Age at diagnosis indicated poor prognosis in locoregionally advanced nasopharyngeal carcinoma

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ABSTRACT

Background: Effect of age at diagnosis on treatment failure and mortality was rarely evaluated in nasopharyngeal carcinoma.

Methods: We analyzed 1252 patients staged III-IVb and underwent concurrent chemoradiotherapy. Age was categorized as 20 to 49 years (*n*=804), 50 to 59 years (*n*=282) and 60 years or older (*n*=166). Distant metastasis-free survival (DMFS), cancer-specific survival (CSS), overall survival (OS) and locoregional relapse-free survival (LRFS) were assessed by age group.

Results: The 4-years DMFS decreased with age group (86.7% [20-49 years], 86.7% [50-59 years], 77.1% [≥60 years]; *P*=0.014); likewise, 4-years CSS were 91.0%, 87.4% and 74.2% (*P*<0.001); 4-years OS were 90.8%, 87.4% and 73.6% (*P*<0.001), respectively. In multivariate analysis, compared with patients aged 20 to 49 years, DMFS decreased with age for patients aged 50 to 59 years (HR=1.10, 95% CI 0.77-1.57) and aged 60 years or older (HR=1.75, 95% CI 1.20-2.56) (*P*=0.015). Similarly, both CSS and OS were inferior in patients aged 50 to 59 years (HR=1.77, 95% CI 1.25-2.52 for CSS; HR=1.71, 95% CI 1.21-2.43 for OS) and aged 60 or older (HR=3.73, 95% CI 2.63-5.29 for CSS; HR=3.96, 95% CI 2.83-5.54 for OS) (*P*<0.001). Yet age did not affect LRFS in univariate and multivariate analysis.

Conclusions: Increasing age at diagnosis of locoregionally advanced nasopharyngeal carcinoma was associated with higher risk of distant metastasis and mortality.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a squamous-cell carcinoma specially endemic in Southern China. Almost 70% patients are initially diagnosed with locoregionally advanced disease [1], except those detected by regular physical examination of the nasopharynx. Unfortunately, these patients can hardly avoid the high risk of distant metastasis [2], treatment failure and mortality [3], despite the assistance of recommended concurrent chemotherapy plus advanced intensity-modulated radiotherapy.

Apart from such classic tumor-related factors as TNM stage [1] and copy number of Epstein-Barr viral deoxyribonucleic acid [4, 5], patient characteristics (e.g., sex [6]) may be associated with NPC outcomes as well. Interestingly, prior randomized controlled trials [7, 8] hinted at age-specific association with mortality, while others [9, 10] observed no association at all. Undoubtedly, strict eligibility criteria make the trial cohort unlikely to

Table 1: Baseline characteristics by age at diagnosis

	20-49 years (n=804)	50-59 years (n=282)	≥60 years (n=166)	*P*
Sex				**0.483**
Male	586 (72.9)	195 (69.1)	120 (72.3)	
Female	218 (27.1)	87 (30.9)	46 (27.7)	
Histology *				**0.914**
I+II	57 (7.1)	18 (6.4)	11 (6.6)	
III	747 (92.9)	264 (93.6)	155 (93.4)	
VCA-IgA				**0.007**
<80	135 (16.8)	44 (15.6)	13 (7.8)	
80-320	277 (34.5)	95 (33.7)	48 (28.9)	
≥320	392 (48.8)	143 (50.7)	105 (63.3)	
EA-IgA				**0.007**
<10	231 (28.7)	72 (25.5)	27 (16.3)	
10-40	255 (31.7)	86 (30.5)	52 (31.3)	
≥40	318 (39.6)	124 (44.0)	87 (52.4)	
T-stage				**0.373**
T1+T2	82 (10.2)	24 (8.5)	21 (12.7)	
T3+T4	722 (89.8)	258 (91.5)	145 (87.3)	
N-stage				**0.563**
N0+N1	576 (71.6)	207 (73.4)	114 (68.7)	
N2+N3	228 (28.4)	75 (26.6)	52 (31.3)	
Clinical stage				**0.010**
III	522 (64.9)	175 (62.1)	87 (52.4)	
IV	282 (35.1)	107 (37.9)	79 (47.6)	
Radiotherapy				**0.378**
2DCRT	496 (61.7)	174 (61.7)	93 (56.0)	
IMRT	308 (38.3)	108 (38.3)	73 (44.0)	

Abbreviations: IMRT = intensity-modulated radiotherapy, 2DCRT = two-dimensional conventional radiotherapy, VCA = viral capsid antigen, EA = early antigen, IgA = immunoglobulin A
* Based on the criteria of WHO histological type (1991): II - Differentiated non-keratinising carcinoma, III - Undifferentiated non-keratinising carcinoma

represent the general cancer population with respect to cancer histology, stage and other basic characteristics. For instance, older patients are often excluded from clinical trials due to age restrictions. Thus the prognostic significance of age was essential to be assessed in a cohort out of trials.

In this study, we aimed to evaluate distant metastasis rate among age groups in locoregionally advanced NPC patients treated with concurrent chemoradiotherapy. Secondarily, age-specific locoregional relapse, cancer specific mortality and overall mortality were evaluated as well.

RESULTS

A total of 1252 patients (age range, 20-78 years; median age, 45 years) were included, of which 804 (64.2%) were aged 20 to 49 years (median age, 40 years), 282 (22.5%) were aged 50 to 59 years (median age, 54 years), and 166 (13.3%) were aged 60 years or older (median age, 63 years). As showed in Table 1, there was a significant age-associated increase in higher titer of immunoglobulin A against viral capsid antigen (VCA-IgA) and early antigen (EA-IgA). Besides, the proportion of advanced clinical stage increased significantly with age.

With median follow-up of 56.9 months (3.5-108.3 months) for patients aged 20 to 49 years, 52.4 months (5.2-107.1 months) for patients aged 50 to 59 years, and 47.6 months (3.3-111.1 months) for patients aged 60 or older respectively, 111 (13.8%), 42 (14.9%) and 35 (21.1%) patients had distant metastasis. As illustrated in Figure 1, 4-years distant metastasis-free survival (DMFS) significantly decreased from 86.7% in patients aged 20 to 49 years, 86.7% in patients aged 50 to 59 years, to 77.1%

Table 2: Summary of pivotal prognostic factors in multivariate analysis

	Multivariate hazard ratio (95% CI)	*P* †
Distant metastasis-free survival		
Age		0.015
20-49 years	1 (reference)	
50-59 years	1.10 (0.77-1.57)	0.591
≥60 years	1.75 (1.20-2.56)	0.004
T-stage (T1+T2 vs T3+T4)	1.73 (1.05-2.86)	0.031
N-stage (N0+N1 vs N2+N3)	2.44 (1.78-3.35)	<0.001
Cancer specific survival		
Age		
20-49 years	1 (reference)	
50-59 years	1.77 (1.25-2.52)	0.001
≥60 years	3.73 (2.63-5.29)	<0.001
T-stage (T1+T2 vs T3+T4)	2.54 (1.50-4.31)	0.001
N-stage (N0+N1 vs N2+N3)	2.82 (2.05-3.87)	<0.001
Overall survival		
Age		
20-49 years	1 (reference)	
50-59 years	1.71 (1.21-2.43)	0.003
≥60 years	3.96 (2.83-5.54)	<0.001
T-stage (T1+T2 vs T3+T4)	2.69 (1.59-4.55)	<0.001
N-stage (N0+N1 vs N2+N3)	2.83 (2.08-3.85)	<0.001
Locoregional relapse-free survival		
Age		
20-49 years	1 (reference)	
50-59 years	1.19 (0.79-1.81)	0.407
≥60 years	0.84 (0.45-1.58)	0.589
T-stage (T1+T2 vs T3+T4)	1.56 (0.77-3.14)	0.216
N-stage (N0+N1 vs N2+N3)	1.53 (0.99-2.37)	0.055

Abbreviations: CI = confidence interval
† Adjusted for T-stage and N-stage by Enter method, and sex, histology, immunoglobulin A against viral capsid antigen (<80/80-320/≥320), immunoglobulin A against early antigen (<10/10-40/≥40) and radiation technique by Forward Stepwise (Likelihood Ratio) method.

in patients aged 60 or older (P = 0.014). Likewise, the 4-years cancer specific survival (CSS) were 91.0%, 87.4% and 74.2% (P < 0.001); the 4-years overall survival (OS) were 90.8%, 87.4% and 73.6% (P < 0.001), respectively. In addition, 4-years locoregional relapse-free survival (LRFS) were 91.7%, 91.4% and 94.4% (P = 0.544). When adjusted for unequal distributions among age categories (Table 2) by multivariate analyses, DMFS still decreased with age at diagnosis, with a HR of 1.10 (95% CI 0.77-1.57) for patients aged 50 to 59 years and a HR of 1.75 (95% CI 1.20-2.56) for patients aged 60 or older (P = 0.015). Similarly, both CSS (HR = 1.77, 95% CI 1.25-2.52 for patients aged 50 to 59 years; HR = 3.73, 95% CI 2.63-5.29 for patients aged 60 or older; P < 0.001) and OS (HR = 1.71, 95% CI 1.21-2.43 for patients aged 50 to 59 years; HR = 3.96, 95% CI 2.83-5.54 for patients aged 60 or older; P < 0.001) remarkably declined with age. But no association was observed between age and LRFS (HR = 1.19, 95% CI 0.79-1.81 for patients aged 50 to 59 years; HR = 0.84, 95% CI 0.45-1.58 for patients aged 60

Table 3: Association of age with survival in subgroup analysis by tumor stage

	Stage III		Stage IV	
	Multivariate hazard ratio (95% CI)	*P* †	Multivariate hazard ratio (95% CI)	*P* †
Distant metastasis-free survival				
20-49 years	1 (reference)		1 (reference)	
50-59 years	1.24 (0.75-2.06)	0.407	0.90 (0.55-1.48)	0.671
≥60 years	1.88 (1.06-3.33)	0.032	1.45 (0.87-2.42)	0.150
Cancer specific survival				
20-49 years	1 (reference)		1 (reference)	
50-59 years	2.31 (1.41-3.79)	0.001	1.28 (0.77-2.12)	0.338
≥60 years	3.67 (2.13-6.33)	<0.001	3.34 (2.13-5.23)	<0.001
Overall survival				
20-49 years	1 (reference)		1 (reference)	
50-59 years	2.31 (1.41-3.79)	0.001	1.20 (0.73-1.98)	0.476
≥60 years	3.86 (2.26-6.59)	<0.001	3.46 (2.25-5.33)	<0.001
Locoregional relapse-free survival				
20-49 years	1 (reference)		1 (reference)	
50-59 years	1.27 (0.72-2.22)	0.411	1.09 (0.59-2.04)	0.777
≥60 years	0.95 (0.40-2.23)	0.899	0.69 (0.27-1.76)	0.430

Abbreviations: CI = confidence interval
† Adjusted for sex, histology, immunoglobulin A against viral capsid antigen (<80/80-320/≥320), immunoglobulin A against early antigen (<10/10-40/≥40) and radiation technique by Forward Stepwise (Likelihood Ratio) method.

or older; $P = 0.551$).

Since increasing age was correlated with more advanced tumor stage (Table 1), subgroup analyses by stage were conducted to exclude residual confounding (Table 3). Among patients with stage III, multivariate analyses revealed similar results. Within strata of stage IV, increasing age was consistently correlated with decreased CSS and OS, but not the risk of distant metastasis or locoregional relapse.

In order to test the robustness of the cutoff points of age, we conducted a second analysis by regarding age as a continuous variable. As a result, an increased risk of distant metastasis (univariate HR = 1.02, 95% CI 1.00-1.03, $P = 0.009$; multivariate HR = 1.02, 95% CI 1.01-1.03, $P = 0.006$), cancer-specific mortality (univariate HR = 1.05, 95% CI 1.04-1.06, $P < 0.001$; multivariate HR = 1.05, 95% CI 1.04-1.06, $P < 0.001$) and overall mortality (univariate HR = 1.05, 95% CI 1.04-1.07, $P < 0.001$; multivariate HR = 1.05, 95% CI 1.04-1.07, $P < 0.001$) by age was confirmed again. Nevertheless, age was not found to be associated with LRFS (univariate HR = 1.01, 95% CI 0.99-1.02, $P = 0.509$; multivariate HR = 1.00, 95% CI 0.99-1.02, $P = 0.467$).

To investigate whether the association between age and DMFS, CSS and OS was of linear effect or if there was a specific turning point, age was finally categorized into five groups (Table 4). Resultantly, patients younger than 55 years had similar risk of distant metastasis. But the risk of distant metastasis would elevate with increasing age for patients aged 55 years or older. Moreover, CSS and OS significantly decreased with age, especially for patients aged 45 years or older, whereas LRFS was again not correlated with age.

DISCUSSION

Our major finding was that older patients had higher risk of distant metastasis and cancer-specific or overall mortality, independent of host factor, tumor characteristics and radiation technique.

Several tumor characteristics potentially biased our findings. Increasing age correlated with higher titer of VCA-IgA and EA-IgA and more advanced tumor stage. But multivariate analyses adjusted for these tumor characteristics and subgroup analyses by tumor stage did not significantly alter the results.

Table 4: Survival outcomes by age at diagnosis (five groups).

	Multivariate hazard ratio (95% CI)	*P* †
Distant metastasis-free survival		
20-39 years	1 (reference)	
40-44 years	0.99 (0.62-1.59)	0.961
45-49 years	1.38 (0.89-2.13)	0.147
50-54 years	1.19 (0.72-1.96)	0.497
≥55 years	1.58 (1.08-2.31)	0.019
Cancer specific survival		
20-39 years	1 (reference)	
40-44 years	0.92 (0.52-1.62)	0.770
45-49 years	1.80 (1.12-2.91)	0.016
50-54 years	2.04 (1.23-3.36)	0.006
≥55 years	3.16 (2.13-4.69)	<0.001
Overall survival		
20-39 years	1 (reference)	
40-44 years	0.94 (0.54-1.63)	0.814
45-49 years	1.87 (1.17-3.00)	0.009
50-54 years	2.12 (1.28-3.51)	0.003
≥55 years	3.32 (2.25-4.92)	<0.001
Locoregional relapse-free survival		
20-39 years	1 (reference)	
40-44 years	1.06 (0.62-1.84)	0.824
45-49 years	1.22 (0.71-2.09)	0.475
50-54 years	0.98 (0.52-1.86)	0.960
≥55 years	1.24 (0.76-2.03)	0.385

Abbreviations: CI = confidence interval
† Adjusted for T-stage and N-stage by Enter method, and sex, histology, immunoglobulin A against viral capsid antigen (<80/80-320/≥320), immunoglobulin A against early antigen (<10/10-40/≥40), and radiation technique by Forward Stepwise (Likelihood Ratio) method.

Our finding was highly consistent with prior reports in [7, 8] and out of [16, 17] clinical trials. However, age showed no association with survival in another two trials that focused on the effect of concurrent chemotherapy [10] and adjuvant chemotherapy [9] respectively. Of note, age distribution of included patients was greatly biased by the specific selection criteria of trials, whereas randomization of patients to treatment and control arms cannot guarantee balanced characteristics across age group. In addition, patients were separated to two groups at the age point of 45 years in these two trials. This cutoff point maybe underestimated or even falsely covered the association of age with survival.

Several mechanisms may possibly explain the observed results. Firstly, older patients may experience undertreatment. Previous studies [13, 18] showed that less than 40% of elderly NPC patients with locoregionally advanced disease received combined chemoradiotherapy. Despite all included patients in our study underwent standard concurrent chemoradiotherapy, more older patients indeed tended to receive lower total dose (< 200 mg/m^2) of concurrent chemotherapy (P = 0.016). Considering the inferior outcome of concurrent chemotherapy with cisplatin below 200 mg/m^2 [19], older patients possibly achieved poor survival. Next, the incidence of comorbidities significantly increased with age in this sort of cancer [20]. Patients with comorbidities were more likely to experience undertreatment, and comorbidity itself indicated poor prognosis in locoregionally advanced NPC [20]. Besides, older patients were found to be those had higher titer of VCA-IgA and EA-IgA and diagnosed with more advanced clinical stage (Table 1). So it was possible that tumor cells in older patients might be more aggressive and more likely

to spread to distant organs. In addition, it was assumed that overtreatment may be delivered to older patients, and the consequent adverse events can result in mortality attributed to cancer. However, these relatively healthy patients suffered from higher distant metastasis risk with age as well. So overtreatment maybe exerted a tiny effect in our study. Since the association between age and risk of distant metastasis, cancer-specific and overall mortality was maintained despite the adjustment for various characteristics, other unknown factors might help to cause the results. Perhaps, older patients might respond differently to either the tumor or anticancer therapy.

The major strength of this study was the intensive assessment of age-specific association with risk of distant metastasis, cancer specific and overall mortality in a large cohort close to general population but with utilized treatment and complete follow-up. It is a limitation that data on deoxyribonucleic acid (DNA) copy number of the Epstein-Barr virus was missing in most of cases, but VCA-IgA and EA-IgA were taken as the surrogate for tumor burden. In addition, some patients might be delayed in detecting lung metastasis and consequently have falsely high DMFS rate, owing to the low sensitivity rate of chest radiography compared with CT. But the intrinsic differences in DMFS might scarcely change, as the chance of delay was equal to patients in each arm.

To summarize, this study found increasing risk of distant metastasis, cancer specific and overall mortality with increasing age at diagnosis in locoregionally advanced NPC patients.

MATERIALS AND METHODS

Patients

Potentially eligible patients were those diagnosed with NPC between Jan 2005 and Jan 2011 by history and physical examination, hematology and biochemistry profiles, fiberoptic nasopharyngoscopy with biopsy, magnetic resonance imaging (MRI) of the nasopharynx and neck, chest radiography or computed tomography (CT), abdominal sonography or CT, Technetium-99m-methylene diphosphonate (Tc-99-MDP) whole-body bone scan or CT/MRI of bones, and/or [18F] fluorodeoxy

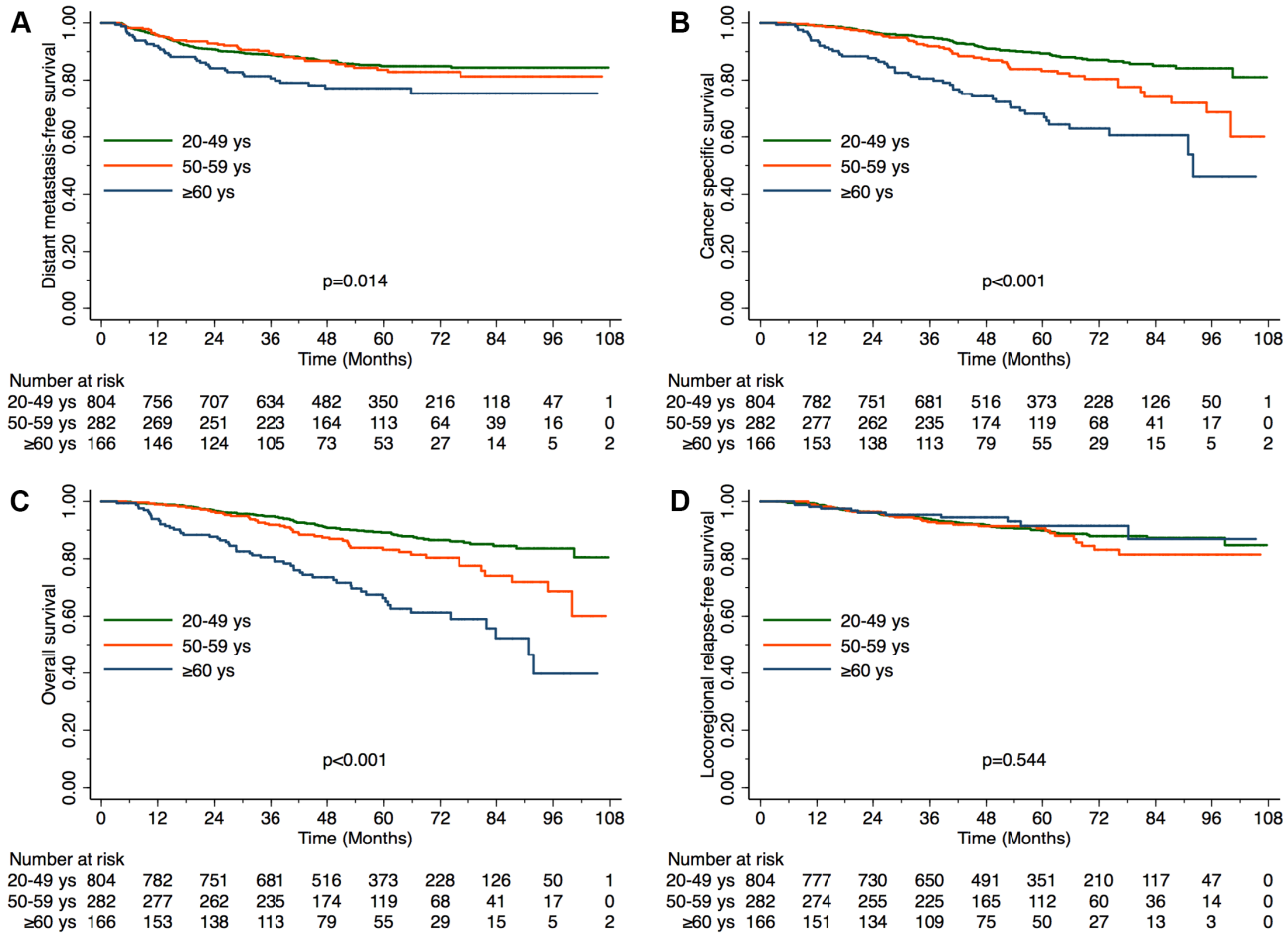

Figure 1: Distant metastasis-free survival (**A**), cancer specific survival (**B**), overall survival (**C**) and locoregional relapse-free survival (**D**) of patients by age at diagnosis**.**

glucose positron emission tomography and computed tomography (PET/CT). The following inclusion criteria were used: (1) age $\geq$ 20 years; (2) restaged III-IVa-b based on the 2010 International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system; (3) treated with concurrent chemoradiotherapy alone; and (4) available data on VCA-IgA and EA-IgA. The exclusion criteria were as follows: (1) receiving anticancer therapy out of our hospital; (2) pregnancy or lactation; (3) a history of previous, synchronous or subsequent malignant tumors; and (4) lack of follow-up.

This study was approved by the Institutional Review Board at our center, and individual informed consent was waived given the anonymous analysis of routine data.

Treatment

All patients underwent definitive intensity-modulated radiotherapy (IMRT) or two-dimensional conventional radiotherapy (2DCRT) plus concurrent chemotherapy. Cumulative radiation doses were 66 Gy or greater to the primary tumor, 60 Gy or greater to involved cervical lymph nodes and 50 Gy or greater to local sites with potential infiltration and uninvolved cervical and supraclavicular areas in 30-33 fractions. Further information of radiation technique had been detailed previously [11]. Concurrent chemotherapy consisted of 80-100mg/m^2 cisplatin- or nedaplatin-based regimen given every three weeks for two to three cycles, or 30-40mg/m^2 cisplatin- or nedaplatin-based regimen or 20-30mg/m^2 docetaxel-based regimen given weekly for up to seven cycles.

Follow-up

Patients were assessed by similar examination to pretreatment evaluation every 3-6 months during the first 3 years and every 6-12 months thereafter until death, to detect possible relapse or distant metastasis. Salvage treatment including reirradiation, surgery and/or chemotherapy was delivered to patients with confirmed relapse, distant metastasis or persistent disease. Patients without recent examination tests in medical records were followed up by telephone call.

Statistical analysis

Since sex significantly affected survival of NPC [6] and median age at natural menopause was 50 years in Chinese [12], patients in this study were categorized into 3 age groups: the premenopausal (20-49 years), the menopausal (50-59 years) and the elderly (60 years or older, in line with prior report [13]). To compare proportional differences between age groups, χ^2 test was used. Primary endpoint was DMFS, measured from treatment to the first distant metastasis or last contact. Other endpoints included CSS (time from treatment to death from cancer and treatment complication or last contact), OS (time from treatment to death from any cause or last contact) and LRFS (time from treatment to the first locoregional relapse or last contact). Kaplan-Meier method [14] and log-rank test were used to examine survival outcomes across age groups. Cox proportional hazard models [15] were used to evaluate associations between covariates and endpoints. All statistical analyses were performed using Stata 14. Two-sided P values < 0.05 were considered to be significant.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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