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Original Article

Paraneoplastic dermatomyositis accompanying nasopharyngeal carcinoma: a systematic review and meta-analysis

鼻咽癌相關的腫瘤伴生皮肌炎：系統性文獻回顧和統合分析

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This systematic review and meta-analysis investigated the prognostic value of paraneoplastic dermatomyositis on the survival of patients with nasopharyngeal carcinoma (NPC). The combined hazard ratio (HR) is 1.43 [95% confidence interval (CI):0.98-2.10, p:0.06]. There was a decreased 3-year survival in NPC cases with dermatomyositis [risk ratio (RR) :0.86, 95% CI:0.74-1.01, p:0.07; risk difference (RD):-0.11, 95% CI:-0.22-0.01, p:0.06] although it was not significantly associated with 5-year survival (RR:0.89, 95% CI:0.71-1.13, p:0.34; RD:0.06, 95% CI:-0.19-0.07, p:0.34). All reported NPC cases accompanying paraneoplastic syndrome were type II non-keratinising carcinomas.

本系統性文獻回顧和統合分析研究了腫瘤伴生皮肌炎伴對鼻咽癌患者存活的預後價值。綜合危險比為 1.43 [95% CI:0.98-2.10, p:0.06]，當中可見皮肌炎降低了鼻咽癌患者的三年生存期 [RR: 0.86, 95% CI:0.74-1.01, p:0.07; RD:-0.11, 95% CI:-0.22-0.01, p:0.06]，但與五年生存率無明顯關聯（RR:0.89, 95% CI:0.71-1.13, p:0.34; RD:0.06, 95% CI:-0.19-0.07, p:0.34）。文獻回顧中所有伴隨副腫瘤綜合徵的鼻咽癌病例均為第二型非角化癌。

Keywords: Corticosteroids, dermatomyositis, nasopharyngeal carcinoma, prognosis

關鍵詞：皮質類固醇、皮肌炎、鼻咽癌、預後

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Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that arises from epithelial cells of the nasopharynx.[1,2] A small percentage of NPC patients present with paraneoplastic syndrome and less than 0.1% NPC are associated with dermatomyositis (DM).[3,4] The prognostic value of DM on the survival of NPC patients warrants further research although there have been few studies on this issue.[5-8] Here, we performed the first meta-analysis of published studies to quantitatively review the prognostic value of DM on the survival of patients with NPC.

Material and methods

Literature search

We performed a systematic literature review after the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement and the Cochrane Handbook for Systematic Reviews of Interventions.[9] We systematically searched PubMed, MEDLINE, Cochrane Library, CNKI (China National Knowledge Infrastructure) Library to identify studies published from 1980 that examined the association of DM with the prognosis of NPC patients. The bibliographic search was performed by two reviewers in May 6, 2019. The following search terms were used: "dermatomyositis" AND "nasopharyngeal carcinoma". Articles written in English or Chinese were included. All original articles on the topic were retrospective study. Five-year survival and 3-year survival were the primary end points of interest.

Studies were selected by two reviewers. Original studies were selected if they met the following criteria: 3-year survival and 5-year survival were provided and control group was included in the study. Studies without enough data were excluded from analysis.

Data extraction

Each included study was reviewed in full by two investigators. The following information was extracted: number of enrolled patients, number of patients included in the primary analysis, key patient characteristics, 3-year survival, 5-year survival. Data were independently cross-checked.

Statistical analysis

The trial-level analysis incorporated 3-year survival and 5-year survival as defined and reported in the published trials. Hazard ratio (HR), risk ratio (RR) and risk difference (RD) were used to quantify the prognostic effect.

Statistical pooling of effect measures was based on the level of heterogeneity among studies, which was assessed with the Cochrane Q test and the I2 statistic. No significant heterogeneity was indicated by $P>0.1$ in Cochrane Q tests and a ratio less than 50% in I2 statistics. HR was calculated using the fixed-effects model inverse variance method.[10,11] RR and RD were calculated using the Mantel-Haenszel method under the fixed-effects model.[10,11] Publication bias that included a small-study effect was evaluated by visual inspection of funnel plots and Egger's test.[10,11] Statistical analyses were performed using Review Manager, version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark) or STATA v.13.0 (College Station, TX, USA). $P\geq0.05$ was considered significant.

Results

Study characteristics

As shown in Figure 1, a total of 300 articles were identified initially using the above search strategy. Three articles written in English and six articles written in Chinese included control group. All those studies were retrospective studies. After further review, five articles were excluded because data in those articles should

be included in the left articles. Finally, four studies were selected for the meta-analysis.[5-8] Three studies were paired studies,[6-8] and one was a controlled study.[5] All were carried out in southern China.

HR of DM on survival

Four studies were selected for the meta-analysis (5-8). Overall, the meta-analysis comprised 119 patients in DM accompanying NPC (NPC with DM) group and 420 patients in NPC without DM (NPC only) group. Table 1 lists the identified studies and their main characteristics. The combined HR of 1.43 [95% confidence interval (CI): 0.98-2.10, p:0.06] suggests that DM may have an impact on survival in NPC patients (Figure 2A). Visual inspection of the corresponding funnel plot revealed no publication bias (Figure 2B).

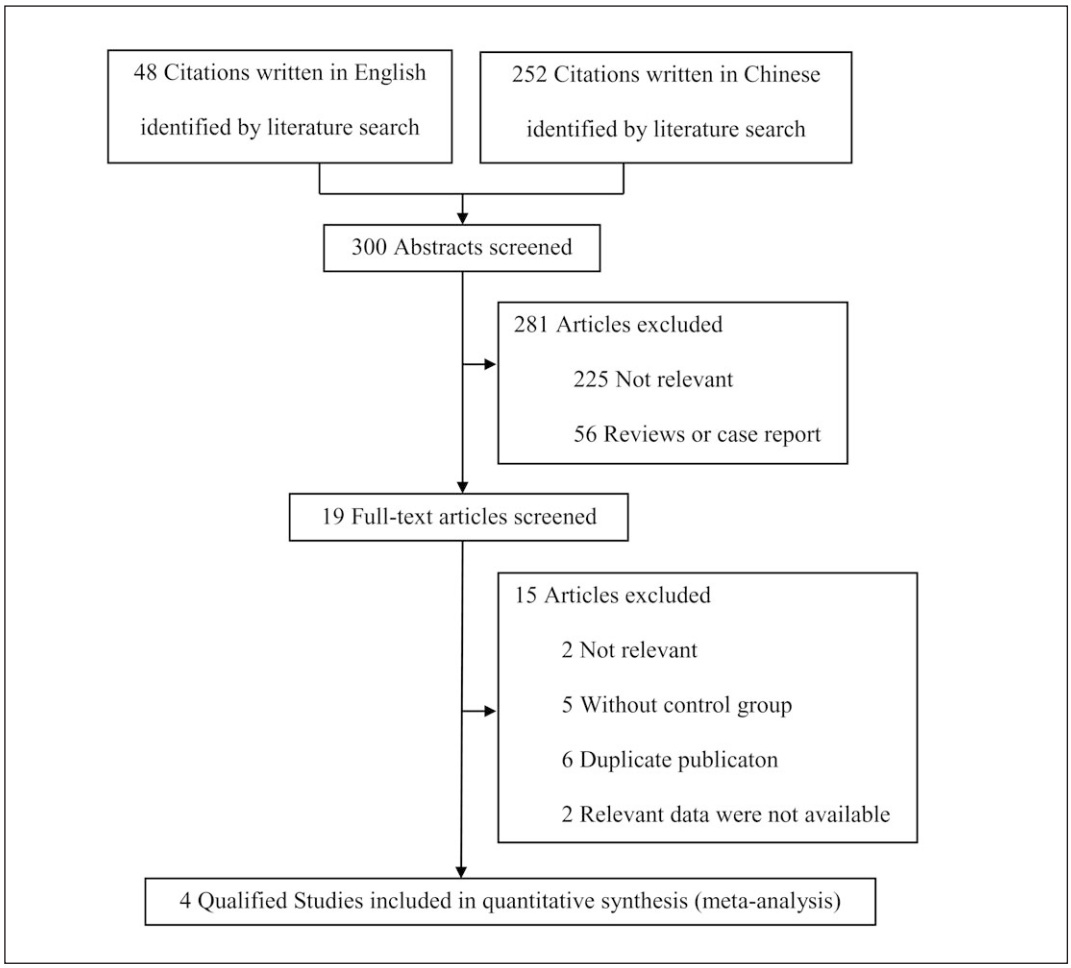

Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow chart.

Table 1. Characteristic of the studies included in the meta-analysis

First author, year of publication	Country	Number of patients	HR (95% CI)
Teo, P. 1989(5)	China	317	3.43 (1.16-10.14)
Ren, ZP. 2001(6)	China	24	1.25 (0.44-3.55)
Han, H. 2005(7)	China	26	1.22 (0.49-3.04)
Huang, PY. 2014(8)	China	172	1.29 (0.78-2.13)

HR=hazard ratio; CI=confidence interval

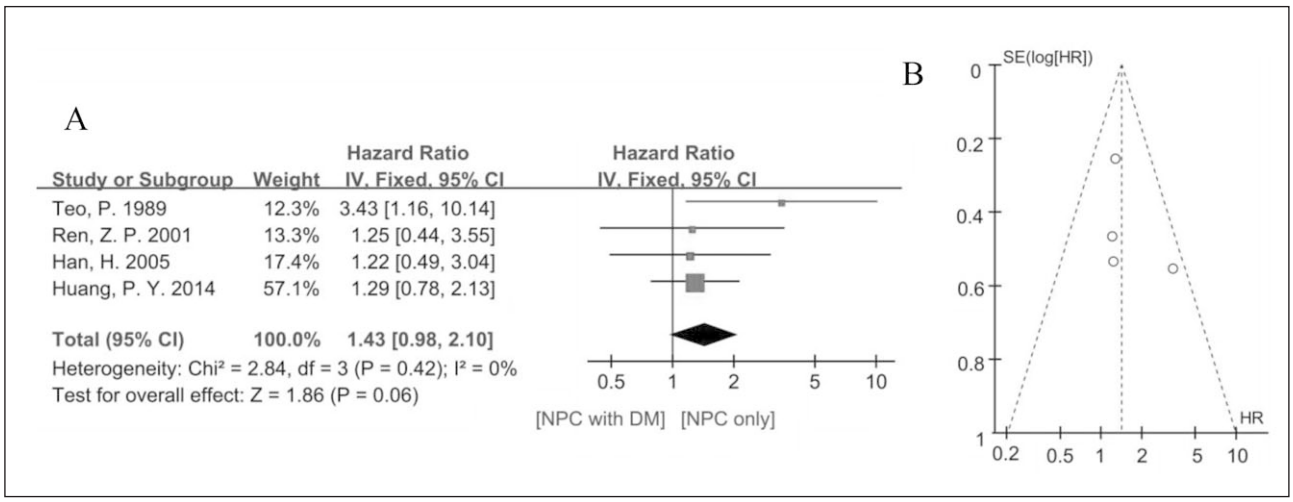

Figure 2. The prognostic value of DM on survival of patients with NPC. (A) Forest plot of HR; (B) Funnel plot of HR.

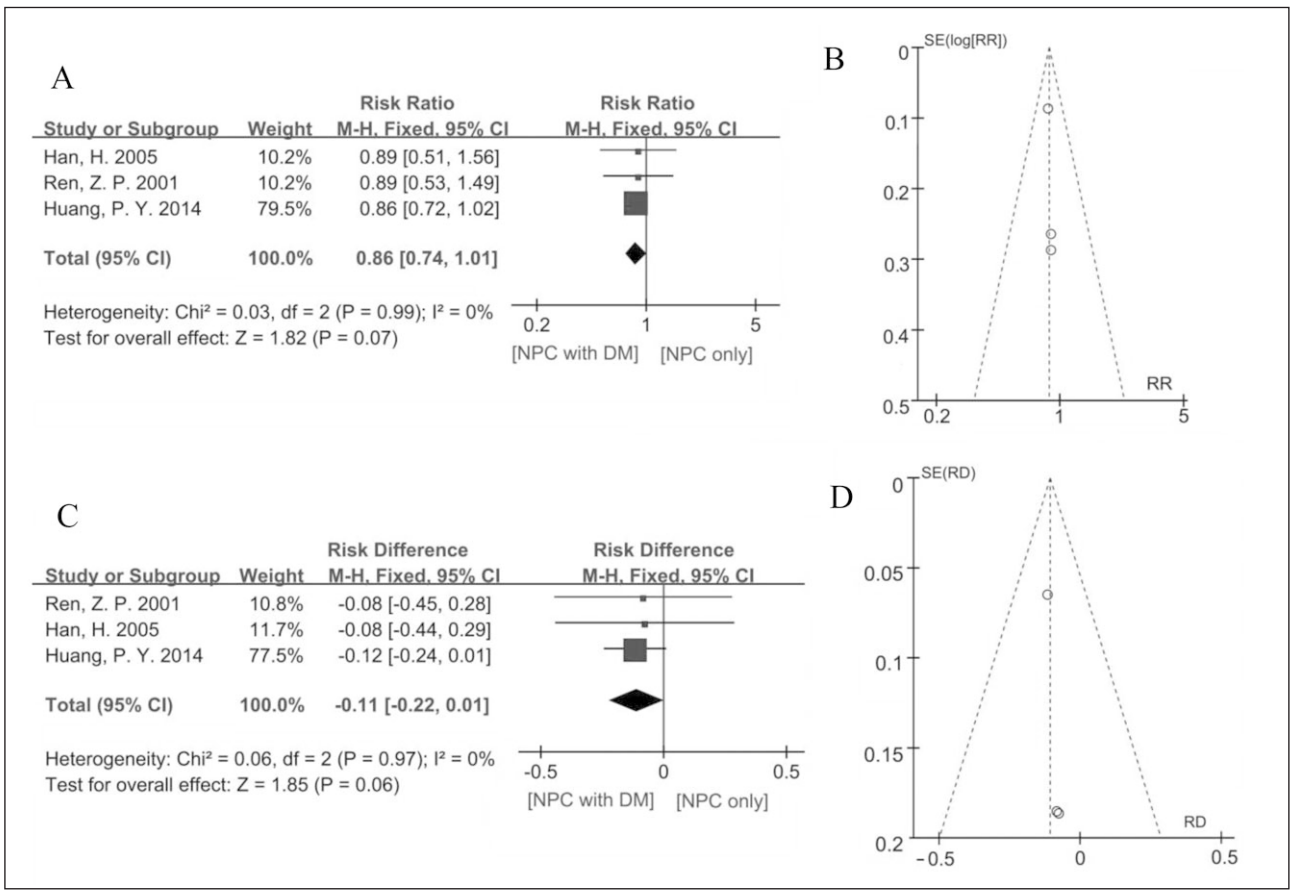

Figure 3. The prognostic value of DM on 3-year survival of patients with NPC. (A) 3-year survival RR Forest plot; (B) 3-year survival RR Funnel plot; (C) 3-year survival RD Forest plot; (D) 3-year survival RD Funnel plot. RD: risk difference; M-H Fixed: the Mantel-Haenszel method under the fixed-effects model.

RRs and RDs of DM on 3-year and 5-year survivals

One article without enough information was excluded.[5] Three studies were selected for the meta-analysis and all were paired studies.[6] Overall, 111 patients had DM accompanying NPC (NPC with DM group) and 111 patients had NPC without DM (NPC only group).

The three-year survival was analysed (Figure 3). Data were homogeneous according to the Cochrane Q test and the I2 statistic.[10-12] The pooled RR was 0.86 (95% CI: 0.74-1.01) with p value being 0.07, it did not reach the significance level, although it was close (Figure 3a). This suggests that, compared to NPC patients without DM, patients with DM has a lower 3-year survival rate. The probability of patients with DM may be only 86% as that of patients without DM. The pooled RD was -0.11 (95% CI: -0.22-0.01) with p value being 0.06, which is very close to significance (Figure 3C). That indicates that DM decreased the chance of 3-year survival in NPC patients by 11%. Visual inspection of corresponding funnel plots revealed no publication bias (Figures 3C and 3D). Results of Egger's test showed p value was close to 0.05. The p value of RR was 0.043 and that of RD was 0.059 (Table 2). This may be due to small number of trials.

Five-year survival was also analysed (Figure 4). Data was analysed with a fixed-effects analysis because the data were homogeneous according to the Cochrane Q test and the I2 statistic. DM was not significantly associated with 5-year survival. The pooled RR was 0.89 (95% CI: 0.71-1.13;

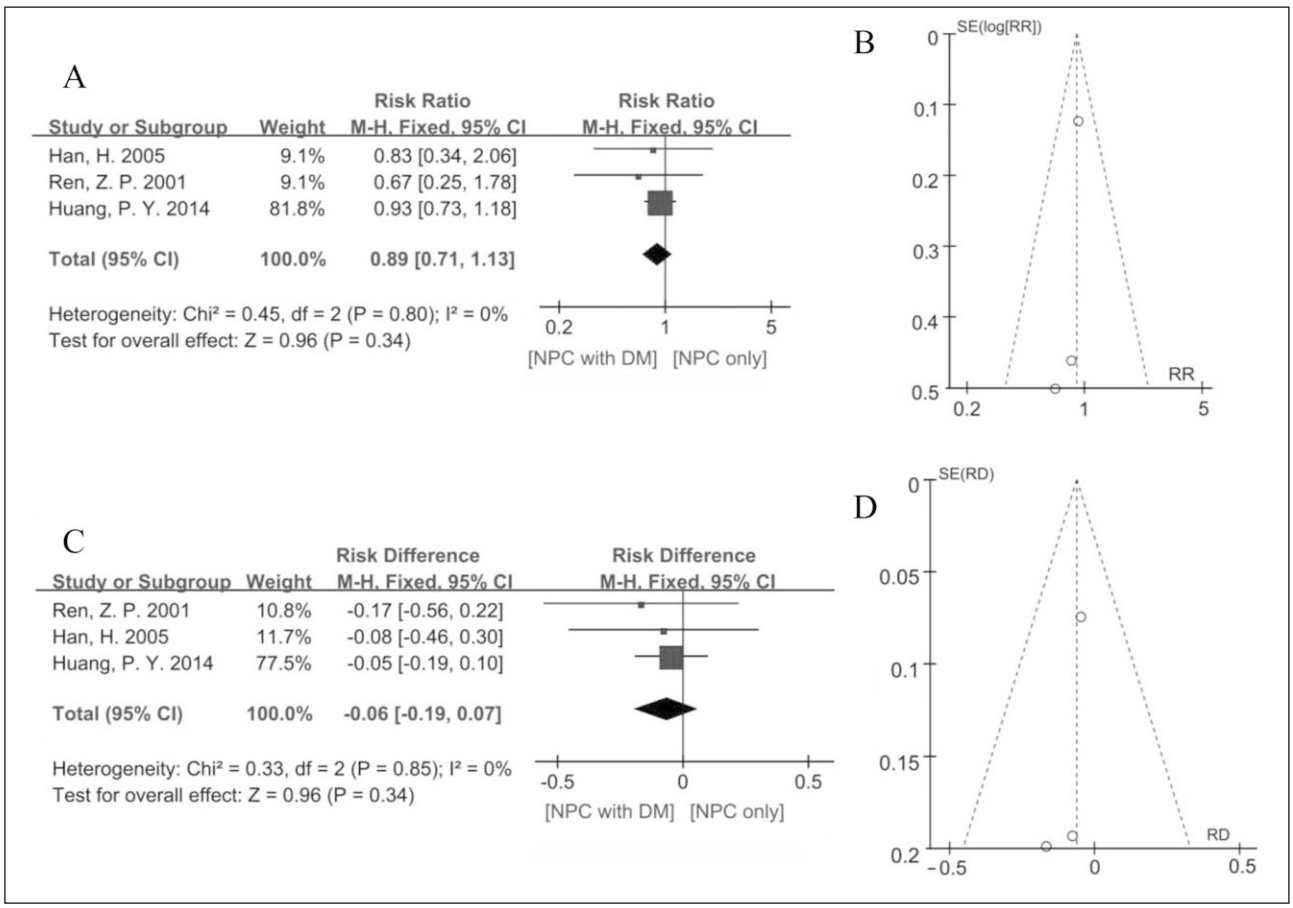

Figure 4. The prognostic value of DM on 5-year survival of patients with NPC. (A) 5-year survival RR Forest plot; (B) 5-year survival RR Funnel plot; (C) 5-year survival RD Forest plot; (D) 5-year survival RD Funnel plot.

p=0.34) (Figure 4A). The pooled RD was 0.06 (95% CI: -0.19-0.07; p=0.34) (Figure 4C). Visual inspection of corresponding funnel plots and results of Egger's test revealed no publication bias (Figures 4B and D, Table 2). The p value of RR was 0.270 and that of RD was 0.368 (Table 2).

The cause of death of NPC

The cause of death was summarised in Table 3. Only two articles reported cause of death.[6,8] Pulmonary infection were reported as the cause of death in NPC cases with DM group in both articles but not in the NPC only group (Table 3). The difference may be due to DM because pulmonary infection is a common condition and one of main causes of death in patients with DM.[13,14] More patients died of metastases in NPC with DM group than in NPC only group in Huang's study while there was no difference in Ren's (Table 3).

The pathology of NPC with paraneoplastic syndrome

The pathology of NPC with paraneoplastic syndrome was reviewed (Table 4) and was classified according to the World Health Organization (WHO) has classification of NPC: (Type I: keratinising squamous cell carcinomas; Type II: non-keratinising carcinomas [Type IIA includes undifferentiated carcinomas and Type III: basaloid squamous cell carcinomas.][15] Excluding cases without detailed pathological diagnosis, all NPC cases accompanying paraneoplastic syndrome, including paraneoplastic DM, were type II non-keratinising carcinomas.

Table 2. Publication bias was evaluated by Egger's test

Comparison	Std. Eff.	Coef.	Std. Err.	t	P>|t|	[95%CI]	p
3-year survival RR	Slope	0.842	0.00160	525.49	0.001	0.822, 0.863	0.043
	Bias	0.169	0.0115	14.64	0.043	0.0224, 0.317	
3-year survival RD	Slope	0.136	0.00282	-48.12	0.013	-0.172, -0.100	0.059
	Bias	0.300	0.280	10.71	0.059	-0.558, 0.656	
5-year survival RR	Slope	0.987	0.0443	22.27	0.029	0.424, 1.550	0.270
	Bias	-0.489	0.220	-2.22	0.270	-3.290, 2.312	
5-year survival RD	Slope	4.27×10^{-6}	0.0460	0.00	1.000	-0.585, 0.585	0.368
	Bias	-0.621	0.405	-1.53	0.368	-5.768, 4.526	

CI=confidence interval; RR=risk ratio; RD=risk difference

Table 3. Causes of death

		Total number	Local recurrence	Metastases	Pulmonary infection	Others
Ren, ZP.(6)	NPC with DM	12	3	4	1	0
	NPC only	12	2	4	0	0
Huang, PY.(8)	NPC with DM	86	20	20	2	0
	NPC only	86	22	11	0	1*

Notes: *, died of an accident

NPC=nasopharyngeal carcinoma; DM=dermatomyositis

Discussion

NPC has a well-defined racial and geographic distribution worldwide.[1,2,4] Compared to Western countries, the incidence is much higher in southeastern Asia and southern China.[1,2,4] In the United States, the incidence in white males and females are only 0.4 and 0.2 cases per 100,000 persons-year, respectively while the incidence in Chinese males and females in Hawaii is 10.7 and 3.8 cases per 100,00 persons-year, respectively.[2] In Hong Kong, NPC incidences in males and females are 21.4 and 8.3 cases per 100,000 persons-year, respectively.[2]

Paraneoplastic syndromes are signs or symptoms which are the consequence of cancer but are not caused directly by the local presence of cancer cells, metabolic abnormalities, nutritional deficits, infection, ischaemia, coagulopathy, or side effects of cancer treatment.[4,16,17] A paraneoplastic syndrome can precede, follow or be concurrent with the diagnosis of a malignancy.[18] The rate of paraneoplastic syndromes accompanying NPC was unclear. Ellouz et al reported that paraneoplastic syndromes were seen in 12 of 485 NPC patients in Tunisia.[19] The incidence of paraneoplastic syndrome accompanying NPC appears related to gender and pathological type (Table 4). According to Table 4, excluding cases without detailed gender, the ratio of male and female in the NPC with paraneoplastic syndromes was 222:96 (2.3:1). Excluding cases without detailed pathological diagnosis, all NPC cases accompanying paraneoplastic syndromes reported in literatures were type II non-keratinising carcinomas (Type II NPC also includes lymphoepithelioma what was used after 1940s.[1,15]

DM is one of the commonest types of paraneoplastic syndrome accompanying NPC (Table 4).[4,16,20,21] Even so, less than 0.1% NPC are associated with DM.[3,4] Thus, paraneoplastic DM accompanying NPC are mostly described in case reports or review articles in the literature (Table 4). The incidence of paraneoplastic DM accompanying NPC appears related to gender and pathological type as that of paraneoplastic syndromes does (Table 4). Huang et al reported

Table 4. Paraneoplastic syndromes with nasopharyngeal carcinoma

Bazex syndrome
Dermatomyositis alone or accompanied with Raynaud's phenomenon, arthritis, urticarial vasculitis or systemic sclerosis
Eosinophilic cellulitis alone or accompanied with migratory erythema
Epilepsia partialis continua
Erythroderma
Hypertrophic osteoarthropathy alone or accompanied with cutaneous vasculitis, mixed-type cryoglobulinemia
Motor neuropathy and inflammatory myopathy
Multicentric reticulohistiocytosis
Neurological disorder
Neutrophilic leukaemoid reaction
Opsoclonus-myoclonus syndrome
Optic neuropathy
Sjogren's syndrome
Systemic sclerosis alone or accompanied with cutaneous vasculitis, mixed-type cryoglobulinemia, systemic capillary leak syndrome
Xerophthalmia, pain in interphalangeal joints

the ratio of male and female in the NPC with DM was 64:22 (2.9:1) in Chinese.[8] According to Table 4, the ratio was 179:73 (2.5:1) and all NPC cases accompanying DM were type II non-keratinising carcinomas.

DM is an idiopathic inflammatory myopathy characterised clinically by proximal muscle weakness, muscle inflammation, characteristic rash and, frequently, the presence of autoantibodies.[22,23] The onset in DM may be acute (days) or insidious (several months).[22] Diagnosis of definite DM requires the presence of characteristic rash as well as at least three of the four signs of muscle inflammation and weakness: symmetrical proximal weakness, elevated levels of muscle enzymes (creatine kinase, aspartate aminotransferase, lactate dehydrogenase and aldolase), electro-myographical changes consistent with irritable myopathy, or necrosis and inflammation on muscle biopsy.[22,23] Typical rashes include a generalised photosensitive erythema, Gottron papules over extensor surfaces and a periorbital heliotrope rash. Usually, skin manifestations precede muscle involvement by several months or years.[22,23] The clinical features, diagnosis and classification of DM were well described previously.[22,24] An association between DM and malignancies has been widely accepted. There is about a three-fold increase in risk of malignant disease after diagnosis of DM but frequency of specific cancer types in DM varies greatly in different reports.[25-27] Therefore, the performance of whole-body FDG-PET/CT for diagnosing occult malignant disease in patients with DM is recommended by some researchers.[25] Usually paraneoplastic DM flare-ups coincide with cancer recurrence. However, flare of DM is often absent in NPC recurrence.[17,28]

No prospective case-control double-blinded studies of therapy for paraneoplastic DM have been performed. Hence, treatment of paraneoplastic DM is based mainly on case reports and remains largely empirical.[4,29] Van de Vlekkert reported that paraneoplastic DM could spontaneously remit.[29] Resolution after anticancer treatment alone healing paraneoplastic DM has also been reported.[30] Therefore, some oncologists regard the treatment of paraneoplastic DM as unnecessary. Some oncologists believe the treatment of paraneoplastic DM should be the same as the treatment of DM without coexisting cancer, or for a shorter period.[4] Treatment of DM is well-described elsewhere.[22,23] Nevertheless, corticosteroids are currently regarded as standard, first-line drugs.[22,23]

Corticosteroids treatment causes immunosuppression, which could theoretically aggravate the progression of malignancy.[4,8] It seems that Huang et al supported this hypothesis because more patients died of metastases in NPC with DM group than in NPC only group. However, this was not supported by Renet al (Table 3). At the same time, paraneoplastic DM itself can be fatal (most commonly due to respiratory failure).[8,13,14] In a study by Marie et al, aspiration pneumonia accounted for 30% of all mortalities in DM patients.[13] Similarly, Murray et al reported that of the 36 patients who died in their study, 9 (25%) died of aspiration pneumonia.[14] This may explain the deaths due to pulmonary infection reported in NPC with DM group while none occurred in NPC only group (Table 3). Paraneoplastic DM also increases radiotherapy side effects, sometimes resulting in interruption of treatment and reduced radiotherapeutic effect.[4,8] Therefore, DM might be an ominous sign of a poorer prognosis in NPC patients. Only a few control studies on DM effect on the prognosis in NPC have been reported.[6-8,31] Almost all indicate that DM might decrease the prognosis of patients with NPC, but the findings did not reach significance. The combined HR is 1.43 [95% CI: 0.98-2.10, p:0.06] and it suggests that DM may have an impact on NPC patient survival (Figure 2). Three-year survival rate of DM accompanying NPC may be less than that of NPC patients without DM (RR: 0.86, 95% CI: 0.74-1.01, p=0.07; RD: -0.11, 95% CI: -0.22-0.01, p=0.06) (Figure 3). The p value is very close to 0.05 and that may be

limited to the number of cases. Additionally, in the three studies selected for the meta-analysis here, the histological type was not taken into account.[6-8] The control group (NPC only group) consisted of patients who were matched with the experimental group (NPC with DM group) according to sex, age, stage, and treatment.[6-8] As mentioned above, all NPC cases accompanying paraneoplastic DM reported in literatures were type II non-keratinising carcinomas (Table 4). Since histological type is strongly associated with prognosis,[32] that factor might affect the conclusion. Visual inspection of the corresponding funnel plot revealed no publication bias (Figure 3D) while results of Egger's test showed p value was close to 0.05 (Table 2). Small number of trials should be one of the most reasonable explanations. All studies analysed HR here were carried out in southern China.[5-8] There have been no controlled studies in Caucasians or Africans. Therefore, more studies are needed to verify whether the findings are the same in different ethnic groups.

Conclusion

This study suggested that the presence of DM may decrease the prognosis, especially 3-year survival, in Chinese NPC patients. All NPC cases with paraneoplastic syndrome, including paraneoplastic DM, as reported in literature, were type II non-keratinising carcinomas. The role of DM in the prognosis of NPC remains to be elucidated, and is limited by the relatively small body of literature on the subject. Therefore, future rigorous clinical trials and published results will provide deeper insight into the influence DM on the prognosis in different ethnic groups.

Disclosure statement

The authors declare that there is no conflict of interests regarding the publication of this article.

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