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Detection of Stage I nasopharyngeal carcinoma by serologic screening and clinical examination

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Abstract

In a prospective study, 42 048 adults residing in Zhongshan City, Guangdong, China, were followed for 16 years, and 171 of them developed nasopharyngeal carcinoma (NPC). Although Epstein-Barr virus (EBV) antibody levels of the cohort fluctuated, the antibody levels of 93% of the patients with NPC were raised and maintained at high levels for up to 10 years prior to diagnosis. This suggests that the serologic window affords an opportunity to monitor tumor progression during the preclinical stage of NPC development, facilitating early NPC detection. We reviewed the clinical records of the 171 patients with NPC in the prospective study to assess the efficacy of early NPC detection by serologic screening and clinical examination. Of the 171 patients, 51 had Stage I tumor (44 were among the 73 patients detected by clinical examination and 7 were among the 98 patients presented to outpatient department). Initial serologic screening predicted 58 (95.1%) of the 61 patients detected within 2 years. The risk of the screened population (58/3093) raised 13 times relative to cohort (61/42 048) during this period. Clinical examination detected all the 58 predicted cases, and 35 (60.3%) of which were diagnosed with Stage I tumor. The serologic prediction rate fell to 33.6% (37/110) 2 to 16 years after screening. The proportion of cases detected by clinical examination fell to 40.5% (15/37). The proportion of Stage I tumors among the cases detected by clinical examination during both periods remained at about 60%. We concluded that early detection of NPC can be accomplished by repeated serologic screening to maintain high prediction rates and by promptly examining screened subjects to detect tumors before the symptoms develop.

Key words NPC, localized tumor, cancer screening, preclinical cancer

Nasopharyngeal carcinoma (NPC) is mainly a non-keratinizing, squamous cell carcinoma [1]. It mainly afflicts middle-aged men and is a common cancer among Chinese, Greenland Eskimos, and North Africans[2]. Tumor cells from patients with NPC usually harbor the Epstein-Barr virus (EBV) [3], a human herpes virus classified as a Type I human tumor virus [4]. In addition, most patients have elevated levels of EBV antibodies [5-8]. Findings that the viral genome was already present in the pre-invasive tumor lesions in these patients [9,10] and that serum levels of EBV antibodies were elevated to high levels for protracted periods before diagnosis [11] have led to the proposal that EBV might be involved in the preclinical phase of the development of NPC [12,13]. NPC can be successfully treated when the tumor is confined to the nasopharynx, with a poor prognosis attending further tumor progression involving adjacent soft and hard tissue, cervical lymph nodes, and beyond[14-17]. However, clinical manifestation is usually delayed, and most patients are diagnosed with advanced NPC.

In a prospective study between December, 1986 and December, 2002, involving 42 048 adults residing in Zhongshan City in south China, Ji *et al.* [18] found that serum levels of EBV antibodies of patients with NPC were raised and maintained at high levels for up to 10

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years before diagnosis. They estimated the mean duration of this preclinical serologic window to be 37 ± 28 months. During this interim, individuals exhibited no signs or symptoms of the tumor. Because such a serologic change occurred among 93% of the cases, they suggested it could afford a convenient and objective window period to monitor tumor progression during the preclinical stage of NPC development. Indeed, serologic screening predicted 55% of the cases detected among the cohort, and follow-up of the screened population significantly advanced diagnosis of the cases to earlier disease stages. Hence, this study aimed to determine how this preclinical window could be exploited for early detection of NPC.

Patients and Methods

Patients

In the prospective study of Ji *et al.*[18], the 42 048 subjects were recruited over 18 months, with each individual screened for serum levels of VCA IgA antibody (immunoglobulin A antibody against EBV viral capsid antigens) and clinically examined, including an indirect mirror examination of the nasopharynx. The individuals with an elevated VCA IgA antibody titer ⩾ 1:10 (designated sero-positive) and a comparable number of randomly selected subjects with a VCA IgA titer < 1:10 (designated sero-negative) were clinically and serologically evaluated 8 times over the following 10 years. NPC cases detected or presented to outpatient departments were confirmed by histopathology. Disease status of patients at the time of diagnosis was assessed on the basis of CT findings according to the 1997 UICC staging. Treatment outcome was assessed by reviewing the clinical records of patients for at least 4 years after treatment or until death.

Statistical methods

Disease-specific and relapse-free survival was analyzed with the Kaplan-Meier method. The influence of patient's age, sex, and disease status at diagnosis on treatment outcomes (clinical remission, loco-regional and distant relapse, treatment-associated neurological complications, and survival) were analyzed by Chi-square test using SPSS13.0 software.

Results

A total of 42 048 adults were recruited over 18 months since December 1986, when each was clinically examined and tested for serum levels of VCA IgA. The serologic screening identified 3093 subjects with elevated titers of VCA IgA antibody ⩾ 1:10 (designated sero-positive). These sero-positive subjects and a comparable number of randomly selected sero-negative subjects with low levels of VCA IgA ⩽ 1:10 were clinically examined and serologically tested 8 times in the following 10 years. A total of 171 non-keratinizing NPC cases were detected from the cohort over the following 16 years ending December 2002: 73 cases were detected by clinical examination and 98 presented to outpatient department (Table 1). According to the 1997 UICC staging, 51 cases were diagnosed as Stage I tumors, and 120 as Stage II, III, or IV tumors. The two groups of patients were of similar age and sex distribution. Forty-four (86.3%) of the 51 Stage I tumors were asymptomatic and were detected by clinical examination.

All patients received radiotherapy, and 3 with advanced tumors also received adjunct chemotherapy. The clinical records were available for 168 of the patients covering at least 4 years after treatment or until death.

Table 1. Disease status of 171 patients with nasopharyngeal carcinoma (NPC) at diagnosis

Item	Disease status at diagnosis		
	Stage I	Stage II, III, or IV	Total
NPC patients [cases (%)]	51 (29.8)	120 (70.2)	171
Age (years)			
Mean ± SD	49 ± 17	50 ± 18	49 ± 20
Median (range)	49 (31–67)	50 (32–71)	49 (31–71)
Male : female	2.1	2.5	2.4
Presented to OPD [cases (%)]	7 (7.1)	91 (92.9)	98
Clinical examination [cases (%)]	44 (60.3)	29 (39.7)	73

Disease status was staged according to the 1997 UICC staging (1997): Stage I tumors were localized tumors, Stage II, III or IV tumors had progressed beyond the nasopharynx to involve adjacent soft and/or hard tissues and/or cervical lymph nodes. Symptomatic cases were detected when patients presented to outpatient department (OPD). Asymptomatic cases were detected by routine clinical examination, including an examination of the nasopharynx by endoscope or by indirect mirror examination. SD, standard deviation.

The records revealed that 161 patients achieved clinical remission, 6 developed treatment-related complications, 24 developed local relapse, and 25 developed distant relapse (Table 2). The overall and relapse-free 5-year survival rates of the cohort were 54.0% and 52.1%, respectively. Compared with the advanced tumors, Stage I tumors were associated with significantly higher clinical remission rate (100%) and overall and relapse-free survival rates (94.0% and 89.7%), and significantly lower local and distant relapse rates (6% and 0%), whereas the rates of treatment-related complications were similar for Stage I and the more advanced tumors.

The above results confirmed previous findings that Stage I tumor can be successfully treated, but further progression is attended by poor prognosis [14-17]. Since 86% of Stage I tumors are asymptomatic, detection depends on clinical examination of apparently health subject. Table 3 shows that Serologic screening contributed to detection of Stage I tumors by identifying a subpopulation with 7.5 times higher risk of NPC than the general cohort (Table 3). It predicted 95 (55.5%) of the 171 cases detected from the cohort over 16 years. Clinical examination of this subpopulation in the first 10 years detected 73 (76.8%) of the 95 predicted cases, with 44 (60.3) of which being diagnosed as Stage I tumors. Higher efficacy for detecting Stage I tumors was observed in the first 2 years after screening. During this period, screening predicted 58 (95.0%) of the 61 cases and relative NPC risk of the subpopulation increased to 12.9. All the 58 predicted cases were detected by clinical examination, with 35 (60.3%) of which being diagnosed as Stage I tumors. In the subsequent 2 to 16 years after screening, however, the relative risk of the screened subpopulation declined to 4.7. Only 37 (33.6%) of 110 NPC cases were detected from the screened subpopulation during this period. Clinical examination of the subpopulation detected fewer cases, with most cases presented to outpatient department. The proportion of Stage I tumors among the asymptomatic cases detected by clinical examination during the early and later periods remained the same.

Discussion

The treatment of NPC critically depends on its early detection, requiring the clinical examination of apparently healthy subjects, including an examination of the nasopharynx. EBV serologic screening facilitates such efforts by identifying subjects at a higher risk of NPC than general cohorts. Ji *et al.* [18] showed that screening identifies tumors at pre-clinical development when EBV antibody levels are raised and maintained at elevated levels for up to 10 years before diagnosis. They estimated that 93% of the cases in the present series would enter this preclinical serologic window and concluded that the serologic window is a common event during the preclinical stage of tumor development. The

Table 2. Treatment outcomes of the 168 patients with nasopharyngeal carcinoma at different stages

Item	Disease status at diagnosis			*P*
	Stage I	Stage II, III, or IV	Total	
Clinical remission [cases (%)]	50 (100)	111 (94.0)	161 (95.8)	< 0.01
Complications [cases (%)]	2 (4.0)	4 (3.3)	6 (3.6)	> 0.05
Local relapse [cases (%)]	3 (6.0)	21 (17.8)	24 (14.3)	< 0.05
Distant relapse [cases (%)]	0 (0.0)	25 (21.2)	25 (14.9)	< 0.01
5-year relapse-free survival (%)	89.7	50.8	52.1	< 0.001
5-year overall survival (%)	94.0	56.6	54.0	< 0.001

Table 3. Efficiency of early NPC detection by EBV serologic screening and routine clinical examination of screened subpopulation

Efficacy of early NPC detection	Years after screening		
	0 to 16 years	0 to 2 years	2 to 16 years
NPC risk of cohort (cases/100 000 person-year)	2.5 (171/42 048)	7.3 (61/42 048)	1.9 (110/42 048)
NPC risk of screened subpopulation (cases/100 000 person-year)	19.3 (95/3093)	93.8 (58/3093)	8.5 (37/3093)
Relative NPC risk of screened subpopulation	7.6	12.9	4.5
Proportion of cases predicted by serologic screening (%)	55.5 (95/171)	95.0 (58/61)	33.6 (37/110)
Proportion of predicted cases detected by clinical examination	76.8 (73/95)	100 (58/58)	40.5 (15/37)
Proportion of Stage I cases detected by clinical examination	60.3 (44/73)	60.3 (35/58)	60.0 (9/15)

A total of 42 048 adults were serologically screened, and 3093 of them were found to have elevated VCA IgA titers ($\geqslant$ 10) and were followed up by clinical examinations.

cases predicted by screeni ng largely comprised those that had already entered the window and hence they were at a more advanced stage of tumor development than those sero-negative cases which had not entered the serologic window yet. The accumulation of such relatively advanced tumors among the sero-positive subjects resulted in an elevated NPC risk of the screened subpopulation by 12.9 times compared to the general cohort and accounted for 95% of the cases detected from the cohort within the first 2 years after screening. On the other hand, the authors[18] showed that the cases detected after the first 2 years were increasingly replaced by those detected among the sero-negative subjects which entered the serologic window after the initial screening. Consequently, the relative risk of NPC of the screened subpopulation fell to 4.7 and the prediction rate fell to 33% in 2 to 16 years after screening. Routine clinical examinations of the screened subpopulation conducted during this period yielded fewer asymptomatic cases than in the earlier period, because 59.5% of the predicted cases presented symptomatically to outpatient department during the interim periods. The onset of NPC is innocuous. Consequently, Stage I tumors comprised about 60% of asymptomatic cases in the present series , and the remaining 40% of the cases had already progressed to more advanced stages. The proportions of Stage I and the more advanced tumors detected by clinical examination remained similar during both the earlier and later periods.

In conclusion, detection of Stage I NPC tumors, which is important for successful treatment, depends on clinical examination of apparently healthy subjects and that this could be accomplished by repeated serologic screening of apparently healthy subjects to monitor tumor progression during preclinical stage of tumor development and prompt clinical examination of screened population.

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