eliminated completely. Thirdly, as stated before, the potential mechanisms should be further investigated.

Conclusion

In conclusion, this is the largest retrospective cohort study with 2077 NPC patients treated with IMRT. We found that high serum cystatin C level was associated with worse prognosis of NPC patients, particularly advanced patients. Serum cystatin C was a significant and independent prognostic predictor of NPC and could guide more effective and accurate clinical therapeutic strategy decision. More future studies are needed to explore the molecular regulatory mechanisms underlying serum cystatin C level and prognosis of NPC patients.

Abbreviations

NPC, nasopharyngeal carcinoma; AJCC, American Joint Committee on Cancer; UICC, International Union against Cancer; OS, overall survival; DFS, disease-free survival; MRI, magnetic resonance imaging; ECT, emission computed tomography; PET/CT, 18F-fluorodeoxyglucose positron-emission tomography/computed tomography; PTV, planning target volume; GTVnx, gross tumor volume of nasopharynx lesion; GTVnd, gross tumor volume of the malignant lymph nodes.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The key raw data have been uploaded onto the Research Data Deposit public platform (http://www.researchdata.org.cn), with the approval number RDDA2021001828. The authors report no conflicts of interest in this work.

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Disclosure

The authors report no conflicts of interest in this work.

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