

RESEARCH ARTICLE

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Compliance with National Guidelines on the Treatment of Stage II–IVB Nasopharyngeal Carcinoma in a Regional Cancer Center of Southern China

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Abstract

Objective: It is unknown whether the treatment provided to patients with stage II-IVB NPC in southern China adheres to the 2015 NCCN guidelines. Consequently, a retrospective analysis was conducted, in order to evaluate the compliance with NCCN guidelines and identify the areas for improvement. **Methods:** The present study was a retrospective study that included patients with stage II-IVB NPC in southern China during the period 2013 and 2014. The treatment regimens were compared with the 2015 NCCN guidelines in order to identify potential noncompliance regarding the treatment for stage II–IVB NPC. The statistical analyses included descriptive statistics, univariate and/or multivariate analysis using SPSS version 16.0.0. **Results:** A total of 215 patients, including 166 men (77.21%) and 49 women (22.79%), were involved in the analysis. Although the overall rate of noncompliance with the NCCN recommendations was 23.26%, the noncompliance rate of concurrent chemoradiation (CCRT), induction of chemotherapy (IC) followed by CCRT and CCRT followed by adjuvant chemotherapy (AC) was 7.02%, 39.76% and 50.00%, respectively. Univariate analysis indicated that NCCN noncompliance regarding the treatment for stage II-IVB NPC did not exhibit a significant correlation with the parameters age, gender, insurance status, education profile, first clinic department, careers, comorbidities and overall clinical stage, but it indicated a significant association with the therapeutic schedule ($P < 0.05$). The multivariate analysis indicated that the NCCN noncompliance regarding the treatment for stage II–IVB NPC exhibited a statistically significant difference between CCRT and CCRT followed by AC (OR=0.10, 95% CI 0.04-0.27, $P < 0.05$), although the difference noted between CCRT and IC followed by CCRT was not significantly different (OR=1.71, 95% CI 0.50-5.87, $P = 0.40$). **Conclusions:** The use of specific therapeutic schedules may affect the noncompliance with NCCN guidelines regarding the treatment for stage II–IVB NPC in southern China, notably with regard to the treatment schedule of CCRT followed by AC.

Keywords: Nasopharyngeal neoplasms- compliance- guideline

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Introduction

Nasopharyngeal carcinoma (NPC) is a rare disease encountered worldwide with an incidence of occurrence of 0.5 to 2 per 105 population in the United States. The disease is a leading form of cancer in the populations of southern China, with a reported annual incidence of 30-80 per 100,000 (Chang and Adami, 2006; Jemal et al., 2011). The majority of patients with NPC present with locally advanced disease, due to high metastatic rate of NPC that occurs at an early stage in the regional lymph nodes (Ho et al., 2012). The clinical symptoms of nasopharyngeal carcinoma are usually detected at the late stages of the disease.

The National Comprehensive Cancer Network

(NCCN) guidelines of NPC were established in order to improve the quality of NPC treatment and reduce the cost of treatment. However, noncompliance with the NCCN guidelines is frequently encountered, as a result of inadequate dose intensity of radiotherapy and/or chemotherapy and inadequate number of cycles of chemotherapy treatment (Lewis et al., 2010; Schwam et al., 2016). Inadequate compliance may reduce the quality of NPC treatment and increase the incidence of radiation or drug resistance of NPC patients (Tan et al., 2016). Hence, adequate treatment regimens delivered to NPC patients and complete compliance with guidelines are vital parameters in order to prevent the radiation or drug resistance to the NPC treatment.

A number of studies have demonstrated that the

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adherence to cancer guidelines is associated with improved survival outcomes in patients with cancer (Boland et al., 2013; Worhunsky et al., 2015; Schwam et al., 2016). Furthermore, the studies that have examined the assessment of compliance with the treatment for stage II–IVB NPC patients have not been conducted in southern China. The present study aimed to evaluate the compliance with adequate radiotherapy regimens. In addition, the compliance with adequate chemotherapy programs recommended by the NCCN guidelines was explored. The overall objective of the study was to promote the current performance of the doctor on the treatment of stage II–IVB NPC and the quality of the medical care provided to stage II–IVB NPC patients.

Materials and Methods

Summary of NCCN treatment guidelines for NPC

The NCCN guidelines that were established during the period 2004 and 2006 (Forastiere et al., 2004; Forastiere et al., 2005; Forastiere et al., 2006) for NPC demonstrated that patients with stage I and certain patients with stage II NPC should receive the treatments of definitive radiation (RT) to the main lesion and selective radiation to the neck. The patients that develop distant metastases are instructed to receive initially chemotherapy and subsequently RT, provided a complete response is noted. The patients that do not fall in the aforementioned categories are instructed to receive concurrent chemoradiation (CCCT) followed by chemotherapy, with a neck dissection for residual nodal lesion. Despite this guideline, it has been shown that resection does not contribute therapeutically to the primary lesion. The difference noted in the case of the 2015 NCCN guidelines (Pfister et al., 2015) is that patients with stage II–IVB NPC may receive CCCT alone, induction chemotherapy (IC) followed by concurrent chemoradiation (CCRT) and/or CCRT followed by adjuvant chemotherapy (AC). The patients that exhibit distant metastases may receive CCRT or chemotherapy followed by adjuvant RT or chemoradiation.

Data collection

A retrospective review of NPC patients admitted to inpatient care was conducted between November 2013 and August 2014 in the Guangxi cancer center that is located in Nanning, Guangxi, China.

The inclusion and exclusion criteria were established before examining the medical records of NPC patients. The patients were considered eligible and were included in the study, based on the following criteria: (1) patients who were newly diagnosed as NPC confirmed by histological results, (2) patients with NPC who were in the stage of II–IVB (the 7th edition of UICC/AJCC staging system, 2010), (3) patients who completed the process of radiotherapy. The exclusion criteria were as follows: (1) patients who requested hospital discharge, (2) patients who participated in clinical trials, (3) patients with any missing data for the parameters age, gender, clinical TNM classifications and/or treatment-related data such as receipt of chemotherapy, RT, and chemoradiation.

The essential data for the study conduct were extracted

from the electronic medical record system of the Guangxi cancer center by two independent investigators (Jia-xiang Ye, Xia Liang), according to the aforementioned inclusion and exclusion criteria. The data were checked and potential discrepancies were resolved following a consensus between the two investigators. The following demographic and clinical parameters were collected for each patient: age, gender, insurance status, education, clinical TNM classifications, overall clinical stage, therapeutic schedules, dose of RT, drug dose of chemotherapy and drug cycle of chemotherapy.

The data that corresponded to the treatment of the patients were compared with the 2015 NCCN guidelines (Pfister et al., 2015) by the two investigators independently. A total of three therapeutic schedules, including CCCT alone, IC followed by CCRT and CCRT followed by AC, were selected for NPC patients with stage II–IVB disease. Noncompliance was defined as the failure to adhere to either radiotherapy or chemotherapy that included the treatment schedule, dose and cycle, according to the guidelines. In addition, noncompliance was the failure to comply with the treatment guidelines, regarding neck cancer.

Statistical analysis

The statistical analysis was carried out using SPSS version 16.0.0 (Chicago, IL, USA). Standard descriptive statistics were used to summarize patient demographic and treatment-related data. The count data were in the form of percentages, whereas the measurement data were in the form of standard deviation and/or average/median. A chi-square test was carried out for the univariate analysis of the determination of the risk factors associated with the compliance with the NCCN guidelines. The multivariate logistic regression model was carried out for the multivariate analysis using the inclusion method of “enter” for the various variables. The tests used were two-sided and the final cut-off for significance was set at $P \leq 0.05$.

Results

A total of 239 NPC patients were identified in a regional cancer center of southern China between November 2013 and August 2014. A total of 14 patients that did not present with the II–IVB stage of the disease were excluded, whereas ten patients were ruled out due to missing data for clinical TNM classifications. As a result, 215 patients, including 166 men (77.21%) and 49 women, (22.79%) were involved in the analysis. The mean age of the disease presentation was 46.29 years (median age, 46.00 years; age range, 11.00–75.00 years) in the cohort. The classification of the disease was conducted according to the 7th edition of UICC/AJCC staging system in 2010. The clinical stages of the disease were classified as II, III, IVa, and IVb and comprised 9.30%, 33.95%, 44.65%, and 12.09% of the study population, respectively. The demographic data are summarized in Table 1.

Univariate analysis indicated that the noncompliance with the NCCN guidelines regarding the treatment for stage II–IVB NPC was not associated with age

Table 1. Patient Demographics and Statistical Analyses

Variable	No. (%) of Patients(n=215)	Non-compliant rate	P (χ^2)	Multivariable analysis OR(95%CI)	P
Age(years)			0.9		
≤35	39/215 (18.14)	10/39(25.64)*			
>35 and ≤60	152/215 (70.70)	35/152(23.03)		0.89(0.20-3.86)	0.87
>60	24/215 (11.16)	5/24(20.83)		1.00(0.28-3.52)	0.99
Gender			0.54		
Female	49/215 (22.79)	13/49(26.53)*			
Male	166/215 (77.21)	37/166(22.29)		1.41(0.59-3.35)	0.44
Insurance status			0.31		
Urban medical insurance	19/215 (8.84)	2/19(10.53)*			
Rural cooperative medical insurance	148/215 (68.84)	38/148(25.68)		0.40(0.06-2.47)	0.32
self-paying	48/215 (22.33)	10/48(20.83)		1.01(0.26-3.83)	0.99
Education			0.19		
Elementary school	62/215 (28.84)	14/62(22.58)*			
High school	112/215 (52.09)	27/112(24.11)		0.18(0.02-2.12)	0.17
College	36/215 (16.74)	6/36(16.67)		0.21(0.02-2.16)	0.19
others	5/215 (2.33)	3/5(60.00)		0.18(0.02-2.27)	0.19
Clinic department at first careers			0.48		
Radiotherapy	190/215 (88.37)	42/190(22.11)*			
Internal medicine	11/215 (5.12)	3/11(27.27)		1.16(0.30-4.46)	0.83
Surgery	14/215 (6.51)	5/14(35.71)		0.51(0.06-4.47)	0.54
Peasant	116/215 (53.95)	30/116(25.86)*	0.61		
Office clerk	50/215 (23.26)	10/50(20.00)		1.02(0.26-4.04)	0.98
Worker	31/215 (14.42)	5/31(16.13)		0.99(0.19-5.25)	0.99
others	18/215 (8.37)	5/18(27.78)		0.63(0.11-3.61)	0.6
Comorbidities			0.33		
No	147/215 (68.37)	37/147(25.17)*			
Yes	68/215 (31.63)	13/68(19.12)		1.60(0.67-3.81)	0.29
T-classification&			0.54		
1	10/215 (4.65)	2/10(20.00)			
2	39/215 (18.14)	11/39(28.21)		-	-
3	59/215 (27.44)	10/59(16.95)		-	-
4	107/215 (49.77)	27/107(25.23)		-	-
N-classification &			0.47		
0	4/215 (1.86)	0/4(0.00)			
1	73/215 (33.95)	19/73(26.03)		-	-
2	111/215 (51.63)	23/111(20.72)		-	-
3	27/215 (12.56)	8/27(29.63)		-	-
Overall stage			0.53		
II	20/215 (9.30)	5/20(25.00)*			
III	73/215 (33.95)	13/73(17.81)		3.22(0.65-16.03)	0.15
IVa	96/215 (44.65)	24/96(25.00)		1.06(0.33-3.37)	0.92
IVb	26/215 (12.09)	8/26 (30.77)		1.14(0.37-3.45)	0.82
Therapeutic schedule			<0.05		
CCRT	114/215 (53.02)	8/114(7.02)*			
CCRT + AC	18/215 (8.37)	9/18(50.00)		0.10(0.04-0.27)	<0.05
IC+ CCRT	83/215 (38.60)	33/83(39.76)		1.71(0.50-5.87)	0.4

RT, radiotherapy; CCRT, concurrent chemoradiation; IC, induction chemotherapy; AC, adjuvant chemotherapy; IC+ CCRT: IC followed by CCRT; CCRT+ AC: CCRT followed by AC; CCRT, CCRT alone *The references of variable factors &As overall clinical stage is from T–classification and N–classification, various variables of multivariate analysis included all the factors except T–classification and N–classification.

Table 2. Rates(No. (%) of Patients) of National Comprehensive Cancer Network (NCCN) Noncompliance and Reasons

Items	Therapeutic method [No. (%) of Patients]		
	IC+CCRT (n=83)	CCRT+AC (n=18)	CCRT (n=114)
Overall noncompliance	50/215(23.26)		
Noncompliance of different therapeutic schedule	33(39.76)	9 (50.00)	8 (7.02)
Reason for noncompliance			
Inadequate dose of RT	0 (0)	0 (0)	1 (0.88)
Inadequate drug dose of IC or AC	2 (2.41)	1 (5.56)	NA
Inadequate drug cycle of IC or AC	33 (39.76)	9 (50.00)	NA
Inadequate drug dose of CC	1 (1.20)	1 (5.56)	1 (0.88)
Inadequate drug cycle of CC	8 (9.64)	1 (5.56)	6 (5.26)

Note: RT, radiotherapy; CCRT, concurrent chemoradiation; IC, induction chemotherapy; AC, adjuvant chemotherapy; CC, concurrent chemotherapy; NA, not available; IC+ CCRT: IC followed by CCRT; CCRT+ AC: CCRT followed by AC; CCRT: CCRT alone.

($P=0.90$), gender ($P=0.54$), insurance status ($P=0.31$), education profile ($P=0.19$), first clinic department ($P=0.48$), careers ($P=0.61$), comorbidities ($P=0.33$), T-classification($P=0.54$), N-classification($P=0.47$) and overall clinical stage($P=0.53$). In contrast to the aforementioned observations, noncompliance with the NCCN guidelines regarding the treatment for stage II-IVB NPC indicated a significant association with the therapeutic schedule ($P<0.05$). The variables of the multivariate analysis included all the factors except T-classification and N-classification. The multivariate analysis showed that the noncompliance with the NCCN guidelines regarding the treatment with the stage II-IVB NPC exhibited a significant difference between CCRT and CCRT followed by AC (OR=0.10, 95% CI 0.04-0.27, $P<0.05$), whereas no significant difference was noted between CCRT and IC followed by CCRT (OR=1.71, 95% CI 0.50-5.87, $P=0.40$) (Table 1).

A total of 51 out of 215 (23.26%) patients who presented with stage II-IVB NPC received treatment that was not in compliance with the NCCN guidelines. As regards the therapeutic schedule, the noncompliance rate of induction of CT and concurrent CR was 39.76%, whereas the respective rate for the concurrent CR and adjuvant CT was 50.00%, and for the concurrent CR 7.02%. The detailed reasons for the noncompliance with the treatment are summarized in Table 2.

Discussion

The NCCN Guidelines in oncology recommend specific types of treatment for patients, according to the evidence provided by a consensus procedure for 97% of cancers. Despite the guidelines, approximately 43% of head and neck cancer patients had received NCCN-discordant treatment in a previous study (Lewis et al., 2010). Consequently, it is imperative to develop a uniform quality indicator in order to optimize the quality of medical treatment. In the present study, the parameter compliance with the NCCN guidelines was used as an indicator of treatment quality assessment.

In the present study, a total of 215 new stage II-IVB NPC patients were included for analysis in a regional cancer centre of southern China. A total of 51 out of 215

patients (23.6%), were administered treatment that was not compliant with the NCCN guidelines. As regards the different therapeutic schedules, the noncompliance rate of IC followed by CCRT, and of CCRT followed by AC and CCRT alone was 39.76%, 50.00%, and 7.02%, respectively. The data suggested that the rate of noncompliance with the NCCN guidelines may be elevated in the regional cancer center. In addition, univariate and multivariate analysis demonstrated that the therapeutic schedules exhibited a significant association with the compliance with the NCCN guidelines regarding the treatment for stage II-IVB NPC. The latter finding suggests that different therapeutic schedules may affect the compliance with the NCCN guidelines regarding the treatment, notably the treatment schedule of CCRT followed by AC.

CCRT is currently used as the standard treatment for locally advanced NPC. Although substantial improvements have been reported for the regional control according to the Response Evaluation Criteria in Solid Tumors (Eisenhauer et al., 2009), the progression free survival (PFS) and the overall survival (OS) of patients with locally advanced NPC, the metastasis of the cancer cells to distant tissues comprises a major disadvantage that can lead to treatment failure (Xu et al., 2012; Zhong et al., 2013; Xu et al., 2014). Additional cycles of chemotherapy, such as the addition of adjuvant or induction chemotherapy to CCRT, may improve the metastatic spread of the cancer to distant areas in patients with a high risk of treatment failure (Sun et al., 2016). However, additional treatment may increase further the treatment-related toxicities.

In the present study, the stage II-IVB NPC patients that were administered the two therapeutic approaches (IC followed by CCRT and CCRT followed by AC) exhibited greater noncompliance rate compared with the patients that received CCRT monotherapy. The inadequate drug cycle of the adjuvant or induction chemotherapy was the primary reason for the aforementioned observations (Table 2). This finding may be associated with the more severe grade 3-4 toxicities of chemotherapy or the patient refusal to participate to the recommended treatment. Song et al., (2015) conducted a multi-institutional retrospective study in order to compare CCRT alone with IC followed

by CCRT and reported greater incidence of \geq grade 4 hematological toxicity in the IC followed by the CCRT arm. Chen et al., (2012) conducted a phase III multicentre randomized controlled trial that compared CCRT plus AC with CCRT alone in patients with locally advanced NPC. The study demonstrated that 37% of the participants did not complete all cycles of AC, while the refusal of the patients to participate in the treatment was the main reason for the incomplete adjuvant chemotherapy. Furthermore, Lewis et al., (2010) demonstrated that 15% of patients with head and neck cancer refused to receive appropriate treatment that in turn resulted in noncompliance with the NCCN guidelines.

Schwam et al., (2016) assessed 1,741 NPC patients in the National Cancer Data Base for compliance with the NCCN guidelines. The authors reported that the overall rate of noncompliance with the NCCN recommendations was 25.9%, whereas the rate with stages II–IVB NPC was 24.1%, which is in accordance with the findings reported in the present study. However, independent risk factors in the multivariate analysis conducted in the study by Schwam et al., (2016) did not include the therapeutic schedules compared with the present study that analyzed thoroughly the different therapeutic schedules. The toxicities associated with the different therapeutic schedules were apparent that resulted in different treatment compliance (Hui et al., 2009; Zhong et al., 2013). The requirement for the analysis of the different therapeutic schedules was based on the determination of specific causes for noncompliance with the treatment schedule. In addition, the present study demonstrated a therapeutic schedule that affected significantly the NCCN compliance. Finally, in the present study a further analysis of the causes of noncompliance was carried out and the inadequate drug cycle of IC or AC was identified as the main contributor that affects the compliance.

Lewis et al., (2010) evaluated the treatment of 566 patients with recurrent or persistent head and neck cancer who were referred to the Anderson Cancer Center. The authors of the latter study reported that 43.0% of patients received treatment that deviated from the NCCN recommendations. Despite this finding, 9 patients exhibited NPC in the study population examined. The present study included a larger number of NPC patients compared with Lewis et al., (2010).

Despite the aforementioned advantages the present study had several limitations. The relatively small number of patients with stage II–IVB NPC that was included in the study represented a highly selected population that may exhibit a different response to the treatment compared with the general population and various therapeutic regimens have certain internal differences. Those may raise the risk of selective bias. Furthermore, the present study can be expanded to include additional national and institutional NPC guidelines (Saba et al., 2016). The selection of the NCCN recommendations was based on the broad application and appeal to an international population. In addition, the study may be further improved by the inclusion of a greater number of centers, rather than focusing on a single cancer center. This selection can reduce the noncompliance rate compared to community

hospitals, as reported at an earlier study by Benasso et al., (2003). Moreover, due to a short period of time after treatment, survival analysis was not conducted.

In conclusion, the use of different therapeutic schedules may affect the compliance with the NCCN guidelines regarding the treatment for stage II–IVB NPC, notably for the treatment schedule of CCRT followed by AC.

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Statement conflict of Interest

All patients provided written informed consent for their participation in the study. The authors declare that they have no conflicts of interest.

Acknowledgements

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and ensure that the safety and well-being of the participants are safeguarded and that the integrity of the data is preserved. Ethical approval was obtained from the medical ethics committee at the Guangxi cancer center, prior to the initiation of the study.

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